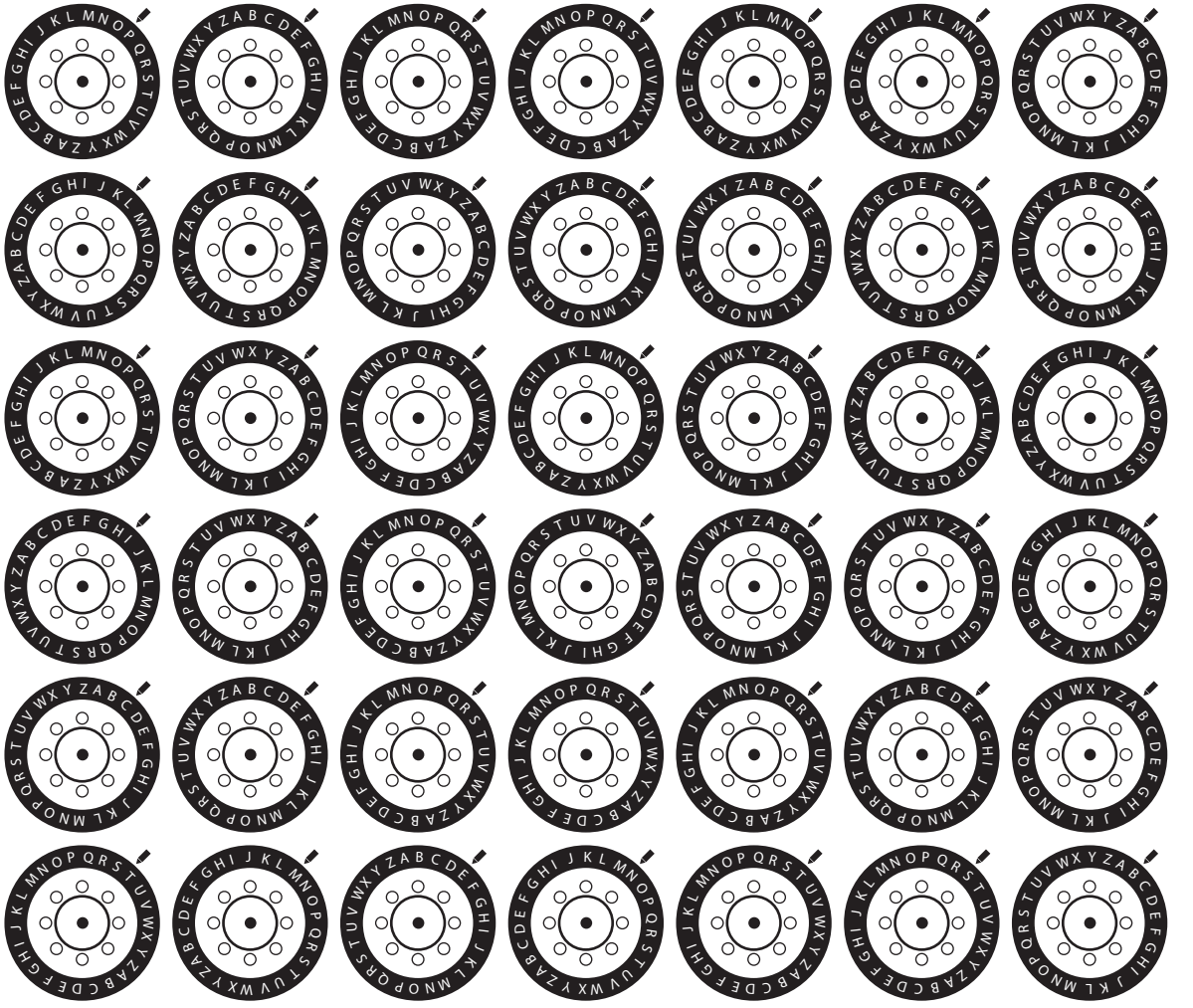
Personalized Hepatobiliary Cancer Treatment



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INTRODUCTION

Biliary Tract Cancer

Biliary tract cancers (BTC) are a group of malignancies developing in the intra- and extrahepatic biliary tracts, as well as in the gallbladder. Four separate groups of biliary cancers are recognized, intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (PHC), gallbladder carcinoma (GBC) and distal cholangiocarcinoma.[1] ICC is an adenocarcinoma developing in the peripheral bile ducts within the liver.[1] With an incidence of 1-2 per 100,000 in the Western world, it is the second most common primary malignancy forming in the liver.[2,3] Perihilar cholangiocarcinoma originates from the left and right hepatic ducts as well as the common bile duct in the hilum of the liver. Its incidence is slightly higher than that of intrahepatic cholangiocarcinoma with an average of 2 per 100,000.[2,4] Gallbladder is a malignancy often accidentally diagnosed in the gallbladder after cholecystectomy. It has an incidence of 2.5 per 100,000, mostly in women, and is perhaps the most aggressive biliary tract tumor.[5-7] Distal cholangiocarcinoma, finally, forms in the distal common bile duct, close to the pancreas.[1] Because of the differences in operation techniques resulting in different disease course and because of the different anatomical location, this thesis will not focus on patients with distal cholangiocarcinoma.

Etiologically, BTC share many risk factors. A correlation with diseases causing biliary inflammation and fibrosis, such as primary sclerosing cholangitis and primary biliary cirrhosis, has been noted.[8,9] Risk factors primarily associated with ICC are congenital malformations of the bile duct, hepatolithiasis, hepatitis B and C virus, and alcoholic liver cirrhosis[8] In East-Asia hepatic parasite infections, in particular *Opisthorchis viverrini* and *Clonorchis sinensis*, are significant risk factors for both ICC and PHC.[10,11] PHC risk factors are mostly similar to those for ICC, although this may be a consequence of population databases insufficiently differentiating between the two diseases.[12] Risk factors more associated with PHC include Caroli's disease and congenital choledochal cysts.[13] GBC specific risk factors include gallbladder polyps, porcelain gallbladder, as well as H. pylori infection, and S. paratyphi or S. typhi infections.[14,15]

BTC pathologically classify as adenocarcinomas, carcinomas of epithelial origin with glandular features.[16-18] Formation of cholangiocarcinomas is frequently caused by mutations of the KRAS oncogene, a protein normally involved in the cell proliferation, in combination with the deletion of the p53 tumor suppressor gene.[19,20] A critical signaling protein downstream of KRAS and p53 mutations is

interleukin 6 (IL-6), which is a serum biomarker for ICC and PHC.[21-23] Further downstream, ROS1 fusion proteins, regulated by KRAS/IL-6 pathways, have been associated with an aggressive phenotype and metastatic disease at diagnosis.[24,25] Existing candidate gene studies in GBC susceptibility have so far been insufficient to confirm any association.[26]

Surgical Treatment

Surgical resection remains the only curative treatment approach in hepatobiliary malignancies, even though only a minority of patients are eligible for surgery at the time of diagnosis.[1] Resection rates vary from 10%-40% in recent reports. [1,27] Hepatobiliary tumors often necessitate large resections, accompanied by a high rate of complications and severe complications.[1] Major postoperative morbidity and mortality of 5 to 15% are reported in Western centers.[28] The incidence of postoperative liver failure, a complication associated with 30% mortality, is currently reported to be between 0.7% and 34%.[29-33]

Resection strategies for BTC often include radical en-bloc extirpation of the affected part of the biliary tree and its neighboring anatomical structures in order to achieve negative resection margins.[34] For peripheral ICC, a left or right hemihepatectomy is often required, while for central ICC an extended hepatectomy is performed.[34] PHC usually requires extirpation of the common bile duct and, conditional on the Bismuth-Corlette stage, an (extended) hepatectomy in the direction of growth.[35] When lymph node metastases are found, lymphadenectomy up to the hepatoduodenal ligament is often performed, and sometimes extended to the celiac or aorto-caval lymph nodes.[34] GBC is sometimes found during routine laparoscopic cholecystectomy. In these cases, resection of the cystic duct and Couinaud segment IVb and V of the liver is performed.[36,37] The role of common bile duct resection is more controversial.[38,39] Lymphadenectomy is performed dependent on the presence of suspicious lymph nodes.[36,37] When the diagnosis of GBC is known in advance, these procedures are performed during the same operation, usually after laparotomy.[36,37]

There is disagreement about the place of palliative surgery. Non-operative management is recommended among patients with a life expectancy of less than 6 months, and the best course of treatment among patients found to have unresectable disease at the time of surgery is debated.[40-43] Data evaluating the utilization patterns and outcomes of palliative surgery are scarce. Studies into palliative surgery are often conducted in small cohorts. As a result, these reports are limited and may not be generalizable. [40-43]

Non-Surgical Treatment

When surgical treatment is not an option, several non-surgical treatments are available to patients with BTC. Some of these treatments may, in time, replace surgery as a means of curation. In most cases, non-surgical procedures are palliative in nature and aim to extent the patient's life and improve the quality thereof. The main symptom of BTC, which also causes most BTC to be diagnosed, is biliary obstruction.[1] The foundation of palliative treatment therefore is the alleviation of this condition by means of biliary drainage.[44-46] However, procedures for biliary drainage including percutaneous transhepatic cholangiography and endoscopic retrograde cholangiography are invasive and complications following their use may compromise further management and quality of life.[44-46] Best supportive care is recommended for patients with a poor performance status or a life expectancy of less than 6 months.[40-43]

Preoperative and adjuvant chemotherapy are not routinely prescribed for BTC due to a lack of evidence.[47] Preoperative therapy is aimed at occult metastatic disease or used to facilitate resection, while adjuvant chemotherapy is aimed at decreasing the chance of tumor recurrence.[48] Chemotherapy consists of mainly nucleoside analogues, most commonly gemcitabine, sometimes in combination with cisplatin.[48] While a significant portion of US patients receive chemotherapy, no randomized trials have been completed.[48,49] Following the outcomes of the ABC-02 trial for palliative chemotherapy, a combination of gemcitabine and cisplatin is offered most often.[47] The efficacy of chemotherapy regimens is usually poor, and only a small subgroup benefits significantly in terms of quality of life and survival length.[11,48]

For palliative chemotherapy, the aforementioned ABC-02 trial, randomized 410 patients with BTC and found an improvement in overall survival of nearly four months with gemcitabine plus cisplatin compared to gemcitabine alone.[47,50] Gemcitabine plus cisplatin has been the standard palliative regimen for locally advanced or metastatic BTC since.

Other non-surgical treatments for locally advanced BTC include transarterial chemoembolization (TACE) and radio-embolization with Yttrium-90.[51] TACE affects the blood flow to the tumor in addition to locally releasing cytotoxic agents and thereby reducing tumor burden.[51,52] Y-90 radio-embolization is based on administration of beads filled with the radioactive isotope yttrium-90 into the hepatic artery branch supplying the tumor.[53,54]

Prognostication and Prediction

In order to truly personalize treatment, individual patient prognosis has to be determined and response to specific treatments needs to be predicted. For prognostication, several prognostic models have been developed in addition to the classic American Joint Committee on Cancer Tumor-Node-Metastases (TNM) staging system.[55] More accurate prediction of individual patient outcome may provide better individual survival estimates, as well as improve identification of high-risk groups who may benefit from adjuvant therapy.[56] While the AJCC staging and e.g. the Mayo Staging system for PHC concern all diagnosed patients, other models pertain only to patients who have undergone a complete resection.[55,57-59] Few prognostic models for GBC are available. Predictive models are available for the efficacy of adjuvant therapy for GBC, the chance of detection of metastases during laparoscopy for PHC, and finally, postoperative mortality after PHC.[60-62]

Because of the comparatively low incidence of BTC, derivation studies for prognostic models have often lacked statistical power.[63] Underpowered studies are at a risk of over-fitting the model to the data, causing decreased reproducibility.[63] This results in poor results in validation studies.[59,64,65] Although multiple well-known prognostic factors are used in the prognostic models, accurate estimation of their impact on survival remains elusive.

Personalized Treatment

Personalized treatments for BTC patients could improve the overall outcomes, mainly by withholding treatments from patients who are unlikely to benefit from surgery or chemotherapy. In order to determine the best treatment, at the optimal time in the disease course, in the center with the best outcomes, for each individual patient, large databases have to be utilized to construct appropriate validated models. The works included in this thesis aim to contribute to the development of personalized medicine using accurate prognostication and prediction rules.

THESIS OVERVIEW

Part I aims to determine which patients are best selected for the different treatment modalities. More specifically, which patients should be considered eligible for surgery and which patients should rather be treated non-surgically. In **Chapter 1**, the importance of hospital and surgery volume for individual patient outcomes is assessed in a United States (U.S.) national registry. **Chapter 2** is a review of the definitions of post-hepatectomy liver failure, detailing predictive patient-specific factors. **Chapter 3** is a retrospective analysis of perihilar cholangiocarcinoma patients, and tries to determine whether it is prudent to attempt a resection when lymph node metastases are present. In **Chapter 4 and Chapter 5** the prognostic and predictive value of frailty, determined by low skeletal muscle mass, is discussed for general and elderly patients undergoing liver surgery.

In *Part II*, prognosis after surgery is discussed. Prognostic and predictive tools are explored, which can be used for both patient information and treatment allocation. The purpose of **Chapter 6** is to review current literature in hepato-pancreato-biliary model building, discussing current practices and shortcomings in validated models. In **Chapter 7** models for intrahepatic cholangiocarcinoma are validated in a large international cohort. **Chapter 8** introduces the concept of conditional survival, the notion that accrued survival time is the most important prognostic factor for further survival, to a large cohort of patients with perihilar cholangiocarcinoma. **Chapter 9** gives conditional survival estimates for patients with gallbladder cancer. Finally, **Chapter 10** questions the prognostic impact of routine resection of the common bile duct in patients with gallbladder carcinoma.

In *Part III,* non-surgical techniques and their efficacy in battling biliary tract cancers is discussed. **Chapter 11** gives an overview of novel surgical and non-surgical techniques in patients with intrahepatic cholangiocarcinoma. **Chapter 12** discusses the effect of preoperative chemotherapy in the same population. **Chapter 13** assesses the outcomes and effects of palliative surgery in gallbladder and perihilar cholangiocarcinoma in a large U.S. cohort. Finally, **Chapter 14** gives an overview of utilization of Yttrium-90 for radioembolization of the liver in patients with intrahepatic cholangiocarcinoma in the largest cohort to date, discussing its safety and efficacy.

REFERENCES

1. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. *J Surg Oncol* 2014; **110**(5): 585-91.
2. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**(5): 755-62.
3. Konstantinidis IT, Koerkamp BG, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2015.
4. Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; **228**(3): 385-94.
5. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004; **54**(1): 8-29.
6. Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. *Oncologist* 2010; **15**(2): 168-81.
7. Dutta U. Gallbladder cancer: can newer insights improve the outcome? *J Gastroenterol Hepatol* 2012; **27**(4): 642-53.
8. Brito AF, Abrantes AM, Encarnacao JC, Tralhao JG, Botelho MF. Cholangiocarcinoma: from molecular biology to treatment. *Med Oncol* 2015; **32**(11): 245.
9. Dodson RM, Weiss MJ, Cosgrove D, et al. Intrahepatic cholangiocarcinoma: management options and emerging therapies. *J Am Coll Surg* 2013; **217**(4): 736-50 e4.
10. Casper FW, Seufert RJ. Atrial natriuretic peptide (ANP) in preeclampsia-like syndrome in a rat model. *Exp Clin Endocrinol Diabetes* 1995; **103**(5): 292-6.
11. Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004; **9**(1): 43-57.
12. Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? *J Hepatol* 2012; **56**(4): 848-54.
13. Patel T. Cholangiocarcinoma--controversies and challenges. *Nat Rev Gastroenterol Hepatol* 2011; **8**(4): 189-200.
14. Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. *World J Gastroenterol* 2017; **23**(22): 3978-98.
15. Aloia TA, Jarufe N, Javle M, et al. Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 2015; **17**(8): 681-90.
16. Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. *Oncology* 2004; **66**(3): 167-79.
17. Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. *World J Hepatol* 2010; **2**(12): 419-27.
18. Paraskevopoulos JA, Dennison AR, Johnson AG. Primary carcinoma of the gallbladder. *HPB Surg* 1991; **4**(4): 277-89.

19. O'Dell MR, Huang JL, Whitney-Miller CL, et al. Kras(G12D) and p53 mutation cause primary intrahepatic cholangiocarcinoma. *Cancer Res* 2012; **72**(6): 1557-67.

20. Noguchi R, Yamaguchi K, Ikenoue T, et al. Genetic alterations in Japanese extrahepatic biliary tract cancer. *Oncol Lett* 2017; **14**(1): 877-84.

21. Fava G, Lorenzini I. Molecular pathogenesis of cholangiocarcinoma. *Int J Hepatol* 2012; **2012**: 630543.

22. Johnson C, Han Y, Hughart N, McCarra J, Alpini G, Meng F. Interleukin-6 and its receptor, key players in hepatobiliary inflammation and cancer. *Transl Gastrointest Cancer* 2012; **1**(1): 58-70.

23. Goydos JS, Brumfield AM, Frezza E, Booth A, Lotze MT, Carty SE. Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. *Ann Surg* 1998; **227**(3): 398-404.

24. Lee KH, Lee KB, Kim TY, et al. Clinical and pathological significance of ROS1 expression in intrahepatic cholangiocarcinoma. *BMC Cancer* 2015; **15**: 721.

25. Deng G, Hu C, Zhu L, et al. Downregulation of ROS-FIG inhibits cell proliferation, colonyformation, cell cycle progression, migration and invasion, while inducing apoptosis in intrahepatic cholangiocarcinoma cells. *Int J Mol Med* 2014; **34**(3): 661-8.

26. Srivastava K, Srivastava A, Sharma KL, Mittal B. Candidate gene studies in gallbladder cancer: a systematic review and meta-analysis. *Mutat Res* 2011; **728**(1-2): 67-79.

27. Morise Z, Sugioka A, Tokoro T, et al. Surgery and chemotherapy for intrahepatic cholangiocarcinoma. *World J Hepatol* 2010; **2**(2): 58-64.

28. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)* 2013; **15**(7): 492-503.

29. van den Broek MA, Olde Damink SW, Dejong CH, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 2008; **28**(6): 767-80.

30. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**(5): 713-24.

31. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy Liver Failure. *Digestive Surgery* 2012; **29**(1): 79-85.

32. Ribeiro HSC, Costa WL, Diniz AL, et al. Extended preoperative chemotherapy, extent of liver resection and blood transfusion are predictive factors of liver failure following resection of colorectal liver metastasis. *Eur J Surg Oncol* 2013; **39**(4): 380-5.

33. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. *Hepatogastroenterology* 2012; **59**(115): 782-4.

34. Radtke A, Konigsrainer A. Surgical Therapy of Cholangiocarcinoma. *Visc Med* 2016; **32**(6): 422-6.

35. Clary BM, Jarnagin WR, Blumgart LH. Cholangiocarcinoma. 2001.

36. Singh SK, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Aggressive Surgical Approach for Gallbladder Cancer: a Single-Center Experience from Northern India. *J Gastrointest Cancer* 2015; **46**(4): 399-407.

37. Shimizu H, Kimura F, Yoshidome H, et al. Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. *J Hepatobiliary Pancreat Surg* 2007; **14**(4): 358-65.

38. Sakamoto Y, Kosuge T, Shimada K, et al. Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. *J Surg Oncol* 2006; **94**(4): 298-306.

39. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009; **16**(4): 806-16.

40. Goenka MK, Goenka U. Palliation: Hilar cholangiocarcinoma. *World J Hepatol* 2014; **6**(8): 559-69.

41. Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. *Liver Transpl* 2000; **6**(3): 302-8.

42. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**(8938): 1655-60.

43. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**(8): 1132-5.

44. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**(12): 2893-917.

45. Velu LKP, Chandrabalan V, Carter R, et al. The Glasgow whipple risk score to predict pancreas-specific complications after pancreaticoduodenectomy. *J Clin Oncol* 2015; **33**(3).

46. Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5. *Eur J Cancer* 2015.

47. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**(14): 1273-81.

48. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012; **30**(16): 1934-40.

49. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; **17**(8): 669-80.

50. Valle JW, Furuse J, Jitlal M, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; **25**(2): 391-8.

51. Seidensticker R, Ricke J, Seidensticker M. Integration of chemoembolization and radioembolization into multimodal treatment of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 2015; **29**(2): 319-32.

52. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**(9319): 1734-9.

53. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012; **35**(5): 1066-73.

54. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**(3): 868-78.

55. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology* 2010; **17**(6): 1471-4.

56. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011; **54**(1): 173-84.

57. Chaiteerakij R, Harmsen WS, Marrero CR, et al. A new clinically based staging system for perihilar cholangiocarcinoma. *Am J Gastroenterol* 2014; **109**(12): 1881-90.

58. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 2013; **31**(9): 1188-95.

59. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2016; **27**(4): 753.

60. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* 2011; **29**(35): 4627-32.

61. Coelen RJ, Ruys AT, Wiggers JK, et al. Development of a Risk Score to Predict Detection of Metastasized or Locally Advanced Perihilar Cholangiocarcinoma at Staging Laparoscopy. *Ann Surg Oncol* 2016; **23**(Suppl 5): 904-10.

62. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. *J Am Coll Surg* 2016; **223**(2): 321-31 e1.

63. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating: Springer Science & Business Media; 2008.

64. Doussot A, Groot-Koerkamp B, Wiggers JK, et al. Outcomes after Resection of Intrahepatic Cholangiocarcinoma: External Validation and Comparison of Prognostic Models. *J Am Coll Surg* 2015; **221**(2): 452-61.

65. Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2009; **16**(1): 14-22.

PART I Patient Selection

CHAPTER 1

The Relative Effect of Hospital and Surgeon Volume on Failure to Rescue among Patients Undergoing Liver Resection for Cancer

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Abstract

Background: Although previous reports have focused on factors at the hospital-level to explain variations in postoperative outcomes, less is known regarding the effect of provider-specific factors on postoperative outcomes such as failure-to-rescue (FTR) and postoperative mortality. The current study aimed to quantify the relative contributions of surgeon and hospital volume on the volume-outcomes relationship among a cohort of patients undergoing liver resection.

Methods: Patients undergoing liver surgery for cancer were identified using the Nationwide Inpatient Sample (NIS) from 2001 and 2009. Multivariable hierarchical logistic regression analysis was performed to identify factors with mortality and FTR. Point estimates were used to calculate the relative effects of hospital and surgeon volume on mortality and FTR.

Results: A total of 5,075 patients underwent liver surgery and met inclusion criteria. Median patient age was 62 years (IQR 52-70) and 55.2% of patients were male. Mortality was lowest among patients treated at high volume hospitals and among patients treated by high volume surgeons (both $p<0.001$). Similar patterns in FTR were noted relative to hospital and surgeon volume (hospital volume; low vs. intermediate vs. high; 10.3% vs. 9.0% vs. 5.2%, surgeon volume; low vs. intermediate vs. high; 11.1% vs. 9.1% vs. 4.1%, both $p<0.05$). On multivariable analysis, compared with high volume surgeons, lower volume surgeons demonstrated greater odds for mortality (intermediate; OR 2.27, 95% CI 1.27-4.06, $p=0.006$, low; OR 2.83, 95% CI 1.52-5.27, $p=0.001$) and FTR (intermediate; OR 2.86, 95% CI 1.53-5.34, $p=0.001$; low; OR 3.40, 95% CI 1.75-6.63, $p<0.001$). While hospital volume accounted for 0.5% of the surgeon volume effect on increased FTR for low volume surgeons, surgeon volume accounted for nearly all of the hospital volume effect on increased FTR in low volume hospitals.

Conclusion: The risk of complications, mortality and FTR were lower among both high volume hospitals and high volume surgeons, but the beneficial effect of volume on outcomes was largely attributable to surgeon volume.

Introduction

Treatment at high volume hospitals has been associated with improved perioperative and postoperative outcomes.[1-7] Consistent with reports of improved mortality at high volume hospitals following esophageal, cardiac, lung and pancreatic surgery, the volume-outcomes relationship has also been defined for patients undergoing complex liver surgery.[2,8] As such, policy makers and healthcare organizations such as the Leapfrog Group and the Agency for Healthcare Research and Quality (AHRQ) have promoted the regionalization of care to high volume centers noting that high volume hospitals likely have implemented standardized processes and systems of care that facilitate a better transition between the peri- and post-operative periods.[9,10]

Traditionally, most studies have focused on operative mortality when reporting on the volume-outcomes relationship following major surgery, however more recent reports suggest that differences in mortality may not solely be a function of volume.[11] In particular, failure-to-rescue (FTR: mortality after a major complication) has emerged as a potential quality parameter to explain variations in post-operative outcomes including mortality. For example, Ghaferi and colleagues demonstrated that differences in postoperative mortality following gastric, pancreatic and esophageal surgery could be explained by variations in the development of major complications and therefore FTR rates among hospitals.[11-13] Similarly, in their report of patients undergoing liver surgery, Spolverato et al. demonstrated that while postoperative mortality was lower at high volume centers these differences were attributed to the ability of a high volume center to better identify and subsequently "rescue" patients from postoperative complications.[14] Despite a significant decrease in operative mortality among patients undergoing liver resection in recent years, the incidence of morbidity following liver surgery still remains high at about 20-40%.[15-17] Quality improvements can only be achieved by identifying and subsequently improving factors related to structures and processes of care. Although previous reports have focused on factors at the hospital-level to explain variations in postoperative outcomes, less is known regarding the effect of provider-specific factors on postoperative outcomes such as FTR and postoperative mortality. Furthermore, recent studies assessing the volume-outcomes relationship following cardiothoracic, pancreatic and esophageal surgery suggest that a significant proportion of this relationship may be accounted for by differences in provider characteristics.[3,4] For example, Birkmeyer et al. demonstrated that as much as 54% of the hospital volume-outcomes relationship among patients undergoing complex cancer surgery was attributed to differences in provider volume.[3] Given this, using a nationally representative dataset, the current study

aimed to explore the effect of hospital and surgeon volume on FTR as well as operative mortality. In particular, we sought to quantify the relative contributions of surgeon and hospital volume on the volume-outcomes relationship among a cohort of patients undergoing liver resection for a malignant indication.

Methods

Data Sources and Patient Population

Patient-level discharge data from the Healthcare Cost and Utilization Project (HCUP) - Nationwide Inpatient Sample (NIS) between January 1, 2000 and December 31, 2009 was utilized to identify the study cohort. Maintained by the AHRQ, the NIS represents the single largest all-payer in-patient dataset. Per year, the database contains information from over 30 million in-patients admissions collected from over 1,000 hospitals in more than 40 states. Using a stratified sampling technique based on hospital level characteristics (geographic region, teaching status, hospital bed size and urban vs. rural location), the NIS is a representation of 20% of all in-patient hospital visits in the U.S. The study was approved by the Johns Hopkins Hospital Institutional Review Board.

Patients undergoing major liver surgery were identified using International Classification of Disease, Ninth Revision, Clinical Manifestation (ICD-9-CM) procedure codes "5022", and "5033." To enhance the homogeneity of the patient cohort, only patients undergoing a liver resection for a primary diagnosis of cancer (primary neoplasm of the liver and metastatic disease) were selected using ICD-9-CM diagnosis codes "1550" and "1997." Patient comorbidity was categorized according to the Charlson Comorbidity Index (CCI).[18] Further, as previously described, patients with a CCI score >6 were categorized as "high comorbidity."[14]

Using unique hospital and surgeon identifiers, an annual surgical volume was calculated for each hospital and for each surgeon. In particular, the total numbers of surgeries performed at a hospital or by a surgeon were divided by the total number of years the hospital / surgeon appeared in the dataset. In the instance where a surgeon was practicing at multiple hospitals, surgical volumes for each individual surgeon was calculated at each hospital. For ease of interpretation, surgeon and hospital volumes were described as terciles with volume cut-offs chosen such that each volume group was represented by an equal number of patients. Surgeons were classified as low, intermediate or high based on their annual surgical caseload: ≤4 cases per year, >4 and ≤15 cases per year, and ≥16 cases per year, respectively.

Similarly, hospitals were classified as low, intermediate or high based on their annual surgical caseload: ≤11 cases per year, >11 and ≤45 cases per year, and ≥46 cases per year, respectively. Patient records missing information for hospital and surgeon identifier were excluded from further analysis.

Postoperative complications were described using previously validated ICD-9-CM diagnosis codes.[11] Specifically, postoperative complications included pulmonary edema, respiratory insufficiency, pneumonia, myocardial infarction, surgical site infection, venous thromboembolism, acute renal failure and gastrointestinal bleeding. Using these diagnosis codes, FTR was defined as an inpatient death in a patient who had developed at least one these pre-defined post-operative complications. As previous described, the failure-to-rescue rate for each hospital and provider tercile was evaluated by calculating the proportion of deaths in patients who developed a postoperative complication (numerator) to the total number of patients who developed a postoperative complication (denominator).[11,14,19]

Statistical Analysis

Continuous variables were described as medians with interquartile range (IQR) or means with standard deviation (SD) as appropriate; categorical variables were displayed as whole numbers and percentages. Categorical data were compared using the Pearson χ^2 test. To assess the association between hospital and surgeon volume on postoperative mortality and FTR, multivariable logistic regression analyses were performed adjusting for patient- and hospital-level characteristics. Specifically, patient, surgeon and the hospital characteristics found to be statistically significant on univariable analysis ($p<0.05$) were included in the multivariable model. As we failed to reject the null hypothesis testing for the interdependence of variance between clusters of patients within hospital ($p=0.173$), hierarchical modeling techniques were not employed in subsequent analyses. Of note, further analysis comparing results using hierarchical modeling techniques demonstrated comparable findings and similar conclusions regardless of the modeling approach used (Supplemental Material 1). To quantitate the relative effects of surgeon and hospital volume on postoperative mortality and FTR, three separate models were built for each postoperative outcome. Model 1 quantified the independent effect of surgeon volume, model 2 the independent effect of hospital volume and model 3 included both surgeon and hospital volume effects. As previously described, results from these analyses were subsequently used to calculate the relative effects of surgeon and hospital volume on postoperative mortality and FTR using the formulas $[1- (\ln OR_{SH} / \ln OR_S)]$ and $[1- (\ln OR_{HS} / \ln OR_H)]$, respectively.[20] OR_H represented the risk-adjusted odds ratio for hospital volume and OR_S the

risk-adjusted odds ratio for surgeon volume.[3,20] Similarly, OR_{HS} represented the odds ratio for effects of hospital volume and OR_{SH} the surgeon volume odds ratio obtained from model 3 including both surgeon and hospital volume effects.[3,20] Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY). Statistical significance was defined as $p<0.05$.

Results

Patient and hospital characteristics

A total 5,075 patients underwent liver surgery and met inclusion criteria. The median age of patients was 62 years (IQR 52-70) while a majority of patients were male (n=2,802, 55.2%) and white (n=3,267, 75.0%). Comorbidity was frequently noted among patients as 20.5% of patients had a "high" preoperative morbidity with a CCI>6. Roughly one-half of the cohort was insured by private payers (n=2,583, 50.9%) and 29.3% were categorized among the highest income quartile (n=1,271). Of note, 91.8% (n=4,309) of surgeries were performed on an elective basis with a greater proportion of patients undergoing a partial hepatectomy (3,097, 61.0%) versus hepatic lobectomy (1,978, 39.0%, Table 1). A total of 408 hospitals were identified within the study cohort; 360 (88.2%) hospitals were categorized as low volume hospitals while 38 (9.3%) as intermediate volume hospitals and 10 (2.5%) as high volume hospitals performing >45 liver resections per year. Similarly, a total of 1,099 unique surgeons were identified in the study cohort with only 35 (3.2%) surgeons categorized as high volume surgeon performing more than 15 liver resections per year (Table 2). Of note, 75.1% (n=1,264) of liver resections performed at high volume hospitals were performed by high volume surgeons while a majority of resections performed at low volume centers were performed by low volume surgeons (n=1,275, 69.9%); no surgeon at a low volume center was categorized as a high volume surgeon (Table 2).

Table 1: Patient characteristics and perioperative parameters

Characteristic	Total Cohort (n=5,075)
No. of Hospitals	408
No. of Surgeons	1099
Age	
< 50	921 (18.2)
50-59	1362 (26.8)
60-69	1509 (29.7)
≥ 70	1282 (25.3)
Male Gender	2802 (55.2)
Race	
White	3267 (75.0)
Black	381 (8.7)
Hispanic	352 (8.1)
Other/Unknown	358 (8.2)
Year of Treatment	
2001-2003	1374 (27.1)
2004-2006	1539 (30.3)
2007-2009	2162 (42.6)
Household Income	
Low	932 (22.2)
Medium	1064 (25.6)
High	956 (23.0)
Highest	1217 (29.3)
Household Payer	
Government	2267 (44.7)
Private	2583 (50.9)
Self/Other	224 (4.4)
Admission Type	
Emergency	384 (8.2)
Elective	4309 (91.8)
High Comorbidity	1042 (20.5)
Operation	
Lobectomy	1978 (39.0)
Partial Hepatectomy	3097 (61.0)
Hospital Size	
Small	228 (4.5)
Medium	544 (10.8)

Table 1: Patient characteristics and perioperative parameters (continued)

Characteristic	Total Cohort (n=5,075)
Large	4285 (84.7)
Metropolitan Location	4933 (97.5)
Teaching Hospital	4400 (87.0)
Hospital Region	
North-East	1810 (35.7)
Mid-West	636 (12.5)
South	1910 (37.6)
West	719 (14.2)

Table 2: Hospitals, Surgeon and Patients by Hospital and Surgeon Volume Tertile

	Low Volume Hospital	Intermediate Volume Hospital	High Volume Hospital
*Total Number of Hospitals, n (%)	360 (88.2%)	38 (9.3%)	10 (2.5%)
*Total Number of Surgeons, n (%)	775 (70.5%)	206 (18.7%)	118 (10.7%)
Low Volume Surgeon†	720 (92.9%)	128 (62.1%)	73 (61.9%)
Intermediate Volume Surgeon†	55 (7.1%)	66 (32.0%)	22 (18.6%)
High Volume Surgeon†	0 (0.0%)	12 (5.8%)	23 (19.5%)
*Total Number of Patients, n (%)	1,824 (35.9%)	1,568 (30.9%)	1,683 (33.2%)
Low Volume Surgeon†	1,275 (69.9%)	311 (19.8%)	136 (8.1%)
Intermediate Volume Surgeon†	549 (30.1%)	888 (56.63%)	283 (16.8%)
High Volume Surgeon†	0 (0.0%)	369 (23.53%)	1,264 (75.1%)

*Represents row percentage, †Represents column percentage

Effect of hospital and surgeon volume on in-hospital mortality

The in-hospital mortality for all patients undergoing a liver resection was noted to be 3.2% with marked differences noted among hospitals and providers. In particular, when stratified by hospital volume, mortality among patients treated at a low volume hospital was proportionally higher that that noted for patients treated at high volume hospitals (low vs. intermediate vs. high; 4.5% vs. 3.2% vs. 1.8%, $p<0.001$, Figure 1a). A similar pattern in mortality was also noted by annual surgeon volume (low vs. intermediate vs. high; 4.7% vs. 3.4% vs. 1.4 %, $p<0.001$, Figure 1b). After adjusting for sociodemographic and hospital characteristics on multivariable analysis, both increasing surgeon and hospital volume were associated with decreased odds of mortality (Table 3). In particular, compared with patients treated by high volume surgeons, patients treated by intermediate and low volume surgeons demonstrated over 2.0 times greater odds of mortality following

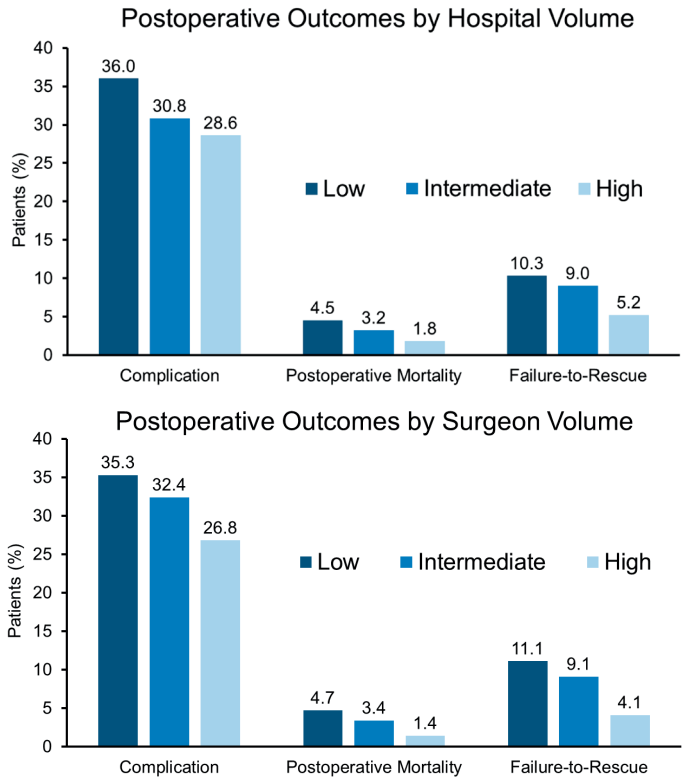

Figure 1: Unadjusted incidence of postoperative complications, postoperative mortality and failure-to-rescue by **(a)** hospital volume terciles **(b)** surgeon volume terciles

surgery (intermediate volume; OR 2.56, 95% CI 1.54-4.26, p<0.001; low volume; OR 3.01, 95% CI 1.80-5.04, p<0.001). Similarly, an inverse relationship was observed between hospital volume and mortality among patients undergoing liver surgery. In comparison to patients treated at high volume hospitals, patients treated at low volume hospitals demonstrated 2.1 times greater odds of mortality (low volume; OR 2.13, 95% CI 1.31-3.47, p=0.002) while patients treated at intermediate volume hospitals demonstrated a 2 times greater odds of mortality (OR 2.00, 95% CI 1.24-3.21, p=0.004). Interestingly, when adjusting for both surgeon and hospital volume, only surgeon volume was found to be associated with a greater odds of mortality (Table 3). Specifically, increasing surgeon volume was associated with a step-wise decrease in the odds of mortality with patients treated by an intermediate volume surgeon demonstrating 2.2 times greater odds of mortality (OR 2.27, 95% CI 1.27-4.06, p=0.006) while those treated by low volume surgeons demonstrated a 2.8 times greater odds of mortality (OR 2.83

Table 3: Multivariable Logistic Regression Analyses of Factors Associated with Postoperative Mortality

Characteristic	Odds Ratio	95% CI	P value
Hospital volume (Without Surgeon Volume)			
High	Ref.	-	-
Medium	2.00	1.24-3.21	0.004
Low	2.13	1.31-3.47	0.002
Surgeon volume (Without Hospital Volume)			
High	Ref.	-	-
Medium	2.56	1.54-4.26	<0.001
Low	3.01	1.80-5.04	<0.001
Hospital volume			
High	Ref.	-	-
Medium	1.33	0.78-2.27	0.293
Low	1.12	0.62-2.03	0.701
Surgeon volume			
High	Ref.	-	-
Medium	2.27	1.27-4.06	0.006
Low	2.83	1.52-5.27	0.001
Age (years)			
<50	Ref.	-	-
50-59	1.26	0.67-2.38	0.474
60-69	1.77	0.96-3.27	0.068
≥ 70	2.35	1.23-4.48	0.009
Male sex	1.63	1.14-2.31	0.007
Year of Treatment			
2001-2003	Ref	-	-
2004-2006	0.80	0.53-1.21	0.294
2007-2009	0.64	0.42-0.97	0.037
Household Payer			
Government	Ref	-	-
Private	0.72	0.47-1.11	0.142
Self/Other	1.68	0.85-3.31	0.136
Emergency Admission	2.03	1.28-3.22	0.003
Operation			
Partial Hepatectomy	Ref.	-	-
Lobectomy	1.94	1.39-2.71	<0.001
Non-teaching Hospital	1.13	0.71-1.81	0.607

95% CI 1.52-5.27, p=0.001) when compared with patients treated by high a volume surgeon.

Effect of Hospital and surgeon volume on failure to rescue

Overall, postoperative complications were noted in 31.6% of patients undergoing a liver resection with differences noted by both surgeon and hospital volume. Of note, postoperative complications were lowest among patients treated by high volume surgeons (low vs. intermediate vs. high; 35.3% vs. 32.4% vs. 26.8%, p<0.001) and highest at low volume hospitals (low vs. intermediate vs. high; 36.0% vs. 30.8% vs. 28.6, p=0.004, Figure 1). The overall rate of FTR was 8.1% and noted most commonly among patients who developed postoperative renal failure (n=85, 54.8%). Further, FTR was noted to vary by surgeon and hospital volume; FTR was lowest among high volume surgeons (low vs. intermediate vs. high; 11.1% vs. 9.1% vs. 4.1%, p<0.001) and at high volume hospitals (low vs. intermediate vs. high; 10.3% vs. 9.0% vs. 5.2%, p<0.001).

To further explore factors associated with FTR, multivariable analysis was performed adjusting for patient, surgeon and hospital level characteristics. On multivariable analyses, an inverse relationship between volume and FTR was observed. Specifically, compared with patients treated by high volume surgeons, patients treated by lower volume surgeons were associated with a 3 times greater odds of FTR (intermediate volume; OR 3.08, 95% CI 1.77-5.34, p<0.001; low volume; OR 3.42, 95% CI 1.98-5.93, p<0.001). Similarly, patients treated at high volume hospitals demonstrated a decreased odds for FTR (intermediate volume; OR 2.04, 95% CI 1.25-3.33, p=0.004; low volume; OR 2.15, 95% CI 1.33-3.48, p=0.002). Interestingly, when adjusting for both surgeon and hospital volumes within the same model, only surgeon volume and not hospital volume was noted to be associated with FTR (intermediate volume; OR 2.86, 95% CI 1.53-5.34, p=0.001; low volume; OR 3.40, 95% CI 1.75-6.63, p<0.001, Table 4). Other factors associated with a greater odds of FTR included increasing patient age, hepatic lobectomy, and surgeries performed on an emergent basis (all p<0.05, Table 4).

Table 4: Multivariable Logistic Regression Analyses of Factors Associated with Failure-to-Rescue

Characteristic	OR	95% CI	P
Hospital volume (Without Surgeon Volume)			
High	Ref.	-	-
Medium	2.04	1.25-3.33	0.004
Low	2.15	1.33-3.48	0.002
Surgeon volume (Without Hospital Volume)			
High	Ref.	-	-
Medium	3.08	1.77-5.34	<0.001
Low	3.42	1.98-5.93	<0.001
Hospital volume			
High	Ref.	-	-
Medium	1.24	0.72-2.14	0.446
Low	1.03	0.57-1.85	0.928
Surgeon volume			
High	Ref.	-	-
Medium	2.86	1.53-5.34	0.001
Low	3.40	1.75-6.63	<0.001
Age (years)			
<50	Ref.	-	-
50-59	1.37	0.70-2.69	0.360
60-69	1.92	1.00-3.68	0.051
≥ 70	2.58	1.30-5.12	0.007
Male sex	1.57	1.09-2.27	0.016
Year of Treatment			
2000-2003	Ref	-	-
2004-2006	0.80	0.52-1.25	0.327
2007-2009	0.66	0.43-1.03	0.067
Household Payer			
Government	Ref	-	-
Private	0.76	0.48-1.19	0.227
Self/Other	1.91	0.96-3.80	0.064
Emergency Admission	1.74	1.06-2.86	0.028
Operation			
Partial Hepatectomy	Ref.	-	-
Lobectomy	1.86	1.31-2.65	<0.001

Relative effects of hospital and surgeon volume on postoperative outcomes

Results of the multivariable analysis were used to obtain risk-adjusted mortality and FTR by surgeon and hospital volume terciles (Tables 5 and 6). While mortality and FTR were noted to decrease with increasing volume, a stronger relationship was observed relative to surgeon volume in comparison to hospital volume. For example, among surgeons practicing at a high volume hospital, the risk-adjusted mortality was noted to decrease with increasing surgeon volume (low vs. intermediate vs. high; 3.5% vs. 3.2% vs. 1.3%, $p<0.05$). In contrast, risk-adjusted mortality was comparable among intermediate volume surgeons, regardless of the hospital volume ($p>0.05$, Table 5). Interestingly, within each hospital volume strata, FTR was noted to decrease with increasing surgeon volume. Of note, among surgeons practicing at a high volume hospital, FTR was lower among high volume surgeons compared with intermediate and low volume surgeons (low vs. intermediate vs. high; 9.4% vs. 9.0% vs. 3.9%, both $p<0.05$). A similar pattern in FTR was also observed at intermediate volume hospitals, with FTR noted to be the lowest among high volume surgeons (low vs. intermediate vs. high; 11.8% vs. 9.5% vs. 5.1%, both $p<0.05$, Table 6).

Point estimates for surgeon and hospital volume obtained from multivariable analyses were used to calculate the relative effects of hospital and surgeon volumes on in-hospital mortality and FTR (Table 7). In particular, hospital volume accounted for 12.8% and 5.6% of the effect of surgeon volume on mortality among patients treated by intermediate and low volume surgeons, respectively. Conversely, surgeon volume accounted for a much larger proportion of the effect of hospital volume on mortality, accounting for 58.9% and 85.0% of the volume-mortality effect observed between intermediate and low volume hospitals, respectively. Similarly, hospital volume accounted for only 6.6% and 0.5% of the effect of surgeon volume on FTR among intermediate and low volume surgeons, whereas surgeon volume was the main contributor to the relationship between volume and FTR accounting for 69.8% of the increased effect of FTR observed among patients treated at intermediate volume hospitals and 96.1% of the effect at low volume hospitals (Table 7).

Table 5: Risk-adjusted Postoperative Mortality by Surgeon and Hospital Volume

	Low Volume Hospital		Intermediate Volume Hospital		High Volume Hospital		Overall	
Surgeon Volume	Mortality	95% CI	Mortality	95% CI	Mortality	95% CI	Mortality	95% CI
Low	5.0%	(4.75-5.15)	4.5%	(4.08-4.82)	3.5%	(3.10-3.97)	4.7%	(4.57-4.91)
Intermediate	3.7%	(3.46-3.88)	3.3%	(3.19-3.50)	3.2%	(2.95-3.45)	3.4%	(3.31-3.53)
High	-	-	1.7%	(1.55-1.80)	1.3%	(1.24-1.34)	1.4%	(1.32-1.42)
Overall	4.5%	(4.39-4.71)	3.2%	(3.07-3.24)	1.8%	(1.72-1.88)	3.2%	(3.10-3.26)

Table 6: Risk-adjusted Failure-to-Rescue by Surgeon and Hospital Volume

	Low Volume Hospital		Intermediate Volume Hospital		High Volume Hospital		Overall	
Surgeon Volume	FTR	95% CI	FTR	95% CI	FTR	95% CI	FTR	95% CI
Low	11.1%	(10.7-11.4)	11.8%	(11.02-12.53)	9.4%	(8.49-10.25)	11.1%	(10.77-11.38)
Intermediate	8.8%	(8.37-9.13)	9.5%	(9.13-9.77)	9.0%	(8.37-9.53)	9.1%	(8.92-9.38)
High	-	-	5.1%	(4.83-5.36)	3.9%	(3.76-4.01)	4.1%	(4.03-4.26)
Overall	10.3%	(10.07-10.61)	9.0%	(8.67-9.22)	5.2%	(5.01-5.39)	8.1%	(7.98-8.29)

Table 7: Relative effects of Surgeon and Hospital Volume of Postoperative Mortality and Failure-to-rescue

	Postoperative Mortality	Failure-to-rescue
Effect of Surgeon Volume on Hospital Volume		
Intermediate	58.9%	69.8%
Low	85.0%	96.1%
Effect of Hospital Volume on Surgeon Volume		
Intermediate	12.8%	6.6%
Low	5.6%	0.5%

Discussion

Over recent years, multiple studies have highlighted the inverse-relationship between hospital volume and operative mortality following complex surgery.[1-3,5] Based on these findings, policymakers and healthcare organizations have promoted the selective regionalization of surgical procedures including liver resections to high volume centers.[21] However, more recent reports have identified FTR as a potential quality parameter to explain variations in surgical outcomes including mortality.[11-13,22] While these reports have identified hospital-level characteristics associated with variability in surgical outcomes, less is known regarding the effects of provider-level characteristics on similar peri-operative outcomes. Using a large nationally representative dataset, the current study explored the effects of surgeon and hospital volume on operative mortality as well as FTR among a cohort of patients undergoing liver surgery for cancer. In particular, operative mortality was noted to be twice as high among patients treated by lower volume centers and among patients treated by lower volume surgeons. Similarly, while over 36% of all patients developed a post-operative complication, patients treated at higher volume centers and by higher volume surgeons were not only less likely to develop a post-operative complication but also were less likely to die following the postoperative complication. Interestingly, while over 80% of the effect of hospital volume was accounted for by surgeon volume, less than 7% of the effect of surgeon volume was attributable to differences in hospital volume.

Consistent with previous reports, this study noted that among patients undergoing liver resection, 36% developed a post-operative complication.[15-17] Although some reports have noted no association between hospital volume and the development of post-operative complications, results from this study support other studies that have demonstrated a correlation between low volume hospitals and high postoperative complications.[11,13,23-25] Specifically, we noted that 36.0% of patients treated at low volume hospitals developed a post-operative complication versus 28.6% of patients treated at high volume centers. These results are likely explained by the fact that low volume centers do not achieve appropriate thresholds for complex surgery and therefore lack certain institutional processes and systems for these procedures.[26] Perhaps more strikingly, the proportion of patients who developed a post-operative complication varied not only by hospital volume but also by surgeon volume. Among patients treated by high volume surgeons, 26.8% developed a post-operative complication compared with 35.3% of patients treated by low volume surgeons. These data suggest that quality improvement should not only target system-level factors, but also include interventions at the provider-level.

Mortality following a post-operative complication (FTR) is an emerging quality indicator and represents an additional system-level factor associated with variations in post-operative outcomes.[11-13,22] Similar to previous reports, the current study of patients undergoing liver resections noted FTR to be 8.1%. FTR varied by hospital with FTR at high volume hospitals almost 2 times lower than FTR observed at low and intermediate hospitals.[11] While there is a growing body of evidence to suggest that the timely recognition and effective management of complications are essential to reducing variations in surgical mortality, it is almost intuitive that a lower rate of complications may translate to a lower FTR and postoperative mortality. Interestingly, we noted that while patients treated by high volume surgeons and hospitals were less likely to develop to a major postoperative complication these patients were also twice as likely to survive following a postoperative complication. These data support calls for regionalization of high-risk procedures such as liver resection. High volume hospitals likely represent a setting where advanced clinical pathways and standardized systems are better able to detect and thereby "rescue" patients following a post-operative complication. In addition, larger hospital bed size, higher nurse-to-patient ratios and the availability of intensive care services may also contribute to decreasing in-hospital deaths following a major postoperative complication noted at high volume centers.[11,13,27,28]

Perhaps more interestingly, we also noted that rates of FTR varied not only by hospital volume but also by the volumes of the individual surgeon. Of note, while hospital volume attributed less than 7% of the effect of surgeon volume on FTR, approximately all of the effect of hospital volume on FTR was accounted for by surgeon volume. Given the technical skill and use of specialized intraoperative processes when performing complex liver surgery; the relative importance of surgeon volume is not surprising. Further, the large variability in intraoperative and postoperative care pathways between and within hospitals likely also contributes the overwhelming effect of surgeon volume. For example, certain providers and institutions may routinely perform low CVP surgery to limit the extent of intraoperatively bleeding. In contrast, other providers may not employ this approach and may allow for more liberal fluid practices, transfusion and postoperative care / recovery that may increase risk for complications and subsequently mortality / FTR. Further, while FTR is undoubtedly influenced by a multitude of surgeon-level factors such as skill and experience, it is likely that a portion of this relative effect of surgeon volume represents a difference in patient mix between providers. To this end, Ghaferi et al. noted that despite appropriate risk-adjustment, large proportions of variation in FTR remain unexplained.[11] Similarly, although the

current study employed a modeling approach that accounted for the interdependence of outcomes between clusters of hospital and surgeons, it is likely that some variability in FTR and mortality was unexplained at the patient level. In aggregate, data such as those presented in the current study lend credence to the movement by some academic medical centers to impose minimum caseload requirements for surgeons to perform certain complex operations within their institutions. Future work, however, is warranted to determine root causes for the variations in postoperative outcomes, as well as understand barriers to implementation and adherence to evidence-based processes of care.

The current study had several limitations. Using administrative claims data, the study lacked specific details pertaining to the extent of disease as well as additional intra-operative details. Moreover, due to the cross-sectional nature of the data, long-term outcomes such as readmission and subsequent prognosis which may have allowed for an assessment of other potential benefits of regionalized care could not be evaluated. However, despite the inherent limitations of administrative data, the use of a nationally representative sample allowed for generalizable results across a large cohort of patients undergoing liver surgery.

In conclusion, this study demonstrated significant variability in post-operative mortality and FTR relative to hospital and surgeon volume. In particular, lower complications, lower FTR and consequently lower post-operative mortality was noted at high volume hospitals and among patients treated by high volume surgeons. Interestingly, even within high volume centers, high volume surgeons reported lower complications, lower FTR and improved operative mortality. Rather than factors related to the hospital, nearly 80% of the inverse relationship observed between volume and FTR / operative mortality was accounted for by differences between individual providers. Further research should explore these microsystems within hospitals that potentially drive variations in post-operative outcomes such as mortality.

References

1 Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37. doi:10.1056/NEJMsa012337.

2 Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011;364:2128–37. doi:10.1056/NEJMsa1010705.

3 Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–27. doi:10.1056/NEJMsa035205.

4 Nathan H, Cameron JL, Choti MA, Schulick RD, Pawlik TM. The volume-outcomes effect in hepato-pancreato-biliary surgery: hospital versus surgeon contributions and specificity of the relationship. J Am Coll Surg 2009;208:528–38. doi:10.1016/j.jamcollsurg.2009.01.007.

5 Schrag D, Cramer LD, Bach PB, Cohen AM, Warren JL, Begg CB. Influence of hospital procedure volume on outcomes following surgery for colon cancer. JAMA 2000;284:3028–35.

6 Schrag D, Earle C, Xu F, Panageas KS, Yabroff KR, Bristow RE, et al. Associations between hospital and surgeon procedure volumes and patient outcomes after ovarian cancer resection. J Natl Cancer Inst 2006;98:163–71. doi:10.1093/jnci/djj018.

7 Schrag D, Panageas KS, Riedel E, Cramer LD, Guillem JG, Bach PB, et al. Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection. Ann Surg 2002;236:583–92. doi:10.1097/01.SLA.0000033036.14533.BC.

8 Birkmeyer JD, Finlayson SR, Tosteson AN, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999;125:250–6.

9 National Quality Measures Clearinghouse | Agency for Healthcare Research and Quality (AHRQ) n.d. http://www.qualitymeasures.ahrq.gov/browse/by-organization-indiv.aspx?orgid=9 (accessed May 1, 2015).

10 The Leapfrog Group n.d. http://www.leapfroggroup.org/ (accessed May 1, 2015).

11 Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg 2009;250:1029–34.

12 Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368–75. doi:10.1056/NEJMsa0903048.

13 Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. Med Care 2011;49:1076–81. doi:10.1097/MLR.0b013e3182329b97.

14 Spolverato G, Ejaz A, Hyder O, Kim Y, Pawlik TM. Failure to rescue as a source of variation in hospital mortality after hepatic surgery. Br J Surg 2014;101:836–46. doi:10.1002/bjs.9492.

15 Mayo SC, Pulitano C, Marques H, Lamelas J, Wolfgang CL, de Saussure W, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. J Am Coll Surg 2013;216:707–16; discussion 716–8. doi:10.1016/j.jamcollsurg.2012.12.029.

16 Mayo SC, Heckman JE, Shore AD, Nathan H, Parikh AA, Bridges JFP, et al. Shifting trends in liver-directed management of patients with colorectal liver metastasis: a population-based analysis. Surgery 2011;150:204–16. doi:10.1016/j.surg.2011.06.013.

17 Mavros MN, de Jong M, Dogeas E, Hyder O, Pawlik TM. Impact of complications on long-term survival after resection of colorectal liver metastases. Br J Surg 2013;100:711–8. doi:10.1002/bjs.9060.

18 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

19 Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in Hospital Volume and Failure to Rescue for Pancreatic Surgery. J Gastrointest Surg 2015. doi:10.1007/s11605-015-2800-9.

20 Brotman DJ. Mediators of the association between mortality risk and socioeconomic status. JAMA 2006;296:763–4; author reply 764. doi:10.1001/jama.296.7.763-b.

21 Richardson AJ, Pang TCY, Johnston E, Hollands MJ, Lam VWT, Pleass HCC. The volume effect in liver surgery--a systematic review and meta-analysis. J Gastrointest Surg 2013;17:1984–96. doi:10.1007/s11605-013-2314-2.

22 Ghaferi AA, Dimick JB. Variation in mortality after high-risk cancer surgery: failure to rescue. Surg Oncol Clin N Am 2012;21:389–95, vii. doi:10.1016/j.soc.2012.03.006.

23 Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137:511–20.

24 Bianco FJ, Riedel ER, Begg CB, Kattan MW, Scardino PT. Variations among high volume surgeons in the rate of complications after radical prostatectomy: further evidence that technique matters. J Urol 2005;173:2099–103. doi:10.1097/01.ju.0000158163.21079.66.

25 Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Role of surgeon volume in radical prostatectomy outcomes. J Clin Oncol 2003;21:401–5.

26 Nathan H, Cameron JL, Choti MA, Schulick RD, Pawlik TM. The volume-outcomes effect in hepato-pancreato-biliary surgery: hospital versus surgeon contributions and specificity of the relationship. J Am Coll Surg 2009;208:528–38. doi:10.1016/j.jamcollsurg.2009.01.007.

27 Englesbe MJ, Fan Z, Baser O, Birkmeyer JD. Mortality in medicare patients undergoing surgery in July in teaching hospitals. Ann Surg 2009;249:871–6. doi:10.1097/SLA.0b013e3181a501bd.

28 Dimick JB, Cowan JA, Colletti LM, Upchurch GR. Hospital teaching status and outcomes of complex surgical procedures in the United States. Arch Surg 2004;139:137–41. doi:10.1001/archsurg.139.2.137.

Supplementary Table 1 – Multivariable analysis of factors associated with in-hospital mortality

	Multivariable Logistic (In Paper)			Hierarchical Multivariable		
	OR	95% CI	P	OR	95% CI	P
Hospital volume (Without Surgeon Volume)						
High	Ref.	-	-	Ref.	-	-
Medium	2.00	1.24-3.21	0.004	1.49	0.81-2.74	0.196
Low	2.13	1.31-3.47	0.002	1.82	1.00-3.30	0.049
Surgeon volume (Without Hospital Volume)						
High	Ref.	-	-	Ref.	-	-
Medium	2.56	1.54-4.26	<0.001	2.34	1.26-4.32	0.007
Low	3.01	1.80-5.04	<0.001	3.04	1.63-5.59	<0.001
Hospital volume						
High	Ref.	-	-	Ref.	-	-
Medium	1.33	0.78-2.27	0.293	1.09	0.59-2.00	0.782
Low	1.12	0.62-2.03	0.701	1.08	0.57-2.08	0.807
Surgeon volume						
High	Ref.	-	-	Ref.	-	-
Medium	2.27	1.27-4.06	0.006	2.23	1.12-4.48	0.023
Low	2.83	1.52-5.27	0.001	2.89	1.38-6.06	0.005
Age (years)						
<50	Ref.	-	-	Ref.	-	-
50-59	1.26	0.67-2.38	0.474	1.26	0.67-2.40	0.474
60-69	1.77	0.96-3.27	0.068	1.77	0.95-3.30	0.070
≥ 70	2.35	1.23-4.48	0.009	2.42	1.26-4.65	0.008
Male sex	1.63	1.14-2.31	0.007	1.61	1.13-2.31	0.009
Year of Treatment						
2001-2003	Ref	-	-	Ref.	-	-
2004-2006	0.80	0.53-1.21	0.294	0.78	0.50-1.21	0.261
2007-2009	0.64	0.42-0.97	0.037	0.63	0.41-0.98	0.042
Household Payer						
Government	Ref	-	-	Ref.	-	-
Private	0.72	0.47-1.11	0.142	0.73	0.47-1.13	0.156
Self/Other	1.68	0.85-3.31	0.136	1.69	0.84-3.40	0.140
Emergency Admission	2.03	1.28-3.22	0.003	2.00	1.24-3.23	0.005
Operation						
Partial Hepatectomy	Ref.	-	-	Ref.	-	-
Lobectomy	1.94	1.39-2.71	<0.001	1.92	1.37-2.71	<0.001
Non-teaching Hospital	1.13	0.71-1.81	0.607	1.05	0.64-1.71	0.854

Supplementary Table 2 – Multivariable analysis of factors associated with failure-to-rescue

	Multivariable Logistic (In Paper)			Hierarchical Multivariable		
	OR	95% CI	P	OR	95% CI	P
Hospital volume (Without Surgeon Volume)						
High	Ref.	-	-	Ref.	-	-
Medium	2.04	1.25-3.33	0.004	1.49	0.79-2.84	0.222
Low	2.15	1.33-3.48	0.002	1.73	0.94-3.21	0.079
Surgeon volume (Without Hospital Volume)						
High	Ref.	-	-	Ref.	-	-
Medium	3.08	1.77-5.34	<0.001	2.71	1.46-5.01	0.002
Low	3.42	1.98-5.93	<0.001	3.49	1.91-6.39	<0.001
Hospital volume						
High	Ref.	-	-	Ref.	-	-
Medium	1.24	0.72-2.14	0.446	1.00	0.54-1.90	0.980
Low	1.03	0.57-1.85	0.928	0.93	0.48-1.81	0.836
Surgeon volume						
High	Ref.	-	-	Ref.	-	-
Medium	2.86	1.53-5.34	0.001	2.76	1.39-5.47	0.004
Low	3.40	1.75-6.63	<0.001	3.67	1.78-7.57	<0.001
Age (years)						
<50	Ref.	-	-	Ref.	-	-
50-59	1.37	0.70-2.69	0.360	1.38	0.70-2.72	0.348
60-69	1.92	1.00-3.68	0.051	1.91	0.99-3.68	0.052
≥ 70	2.58	1.30-5.12	0.007	2.66	1.33-5.31	0.005
Male sex	1.57	1.09-2.27	0.016	1.56	1.08-2.26	0.019
Year of Treatment						
2000-2003	Ref	-	-	Ref.	-	-
2004-2006	0.80	0.52-1.25	0.327	0.77	0.49-1.22	0.273
2007-2009	0.66	0.43-1.03	0.067	0.66	0.42-1.04	0.073
Household Payer						
Government	Ref	-	-	Ref.	-	-
Private	0.76	0.48-1.19	0.227	0.76	0.48-1.20	0.236
Self/Other	1.91	0.96-3.80	0.064	1.93	0.96-3.88	0.064
Emergency Admission	1.74	1.06-2.86	0.028	1.72	1.03-2.86	0.038
Operation						
Partial Hepatectomy	Ref.	-	-	Ref.	-	-
Lobectomy	1.86	1.31-2.65	<0.001	1.84	1.29-2.63	0.001

CHAPTER 2

Defining Post Hepatectomy Liver Insufficiency: Where do We stand?

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ABSTRACT

Background

Post-hepatectomy liver failure (PHLF) is a major source of morbidity and mortality in patients undergoing liver resection. The aim of this review is to summarize the recent literature available on PHLF including its definition, predictive factors, preoperative risk assessment, severity grading, preventative measures, and management strategies.

Methods

A systematic literature search was carried out with the search engines PubMed, Medline, and Cochrane Database using the keywords related to "liver failure", "posthepatectomy", and "hepatic resection".

Results

Liver resection is a curative treatment of liver tumors. However, it leads to concurrent death and regeneration of the remaining hepatocytes. Factors related to the patient, liver parenchyma and the extent of surgery can inhibit regeneration leading to PHLF.

Conclusion

Given its resistance to treatment and the high postoperative mortality associated with PHLF, great effort has been put in to both accurately identify patients at high risk and to develop strategies that can help prevent its occurrence.

Introduction

Liver resection remains the mainstay of treatment for both primary and secondary liver tumors. Advances in operative techniques, perioperative care, and patients selection have resulted in an increase in the number of patients who are amenable to surgical resection, as well as decreased the morbidity and mortality associated with liver surgery.[1-3] However, one of the most serious complications following liver resection is the development of post-hepatectomy liver insufficiency/ failure (PHLF), which can be a major cause of morbidity and mortality.[4-6] The reported incidence of PHLF varies between 0.7 and 34 % in the literature.[4,7-10] This wide range of incidence may be explained, in part, by the different definitions of PHLF, variability of the extent of hepatic resection (wedge resection vs. minor vs. major hepatectomy), as well as the diverse characteristics of the patients analysed.[4,11] We herein review the risk factors associated with PHLF, as well as the different definitions and predication models reported in the literature. In addition, we highlight several proposed prevention and treatment strategies for PHLF.

Methods

A systematic literature search was carried out with the search engines PubMed, Medline, and Cochrane Database using the keywords related to "liver failure", "liver insufficiency", "post-hepatectomy", "morbidity", "mortality", and "hepatic resection". The resulting relevant English language studies were identified and reviewed.

Incidence

The incidence of PHLF varies between 0.7 and 34 % in the literature with most recent reports noting an incidence around 5–10 %.[4,7-10] The wide range of incidence may partially be explained by the lack of a uniform definition of PHLF.[4,11] There has been a decrease in incidence of PHLF over the past two decades likely due to improvements in surgical technique and perioperative care that have led to decreased mortality following hepatic resection. Mortality following partial hepatectomy in the past two decades still ranges from 0 to 6 %, however, and PHLF has been implicated as contributing to mortality in the majority of cases.[4,12,13]

Risk Factors for Post Hepatectomy Liver Failure

Identification of the risk factors for PHLF is critical to help identify patients most at risk, as well as to inform strategies aimed at decreasing the incidence

and mortality associated with PHLF. Independent predictors of PHLF can be categorized into three main categories: patient- related, liver- related, and surgery/ postop-related factors (Table 1).

Table 1 Risk factors for PHLF

Patient-related factors
Age (>65 years)
Male gender
Metabolic disorders
Preoperative chemotherapy
Sepsis
Malnutrition
ASA score
Liver- related factors
Grade of the tumour
Hepatitis
Portal venous pressure
Cirrhosis
Cholestasis
Surgery- related factors
Complex operations
Extent of resection
General surgical models
Large blood transfusion
Left hepatectomy
Duration of Pringle Maneuvre

Patient-Related Factors

Patient-related factors associated with PHLF include age, male gender, malnutrition, diabetes, and American Society of Anesthesiology (ASA) score. Some studies had implicated older age as a risk factor for PHLF; however, other studies have documented the safety of liver resection in the elderly. Animal models have suggested a loss of the liver's regenerative capacity, as well as impaired liver function with increased age.[14-17] In a study of 775 patients, Balzan et al. reported age over 65 years as an independent predictor of death in multivariate analysis.[18] In a subsequent study, Mullen et al. evaluated 1509 non-cirrhotic patients undergoing hepatectomy and found older age to be an independent predictor of morbidity as well as death from liver failure.[19] However, clinical data from several major centers have documented that hepatectomy can be performed with low morbid-

ity in older patients. For example, in a study of 129 patients, Aldrighetti et al. reported that age >70 years did not correlated with an increased morbidity or mortality following partial liver resection.[20] In a separate study, while an increase in the incidence of systemic complications was noted among elderly patients following hepatectomy for hepatocellular carcinoma (HCC), Nanashima et al. failed to detect a difference in the incidence of hepatic failure.[21] Similarly, Kim et al. in a study of 279 patients undergoing both minor and major liver resections did not find any age-related differences in postoperative PHLF.[22]

Diabetes, either alone or in combination with metabolic syndrome, has also been associated with a greater risk of PHLF. Little et al. reported on 727 patients who underwent liver resection and demonstrated an increase in 30-day mortality among diabetic versus non-diabetic patients ($p < 0.02$); in fact, 80 % of the deaths in this study were attributable to PHLF.[23] The association of diabetes with the risk of PHLF may be due to the important role insulin plays in the regulation of hepatocyte function and regeneration. Specifically, a lack of insulin has been noted to cause hepatic atrophy in animal models.[24] In one clinical study, Zarzavadjian Le Bian et al. reported that in the 30 (19.8 %) of the 151 patients undergoing right hepatectomy who had two or more metabolic disorders (diabetes mellitus, hypertension, dyslipidemia, or obesity) perioperative mortality was 30 %.[25] In a different study of 245 patients with well-preserved liver function undergoing liver resection for HCC, Huo et al. reported that diabetes was an independent prognostic factor associated with over a twofold increased risk of PHLF (RR=2.3, 95 % CI=1.4–3.7, p=0.001).[26]

Similar to diabetes, obesity—another factor related to metabolic syndrome—has been associated with an increased risk of PHLF.[25] Schlindl et al. in a study of 104 patients who underwent major liver resection reported that the body mass index (BMI) was higher among patients who experienced postoperative PHLF (median=29.9, SD=6.1) versus patient who did not (median=24.6, SD=4.2, $p < 0.001$).[27]

Interestingly, malnutrition has also been associated with PHLF. The reasons for this are unclear, but may be due to an altered immune response in malnourished patients, as well as a decrease in hepatocyte regenerative capacity.[28,29] In a prospective study of 124 patients undergoing hepatectomy in Hong Kong, Fan et al. demonstrated that patients who were given perioperative nutritional therapy had a reduction in overall postoperative morbidity (34 vs. 55 %; RR=0.66; 95%

CI=0.34 to 0.96), as well as less deterioration of liver function measured by rate of clearance of indocyanine green (–2.8 vs. –4.8 % at 20 min, p=0.05).[28]

Liver-Related Factors

Patients undergoing hepatectomy present with a wide range of underlying hepatic parenchymal disease including cirrhosis, steatosis, steatohepatitis, and chemotherapy induced liver injury that can affect the ability of the liver to regenerate after liver resection.

Cirrhosis is one of the most important and well-studied factors limiting the regenerative ability of the liver. Animal models have demonstrated that after resection, cirrhosis is associated with decreased levels of hepatocyte growth factor,[30] impaired transcription factors,[31] and a reduction of DNA synthesis, leading to lower volumes of regenerated liver.[32] Largely due to the risk of PHLF, mortality following liver resection has traditionally been associated with a high mortality, reaching 30 % in some series.[33,34] While mortality among cirrhotic patients has decreased over the past several decades, 90-day mortality following liver resection still remains higher than among patients without underlying cirrhosis. Not surprisingly, mortality is also associated with the degree of cirrhosis, as Capussotti et al. demonstrated that Child Pugh class A patients had a lower in-hospital mortality versus Child-Pugh class B or C patients (4.7 vs 21.3 %, respectively; p<0.001).[35]

In addition to cirrhosis, steatosis and steatohepatitis can affect liver function and regeneration post resection. For example, an increased integrated stress response impairs regeneration of the liver in animal models in the setting of hepatic steatosis.[36] de Meijer et al. published a meta- analysis in which hepatic steatosis was noted to be a risk factor for increased perioperative morbidity and mortality in patients undergoing major hepatic resection.[37] Specifically, patients with at least 30 % steatosis had an increased risk both of postoperative death (RR= 2.79, 95 % CI= 1.19– 6.51) and of developing postoperative complications (RR=2.01, 95 % CI = 1.66–2.44) versus patients without steatosis.[37] In a recent different study that compared 174 patients with steatohepatitis or >33 % simple steatosis versus patients with a normal liver, 90-day postoperative overall morbidity (56.9 vs. 37.3 %; p = 0.008), any hepatic-related morbidity (28.4 vs. 15.7 %; p = 0.043), surgical hepatic complications (19.6 vs. 8.8 %; p = 0.046), and hepatic decompensation (16.7 vs. 6.9 %; p = 0.049) were all greater among patients with steatohepatitis versus those with normal liver parenchyma.[38]

With the increasing utilization of neoadjuvant chemotherapy, possible chemotherapy-related hepatotoxicity presents another factor that may impact the regenerative ability of the liver. Several studies have suggested that chemotherapy-associated liver injury is regimen specific. In a study of 248 patients who underwent neoadjuvant chemotherapy for colorectal liver metastasis (CRLM) followed by hepatic resection, Vauthey et al. reported that an oxaliplatin-based regimen was associated with sinusoidal dilation on pathologic analysis compared with chemotherapy-naïve livers (18.9 vs. 1.9 %, respectively; p<0.001 ; OR=8.3, 95 % CI=2.9–23.6).[39] In addition, irinotecan-based therapy was associated with steatohepatitis versus no chemotherapy (20.2 vs. 4.4 %, respectively; p<0.001; OR=5.4, 95 % CI=2.2–13.5) (Fig. 1). Of note, patients with steatohepatitis on pathologic review had an increased 90-day mortality compared with patients without steatohepatitis (14.7 vs. 1.6 %, respectively; p=0.001; OR=10.5; 95 % CI=2.0–36.4).[39] Robinson et al. corroborated these findings in a meta-analysis of 28 studies as neoadjuvant chemotherapy was associated with an increased risk of regimen-specific hepatic parenchymal injury.[40] Patients receiving oxaliplatin-based regimens had over a fourfold increased risk of sinusoidal injury compared with chemotherapy-naïve patients (95 % CI=1.36–13.97; p=0.01).[40] Several studies have associated sinusoidal injury and steatohepatitis with compromised liver regeneration as well as increased morbidity following hepatic resection.[41-44]

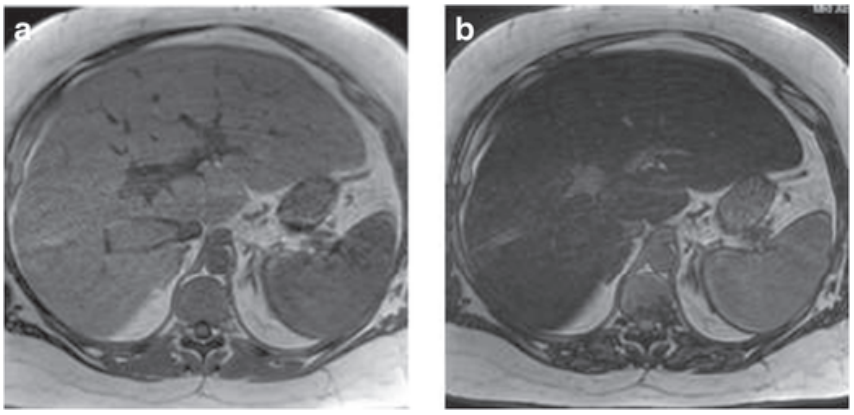

Fig. 1 MRI images of normal liver parenchyma and severe steatohepatitis. a In phase axial image of the liver showing normal liver signal. b Opposed phase axial image of the liver showing significant signal drop, indicating severe steatohepatitis in a patient following neoadjuvant chemotherapy

Surgery-Related Factors

In addition to patient- and liver-specific factors, the surgical procedure itself may influence the risk of PHLF in both the immediate postoperative period and in a delayed manner. Intraoperative blood loss and requirement of blood transfusion have been associated with an increase in postoperative complications following hepatectomy.[45,46] In a study of 1056 hepatectomies, intraoperative blood loss >1000 mL was strongly associated with the occurrence of major complications (OR=4.17; 95% CI=1.04–17.5).[47] Excessive blood loss can lead to fluid shifts, which may induce bacterial translocation leading to systemic inflammation and coagulopathy, which predisposes for intra-abdominal hematoma and infection.[48,49] Moreover, postoperative blood transfusions required due to intraoperative blood loss, results an immunosuppressive effect that may contribute to PHLF.[50]

An important surgery-related factor is the extent of resection and avoidance of "small-for-size" liver remnant following hepatectomy. Much of the data regarding "small-for-size" liver remnant and resultant PHLF stems from the living donor liver transplant literature. First documented in 1996 by Emond et al., small for size graft syndrome initially was defined as graft-to-recipient weight ratio (GRWR) of less than 0.8 to 1.0 % or less than 30 to 50 % of standard/estimated liver volumes; small-for-size livers are associated with an increase in severe graft dysfunction with increased hepatocyte injury, hyperbilirubinemia, prolonged PT, portal hypertension, and ascites.[51-53] A similar "small-for-size" syndrome can be seen following extended hepatic resections, and therefore, one should take efforts to preoperatively predict adequate FRL in an effort to decrease the risk of PHLF.

While most surgery-related factors may result in an increased risk of PHLF in the immediate postoperative period, PHLF can also occur in a delayed fashion. Specifically, PHLF may be due to a combination of initial patient, liver, and surgery-related factors combined with a postoperative "second hit" such as infection or sepsis, which has been shown to decrease Kuppfer cell function and increase toxic cytokines both of which can inhibit hepatocyte proliferation in animal models.[54,55]

Physiology and Molecular Mechanisms of PHLF

Following hepatecomy, sheer stress on the vascular endothelium can be elevated due to an increase in portal pressure.[56,57] In turn, liver sinusoidal endothelial cells release nitric oxide in response to this increase in sheer stress with resulting sen-

sitization of hepatocytes to hepatocyte growth factor (HGF).[58] HGF stimulates hepatocyte proliferation through activation of multiple signaling pathways as well as an increase in transforming growth factor alpha (TGF α). In addition, several portal hepatotrophic factors, including lipopolysaccharide, are initiated to assist in regeneration.[59] These portal hepatotrophic factors stimulate release of interleukin-6 (IL-6) from Kupffer cells that induces transcription of several cell division and survival genes.[60] In animal models of 70 % partial hepatectomy, 95 % of normally quiescent hepatocytes reenter the cell cycle and undergo mitosis peaking 24 h post- hepatectomy.[61] The resulting hepatocyte proliferation forms clusters of 10–14 unorganized "hepatic islands" that are not functional until connections are reestablished among hepatocytes and endothelial cells via extracellular matrix production by stellate cells.[62] While in animal models, restoration of liver volume occurs quickly (by 72 h post-hepatectomy), the original studies of healthy human hepatic regeneration showed volume restoration at 2 to 6 months with biologic function restored significantly earlier—in less than 3 weeks post major hepatectomy.[63] To facilitate normal hepatic metabolism and regeneration, constant interaction between hepatocytes and biliary endothelial cells is necessary. In the setting of PHLF, there is Kupffer cell dysregulation and a decrease in secretion of prostaglandin E2. This leads to hypersecretion of tumor necrosis factor resulting in necrosis, microvesicular steatosis, and irreversible hepatocyte injury that ultimately decreases the available exchange surface necessary for normal hepatic metabolism to occur.[64]

Preoperative Evaluation of Liver Function

Given the irreversible cellular injury and high mortality associated with PHLF, there has been great effort to preoperatively identify patients at high risk for hepatic dysfunction or failure. The preoperative assessment of a patient's risk of developing PHLF is performed using multiple different techniques to evaluate the quality and the quantity of the future liver remnant (FLR).

Quality Assessment of the Liver

Traditional Liver Function Markers and Clinical Scoring Systems

The correlation between PHLF and conventional laboratory parameters representing different synthetic and excretory functions of the liver such as alanine aminotransferase (ALT), aspartate aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin, lactate dehydrogenase

(LDH), albumin and prothrombin time (PT) has been extensively reported in the literature.[65-72] None of these laboratory factors taken alone have been shown to provide an adequate evaluation of liver function; however, a combination of biochemical parameters has been included in different scoring systems to evaluate preoperative hepatic function.

In clinical practice, one widely used tool for assessment of liver function is the Child-Pugh classification that is based on five biochemical (bilirubin, albumin, and international normalized ration (INR)) and clinical (ascites and hepatic encephalopathy) variables.[73] The other clinical tool is the Model for End-Stage Liver Disease (MELD), which incorporates only three biochemical parameters (creatinine, bilirubin, and INR).[74] Both scoring systems were originally developed to grade chronic liver disease and cirrhosis in liver transplant candidates; however, both are currently also used to screen patients preoperatively for the risk of PHLF as well as to evaluate the perioperative liver function.[73,75,76]

Patients at the extreme of the Child-Pugh classification, such as those classified as advanced B or C (i.e., bilirubin> 50 μmol/L, serum albumin<2.8 g/dL, PT INR>2.3, moderate to severe ascites, and absence of hepatic encephalopathy), are not candidates for hepatectomy due to their risk of PHLF.[4] The use of the Child-Pugh classification to risk stratify patients with more modest or mild cirrhosis has demonstrated a relatively poor ability to predict specific PHLF-related mortality.[77] The role of MELD model as a preoperative predictor of PHLF has similarly been extensively evaluated with mixed results.[74,77-79] Several studies have suggested that MELD can be used in the preoperative setting to risk-stratify patients with regard to postoperative PHLF and death. In one study of 2056 patients, the laboratory values that comprise the MELD score were used to create a risk model in which a biological MELD higher than 10 was associated with a higher risk of PHLF and death.[80] A separate study from the Mayo Clinic reported on 772 patients with cirrhosis who underwent major surgery and noted that MELD was an independent predictor of 30- and 90-day postoperative mortality.[81] While Rahbari et al. noted that MELD score was correlated with morbidity and mortality following hepatectomy, the sensitivity for morbidity and mortality was only 55 and 71 %, respectively.[79] Cucchetti et al. reported that increasing MELD scores between postoperative days (POD) 3 and 5 was correlated with impending PHLF and should be a strong indication for intensive treatment.[78]

Indocyanine Green Retention Rate at 15 min

Preoperative evaluation for the risk of PHLF has included the use of the indocyanine green retention rate at 15 min (ICG- R15) test in some centers.[82,83] ICG is a water-soluble, nontoxic fluorescent dye that is injected intravenously and is eliminated almost exclusively by the liver. The absorption and emission spectrum of ICG are both in the near infrared range allowing for measurements to be performed by non-invasive monitoring.[10,65,84-90] The ICGR-R15 test has been shown to predict more accurately PHLF compared with both the Child-Pugh classification[91] and MELD model.[92]

There is no clear consensus on the cut-off value for ICG- R15 allowing for safe hepatic surgery. Fan et al. reported on 101 patients with cirrhosis who underwent major hepatic resection and suggested an ICG-R15 value of 14 % was the cut- off point that could maximally separate patients with and with- out high postoperative mortality (p=0.01).[93] In a separate study, Lam et al. reported that the cut-off value for a safe major hepatectomy could be increased to 17 % in relatively younger patients with an adequate remnant liver volume (RLV).[94] While the ICG-R15 test is used in the east, its adoption has not been widespread in western centers.

Other Liver Function Tests for the Quality Assessment of the Liver

Several quantitative estimations of liver function based on the principle of clearance of substrate by the liver have been developed. These substances include lidocaine,[73] galactose,[95] aminopyrine,[96] amino acid,[97] and methacetin.[98] None of these various tests have been proven to be superior than ICG-R15 for the prediction of PHLF- or PHLF-related mortality.[91] There are also several tests available that are based on the synthetic functions of the liver including serum levels of hyaluronate[99] and type IV collagen,[100] energy production of the liver (arterial ketone body ratio),[101] and the number of receptors for asialoglycoprotein (technetium-99 m-galactosyl-human serum albumin; 99 m Tc-GSA scan).[68,102-106] While these tests may provide important information regarding the quality of the remaining liver remnant, their high cost and complexity are barriers to their clinical implementation.[91]

Liver-Specific Agents for Contrast-Enhanced MRI

There is an increasing interest in the possibility of integrating both quantitative and qualitative assessments of the functional liver remnant. In particular, the role of magnetic resonance imaging (MRI) for assessment of the liver is well established. Recently, liver-specific contrast agents have been developed which both improve morphological assessment as well as provide functional information.[107] The most

promising liver- specific contrast agent for predicting PHLF after major liver resection is gadoxatic acid.[108] After intravenous injection, this gadolinium-based paramagnetic contrast agent is taken up by functional hepatocytes and excreted into bile ducts via membrane transporters. The temporary accumulation of this contrast agent in the liver and subsequent enhancement of the normal liver parenchyma permits the measurement of relative liver enhancement (RLE).[109] Wibmer et al. reported that the preoperative RLE was strongly related to the probability of developing PHLF compared with both the "50-50 criteria"(OR=0.935, 95% CI=0.884–0.990; p=0.020) and the International Study Group of Liver Surgery (ISGLS) grading system (OR=0.967, 95 % CI=0.951–0.982; p<0.001).[62]

Quantity Assessment of the Liver

Future Remnant Liver Volume

Preoperative determination of the FLR size after hepatectomy is fundamental for effective and safe hepatic resection. Currently, there is no uniform consensus regarding the limit of the FRL volume necessary to achieve a "safe" liver resection or the modality most effective for evaluating FLR size preoperatively.[110] Several studies have tried to validate different imaging techniques for liver volumetry including conventional ultrasound[111] and three-dimensional ultrasound[112]; however, the techniques most frequently utilized to assess FLR include computed tomography (CT) and MRI.[113] Both imaging techniques permit the calculation of the FRL volume, as well as the ratio of FRL volume to the total functioning liver volume (TLV) (Table 2).[39,44,110,114-118]

Table 2 Formulas to determine FLR

Reference	Year	Formula	Threshold for hepatectomy
Yamanaka et al.[114]	1994	−84.6+0.933×PHRR+1.11×ICG-R15+0.999×age	45
Kubota et al.[44]	1997	(resected volume-tumor volume)/(TLV-tumor volume)	40 % non-tumorous parenchyma
Vauthey et al.[118]	2000	(CT FLR)/(706×BSA+2.4)	20 % in normal livers
Ribero et al.[117]	2008	(CT FLR)/(−794+1267×BSA)	20 % in normal livers
Uchiyama et al.[115]	2008	164.8−0.58×albumin−1.07×hepaplastin test+0.062×glutamate oxaloacetate transaminase−685×ICG-K−3.57×oral glucose tolerance test linearity index+0.074×weight of resected liver	25
Du et al.[116]	2011	ICG-K x 22.487+standardized remnant liver volume×0.02	13.1

In a consensus conference on the surgical management of liver metastasis, an expert panel conclude the "acceptable" FLR to be >20 % of TLV for patients with a normal liver, >30 % of TLV in patients with evidence of steatosis/ steatohepatitis, and >40 % of TLV in patients with hepatic fibrosis or cirrhosis.[119] Ribero

et al. confirmed validated these cut-offs in a study of 112 patients with differing status of underlying liver disease (normal, steatosis, fibrosis, or cirrhosis) who underwent major hepatectomy.[120] Specifically, in the group of patients with a FLR<20 % of TLV, the rate of post- operative liver-related complications and hepatic insufficiency was 90 and 30 % compared with 23 and 2 %, respectively, in the group of patients with a FLR>20 % of TLV (p<0.001 and 0.009). Moreover, in a recent study of 301 patients who underwent extended right hepatectomy, Kishi et al. reported that a FLR<20 % of TLV was the strongest predictor of PHLF (OR=3.18; CI 95 %=1.34–7.54) on multivariate analysis.[121]

Criteria for Defining and Predicting the Post Hepatectomy Liver Failure

Prior to this decade, there has been no uniform definition of PHLF. In 2011, the International Study Group of Liver Surgery (ISGLS) reviewed more than 50

Table 3 Predictive models of PHLF

Preoperative Models	Description	Validation studies
MELD Score	A scoring system used for determining the gravity of end-staged liver disease. Takes into account serum creatinine, bilirubin, INR, and dialysis status	74,77
Child-Pugh Score	Child-Pugh scoring system is used for grading liver cirrhosis into three distinct classes. Takes into account serum bilirubin, albumin, INR, ascites, and encephalopathy.	77
Nanashima et al.[149]	GSA, serum bilirubin, hyaluronate, and major hepatectomy were used to construct a regression formula. A cut-off for high risk was introduced.	-
Postoperative Models	**Description**	**Validation studies**
MELD Score	A scoring system used for determining the gravity of end-staged liver disease. Takes into account serum creatinine, bilirubin, INR, and dialysis status.	78,79
Child-Pugh Score	Child-Pugh scoring system is developed for grading liver cirrhosis into three distinct classes. Takes into account serum bilirubin, albumin, INR, ascites, and encephalopathy.	-
50-50 Criteria[18]	The 50–50 criteria state that a combined prothrombin time less than 50 % and a serum bilirubin of more than 50 μmol/L on POD 5 is a significant predictor of postoperative mortality due to PLF.	79,80,122,123,150
Kim et al.[150]	Kim et al. proposed the 50–50 criteria to be adjusted to the combination of PT <65 % and bilirubin ≥38 μmol/L on POD 5.	
Snap peak bilirubin >7 mg/dL[19]	A postoperative peak bilirubin greater than 7 mg/dL was found to be a significant predictor of death as a result of liver failure.	80,122
ISGLS Definition[5]	The ISGLS proposed the general definition of a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR and hyperbilirubinemia on or after postoperative day 5. To be divided further into grade A, B, or C.	79,122
Hyder et al.[80]	A composite integer-based risk score based on international normalized ratio, bilirubin, creatinine, and complication grade at POD 3.	-

studies on hepatic resection between 2003 and 2009, using multiple criteria to define PHLF.[5] In turn, the definition of PHLF involves acquired deterioration of one or more synthetic, excretory, or detoxifying functions of the liver including hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT) or international normalized ration (INR), elevated serum lactate, and hepatic encephalopathy during the postoperative period.[5]

In clinical practice, the most commonly used criteria for defining, predicting, and grading the severity of PHLF are the "50–50 criteria"[18], peak bilirubin >7 mg/dL,[19] the ISGLS criteria,[5] and the more recent risk score proposed by Hyder et al. (Table 3).[80]

50–50 Criteria

In an effort to refine the definition of PHLF and its grades of severity, Balzan et al. proposed the "50-50 criteria".[18] The criteria for PHLF consisted of a combination of PT <50 % (INR>1.7) and serum bilirubin level >50 μmol/L (>2.9 mg/dL) recorded on POD 5.[18] In this study, patients who met these criteria had a 59 % risk of early postoperative mortality versus only a 1.2 % risk of mortality in patients for whom both these conditions were not fulfilled (p<0.001). In the original study, the accuracy of the "50-50" criteria to predict in-hospital mortality was 97.7 % (95 % CI= 96.6–98.7 %; sensitivity=69.6 %; specificity=98.5 %).[18]

The role of the "50-50 criteria" as a predictor of postoperative mortality due to PHLF is still, however, unclear. While several studies have confirmed the ability of the "50-50" criteria to predict post-hepatectomy PHLF-related mortality,[79,122,123] other studies have noted a much more modest performance of the "50-50" criteria.[19,80] For example, in one large series of 1286 patients undergoing hepatic resection, only 14 of 28 patients who died fulfilled the "50-50 criteria".[19] In a second study of 2056 patients who underwent liver resection, on postoperative

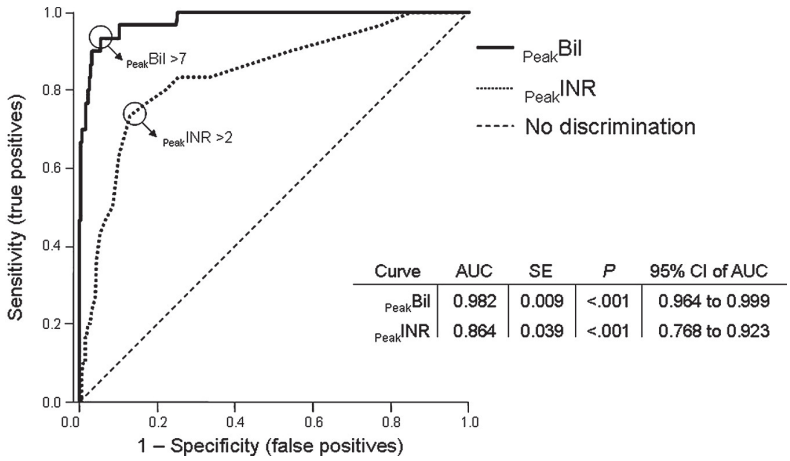

Fig. 2 Receiver operating characteristic (ROC) curves demonstrating that the cut-off peak postoperative bilirubin (PeakBil) value to predict liver failure-related death is 7.0 mg/dL (area under the curve [AUC] 0.982; sensitivity 93.3 %; specificity 94.3 %). Reprinted with permission.[19]

day 5, only 60 (4.7 %) patients had a bilirubin ≥2.9 mg/dL, 3 (0.2 %) patients had an INR ≥1.7, and only 1 (0.07 %) patient had the requisite combination of both bilirubin ≥2.9 mg/dL and INR≥1.7.[80]

Peak Bilirubin >7 mg/dL

Mullen and colleagues have suggested that, rather than the "50-50" criteria, only peak bilirubin be utilized to define PHLF.[19] In a large retrospective study of 1059 patients who underwent major hepatectomy at three high volume centers in the USA and Italy from 1995 to 2005, a peak postoperative bilirubin greater than 7 mg/dL was the most powerful independent predictor of any complication (OR= 83.3), major complication (OR=10.0), 90-day mortality (OR=10.8), and 90-day PHLF-related mortality (OR= 250, all p <0.001).[19] The authors reported an area under the curve (AUC) of 0.982, with a sensitivity and specificity of 93.3 and 94.3 %, respectively (Fig. 2).[19]

While some studies have subsequently validated a peak bilirubin of 7 mg/dL,[121] others reports have questioned the overall accuracy and clinical applicability of this parameter as the sole means to predict post-hepatectomy PHLF-associated death.[80,124] In one study, of the 2056 patients who underwent either minor or major hepatectomy, only 20 patients demonstrated a peak bilirubin concentration >7 mg/dL.[80] Of the 20 patients, five (25 %) died within 90 days for a sensitivity and specificity of the >7 mg/dL rule of 25 and 99.3 %, respectively, with a poor overall accuracy (AUC=0.574).[80]

ISGLS Definition

More recently, in 2011, the ISGLS defined PHLF as an increase in INR and concomitant hyperbilirubinemia on or after POD 5.[5] Grades of PHLF severity were also defined depending on the patient's clinical management: mild disruption of liver function (normal trend after hepatectomy) not requiring management (Grade A); moderate liver dysfunction not requiring invasive therapy (Grade B); and severe dysfunction, requiring invasive therapy (Grade C) (Table 4).[5]

Table 4 Consensus definition and severity grading of posthepatectomy liver failure (PHLF) by the International Study Group of Liver Surgery (ISGLS) (Reprinted with permission)[5]

Definition	A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively<comma>PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out.
Grade	
A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient.
B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

This clinical risk score was validated in a study of 807 patients who underwent hepatic resection that showed the ISGLS criteria for PHLF to be an independent predictor of mortality.[79] However, despite efforts by the ISGLS to define PHLF more accurately to predict prognosis early after hepatectomy, several studies have questioned the accuracy of the ISGLS criteria. Specifically, Skrzypczyk et al. compared the ISGLS definition with the "50-50 criteria" and peak bilirubin >7 md/dL criteria among 680 patients who underwent either minor or major hepatectomy.[122] In this study, the ISGLS definition was found to be the least predictive of both the occurrence of major complications (positive predictive value of 49.2 % for ISGLS vs. 78.9 % for "50–50 criteria" and 65 % for peak bilirubin >7 md/dL), as well as the risk of postoperative death (OR=6.9 for ISLGS vs. OR=21.1 for "50-50" and OR=21.7 for peak bilirubin >7 md/dL).[122]

Hyder et al. Risk Score

In light of prior shortcomings, Hyder et al. proposed the use of an integer-based risk score that combines Clavien-Dindo complication grade, INR, bilirubin, and creatinine level on POD 3.[80] In this study, the proposed model had the ability to estimate a numerical risk of developing PHLF, as well as to predict post-hepatectomy 90-day mortality with high accuracy.[80] Specifically, when patients were stratified accord- ing to the number of points derived from the aforementioned risk score, there was an incremental increased risk of death (<5.9 points, 0.2 % vs. 6.0 to 8.9 points, 1.2 % vs. 9.0 to 10.9 points, 34.3 % vs. ≥11 points, 83.3 %; $p<0.001$). Among patients who had ≥11 points, the prediction score had a sensitivity of 83.3 % and specificity of 98.9 % (Fig. 3).[80] Future studies will need to validate this integer-calculator-based risk score of PHLF and death proposed by Hyder et al.

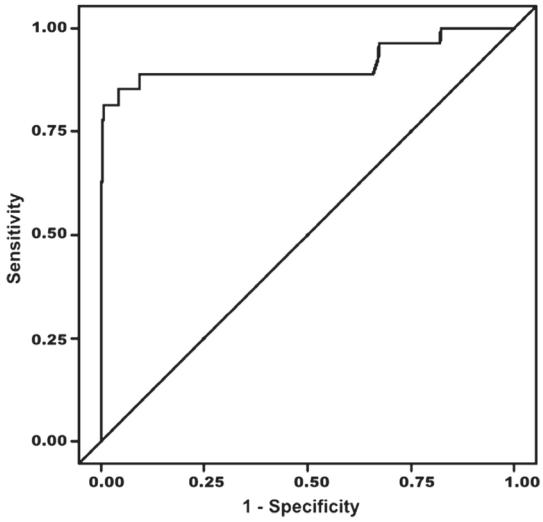

Fig. 3 Receiver-operating characteristic (ROC) of the Hyder et al. composite prediction rule. The composite score consists of weighted values for grade of postoperative complication, as well as INR, bilirubin, and creatinine on POD 5. ROC curve analysis resulted in an area under the curve [AUC] 0.927. Reprinted with permission[75]

Strategies to Prevent Post-Hepatectomy Liver Failure

Given the association of the FLR remnant volume and risk of post-hepatectomy liver function, increasing the remnant volume has been the rationale behind several preoperative procedures.[125,126] Portal vein embolization (PVE) was first described in the 1980s as a technique to increase the remnant liver volume by Kinoshita[127] and later by Makuuchi et al.[128] PVE is typically an ultrasound-guided percutaneous procedure that induces liver hypertrophy following embolization of the portal vein ipsilateral to the side of disease. The blockade of the portal vein results in hypertrophy of the contralateral side and thus an increase in the size of the FLR. PVE also results in an increase in the production of hepatic growth factor (HGF) and TGF, along with redistributing the portal blood flow to the FRL. PVE allows for hypertrophy of the FLR by 30–40 % within 4–6 weeks in more than 80 % of patients.[57] A meta-analysis of 1088 patients who underwent preoperative PVE for major liver resection demonstrated that 4 weeks after PVE, 85 % of patients were able to undergo the planned hepatectomy with an 8 to 27 % increase in FLR.[129]

In some circumstances, a surgeon may prefer portal vein ligation (PVL) rather than PVE. Specifically, PVL has been proposed in those cases in which resection of bilobar malignant liver lesions requires a two-stage approach due to inadequate

FLR volume.[130,131] With this approach, clearance of the FLR is performed using a parenchymal sparing resection approach. At the time of the first surgery, the contralateral portal vein is ligated. Three to six weeks following the first stage after allowing time for hypertrophy of the FLR, the second stage is performed which consists usually of an extended/ major hepatectomy. A meta-analysis reported that there was no statistically significant difference comparing PVE and PVL in terms of increasing FLR volume (+39 % after PVE vs. +27 % after PVL; p=0.06), morbidity (RR=1.08, 95 % CI= 0.55–2.09; p=0.83), and perioperative mortality (RR=0.87, 95 % CI=0.19–3.92; p=0.85).[132]

In 2011, a third strategy combining in situ liver partition, PVL followed by hepatectomy (ALPPS) in a two-stage surgical approach was developed to decrease the time between PVL and resection for patients with borderline FRL volume.[133] This approach allows for clearance of one side of the liver while maintaining the main liver mass in place to assist with liver function while the FLR hypertrophies in order to avoid PHLF. ALPPS may also facilitate superior hypertro- phy of the FLR compared with PVE, with a reported 74 % volume increase of the remnant liver in a mean of 9 days.[133] Schadde et al. reported on 202 patients who underwent ALPS S and noted that a median starting standardized FLR of 21 % increased by 80 % within a median of 7 days, in contrast to approximately 8–27 % within 2–60 days by PVL/PVE.[134] In a recent meta-analysis, reviewing the increase in FLR after dif- ferent procedures, Pandanaboyana et al. reported that ALPPS provided an additional 17 % increment of the FLR compared with PVE (p=0.03).[132] Although these results are promising, the ALPPS procedure has been reported to have high operative morbidity (16–64 % of patients) and perioperative mortality (12–23 % of patients), which has prevented it from becoming widely utilized.[134]

Treatment of Post-Hepatectomy Liver Failure

While patients are ideally screened preoperatively and any comorbid conditions optimized in an attempt to avoid PHLF, patients should also be monitored closely postoperatively with treatment initiated at any early indication of PHLF. Particular attention should be paid to early clinical and laboratory signs of liver failure including chang- es in coagulation factors (including PT and INR), bilirubin, as well as signs of encephalopathy. Patients should also be monitored for early signs of infection, hemodynamic failure, renal failure, malnutrition, or metabolic disorders so that these may be addressed at an early stage.[135,136] Patients who develop any of these complications should be monitored in an ICU setting, and the use of hepatotoxic as well as nephrotoxic medications should be avoided.

Generally, the management principles for PHLF resemble those suggested by the American Association for the Study of Liver Diseases (AASLD) for the management of acute liver failure (ALF).[137] The severity of the PHLF should be followed using laboratory values such as INR, platelets, ammonia, bilirubin, and creatinine. Resuscitative measures and organ support provide the optimal environment for liver regeneration. In early stages of encephalopathy, ammonia levels should be followed and lactulose, polyethylene glycol, or rifaximin used for treatment.[138,139] Volume depletion should be monitored and addressed by fluid replacement. Fluid- refractory hypotension may warrant the use of vasopressor agents. Acute renal failure is common in ALF and associated with increased mortality. Causes may be multifactorial, including direct drug toxicity, acute tubular necrosis, or the presence of the systemic inflammatory response syndrome.[140] The administration of antibiotics in patients suffering from ALF is associated with a significant decrease in infectious complications and therefore early use of antibiotics may also be advantageous in patients suffering from PHLF.[141] Hypoglycemia is seen in up to 45 % of patients with acute liver failure, and thus, glucose levels must be monitored and dextrose infusion used as necessary.[142] There is still no widely effective treatment of PHLF once it has befallen the patient. Albumin, fresh frozen plasma, and antithrombin III may be used to support clotting factors depleted during liver failure.[143]

The introduction of the molecular absorbent recirculating system (MARS®), an extracorporeal albumin dialysis machine, was shown to be effective in bridging patients with fulminant liver failure to orthotopic liver transplant (OLT).[144] Its use in PHLF, however, has been sparsely studied; while improvement in biochemical parameters has been reported with use of MARS for PHLF, there has been no demonstrable survival benefit.[137,145,146]

While rescue OLT remains the most definitive treatment for PHLF, such treatment is not universally available for many patients who develop PHLF. In fact, less than 10 % of liver transplantations are performed in patients with ALF and OLT for PHLF has only been sparsely reported.[147,148] Given that the initial indication for hepatic resection frequently involves a malignancy outside of transplantation criteria, salvage OLT for PHLF is often not feasible.

Conclusion

PHLF is a major cause of postoperative morbidity and mortality in patients following major hepatectomy. Physiologically, with the onset of PHLF, there

is induction of irreversible structural damage and hepatocyte injury in the regenerating liver. Adequate preoperative risk assessment and maximal in- crease of FLR using PVE, PVL, or ALPPS are essential for PHLF prevention. Early diagnosis and treatment of postoperative complications following hepatic resection are essential to mitigate the risk of PHLF. Once PHLF occurs, treatment largely revolves around supporting organ function, use of colloid and crystalloid products, as well as maximal treatment of associated complications. Short of OLT, no definitive "curative" treatment of PHLF exists. Future studies should be aimed at understanding the mechanisms and risk factors of PHLF, as well as targeting means to better avoid and treat this challenging post-hepatectomy complication.

References

1. Silberhumer GR, Paty PB, Temple LK, Araujo RL, Denton B, Gonen M, Nash GM, Allen PJ, DeMatteo RP, Guillem J, Weiser MR, D'Angelica MI, Jarnagin WR, D WW, Fong Y. Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure. Am J Surg. 2014.
2. Imamura H, Seyama Y, Kokudo N, Aoki T, Sano K, Minagawa M, Sugawara Y, Makuuchi M. Single and multiple resections of mul- tiple hepatic metastases of colorectal origin. Surgery 2004;135: 508–17.
3. Spolverato G, Kim Y, Alexandrescu S, Popescu I, Marques HP, Aldrighetti L, Clark Gamblin T, Miura J, Maithel SK, Squires MH, Pulitano C, Sandroussi C, Mentha G, Bauer TW, Newhook T, Shen F, Poultsides GA, Wallis Marsh J, Pawlik TM. Is Hepatic Resection for Large or Multifocal Intrahepatic Cholangiocarcinoma Justified? Results from a Multi- Institutional Collaboration. Ann Surg Oncol. 2014.
4. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R, Saner FH. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int. 2008;28:767–80.
5. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Buchler MW, Weitz J. Posthepatectomy liver fail- ure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149:713–24.
6. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. Dig Surg. 2012;29:79–85.
7. Ribeiro HS, Costa WL, Jr., Diniz AL, Godoy AL, Herman P, Coudry RA, Begnami MD, Mello CA, Silva MJ, Zurstrassen CE, Coimbra FJ. Extended preoperative chemotherapy, extent of liver resection and blood transfusion are predictive factors of liver failure following resection of colorectal liver metastasis. Eur J Surg Oncol. 2013;39:380–5.
8. Filicori F, Keutgen XM, Zanello M, Ercolani G, Di Saverio S, Sacchetti F, Pinna AD, Grazi GL. Prognostic criteria for postop- erative mortality in 170 patients undergoing major right hepatec- tomy. Hepatobiliary Pancreat Dis Int. 2012;11:507–12.
9. Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Kakisaka T, Tsuruga Y, Todo S, Taketomi A. Analysis of the risk factors for early death due to disease recurrence or progression within 1 year after hepatectomy in patients with hepatocellular carcinoma. World J Surg Oncol. 2012;10:107.
10. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. Hepatogastroenterology. 2012;59:782–4.
11. Helling TS. Liver failure following partial hepatectomy. HPB (Oxford). 2006;8:165–74.
12. Bolder U, Brune A, Schmidt S, Tacke J, Jauch KW, Lohlein D. Preoperative assessment of mortality risk in hepatic resection by clinical variables: a multivariate analysis. Liver Transpl Surg. 1999;5:227–37.
13. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94:982–99.
14. Timchenko NA. Aging and liver regeneration. Trends Endocrinol Metab. 2009;20:171–6.

15. Iakova P, Awad SS, Timchenko NA. Aging reduces proliferative capacities of liver by switching pathways of C/EBPalpha growth arrest. Cell. 2003;113:495–506.

16. Simon-Santamaria J, Malovic I, Warren A, Oteiza A, Le Couteur D, Smedsrod B, McCourt P, Sorensen KK. Age-related changes in scavenger receptor-mediated endocytosis in rat liver sinusoidal endothelial cells. J Gerontol A Biol Sci Med Sci. 2010;65:951–60.

17. Le Couteur DG, Warren A, Cogger VC, Smedsrod B, Sorensen KK, De Cabo R, Fraser R, McCuskey RS. Old age and the hepatic sinusoid. Anat Rec (Hoboken). 2008;291:672–83.

18. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg. 2005;242:824–8, discussion 8–9.

19. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, Abdalla EK, Curley SA, Capussotti L, Clary BM, Vauthey JN. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg. 2007;204:854– 62; discussion 62–4.

20. Aldrighetti L, Arru M, Caterini R, Finazzi R, Comotti L, Torri G, Ferla G. Impact of advanced age on the outcome of liver resection. World J Surg. 2003;27:1149–54.

21. Nanashima A, Abo T, Nonaka T, Fukuoka H, Hidaka S, Takeshita H, Ichikawa T, Sawai T, Yasutake T, Nakao K, Nagayasu T. Prognosis of patients with hepatocellular carcinoma after hepatic resection: are elderly patients suitable for surgery? J Surg Oncol. 2011;104:284–91.

22. Kim JM, Cho BI, Kwon CH, Joh JW, Park JB, Lee JH, Kim SJ, Paik SW, Park CK. Hepatectomy is a reasonable option for older patients with hepatocellular carcinoma. Am J Surg. 2015;209: 391–7.

23. Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg. 2002;6:88–94.

24. Bucher NL. Insulin, glucagon, and the liver. Adv Enzyme Regul. 1976;15:221–30.

25. Zarzavadjian Le Bian A, Costi R, Constantinides V, Smadja C. Metabolic disorders, non-alcoholic fatty liver disease and major liver resection: an underestimated perioperative risk. J Gastrointest Surg. 2012;16:2247–55.

26. Huo TI, Lui WY, Huang YH, Chau GY, Wu JC, Lee PC, Chang FY, Lee SD. Diabetes mellitus is a risk factor for hepatic decom- pensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. Am J Gastroenterol. 2003;98: 2293–8.

27. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ, Edinburgh Liver S, Transplantation Experimental Research G. The value of residual liver volume as a predictor of hepatic dys- function and infection after major liver resection. Gut. 2005;54: 289–96.

28. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepa- tocellular carcinoma. N Engl J Med. 1994;331:1547–52.

29. Fan ST. Review: nutritional support for patients with cirrhosis. J Gastroenterol Hepatol. 1997;12:282–6.

30. Kaibori M, Inoue T, Sakakura Y, Oda M, Nagahama T, Kwon AH, Kamiyama Y, Miyazawa K, Okumura T. Impairment of activation of hepatocyte growth factor precursor into its mature form in rats with liver cirrhosis. J Surg Res. 2002;106:108–14.

31. Zhao G, Nakano K, Chijiiwa K, Ueda J, Tanaka M. Inhibited activities in CCAAT/enhancer-binding protein, activating protein- 1 and cyclins after hepatectomy in rats with thioacetamide-induced liver cirrhosis. Biochem Biophys Res Commun. 2002;292:474–81.

32. Garcea G, Maddern GJ. Liver failure after major hepatic resection. J Hepatobiliary Pancreat Surg. 2009;16:145–55.

33. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a Western experience. World J Surg. 1986;10: 311–7.

34. Gozzetti G, Mazziotti A, Cavallari A, Bellusci R, Bolondi L, Grigioni W, Bragaglia R, Grazi GL, De Raffele E. Clinical expe- rience with hepatic resections for hepatocellular carcinoma in pa- tients with cirrhosis. Surg Gynecol Obstet. 1988;166:503–10.

35. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cir- rhosis: analysis of mortality, morbidity and survival–a European single center experience. Eur J Surg Oncol. 2005;31:986–93.

36. Inaba Y, Furutani T, Kimura K, Watanabe H, Haga S, Kido Y, Matsumoto M, Yamamoto Y, Harada K, Kaneko S, Oyadomari S, Ozaki M, Kasuga M, Inoue H. Growth arrest and DNA damage-inducible 34 regulates liver regeneration in hepatic steatosis in mice. Hepatology. 2015;61:1343–56.

37. de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg. 2010;97:1331–9.

38. Reddy SK, Marsh JW, Varley PR, Mock BK, Chopra KB, Geller DA, Tsung A. Underlying steatohepatitis, but not simple hepatic steatosis, increases morbidity after liver resection: a case–control study. Hepatology. 2012;56:2221–30.

39. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006;24:2065–72.

40. Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol. 2012;19:4287–99.

41. Gomez D, Malik HZ, Bonney GK, Wong V, Toogood GJ, Lodge JP, Prasad KR. Steatosis predicts postoperative morbidity follow- ing hepatic resection for colorectal metastasis. Br J Surg. 2007;94: 1395–402.

42. Tevar AD, Clarke C, Wang J, Rudich SM, Woodle ES, Lentsch AB, Edwards ML. Clinical review of nonalcoholic steatohepatitis in liver surgery and transplantation. J Am Coll Surg. 2010;210: 515–26.

43. Narita M, Oussoultzoglou E, Chenard MP, Rosso E, Casnedi S, Pessaux P, Bachellier P, Jaeck D. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surg Today. 2011;41: 7–17.

44. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T. Measurement of liver vol- ume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology. 1997;26: 1176–81.

45. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP, Tuorto S, Wuest D, Blumgart LH, Fong Y. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg. 2003;237:860–9; discussion 9–70.

46. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg. 2004;240:698–708;discussion –10.

47. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M. One thousand fifty-six hepatecto- mies without mortality in 8 years. Arch Surg. 2003;138:1198– 206; discussion 206.

48. Silva MA, Muralidharan V, Mirza DF. The management of coag- ulopathy and blood loss in liver surgery. Semin Hematol. 2004;41: 132–9.

49. Luyer MD, Buurman WA, Hadfoune M, Jacobs JA, Konstantinov SR, Dejong CH, Greve JW. Pretreatment with high-fat enteral nutrition reduces endotoxin and tumor necrosis factor-alpha and preserves gut barrier function early after hemorrhagic shock. Shock. 2004;21:65–71.

50. Jensen LS, Andersen AJ, Christiansen PM, Hokland P, Juhl CO, Madsen G, Mortensen J, Moller-Nielsen C, Hanberg-Sorensen F, Hokland M. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colo- rectal surgery. Br J Surg. 1992;79:513–6.

51. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, Egawa H, Fujita S, Hayashi M, Tanaka K. Impact of graft size mismatching on graft prognosis in liver transplanta- tion from living donors. Transplantation. 1999;67:321–7.

52. Furukawa H, Kishida A, Omura T, Kamiyama T, Suzuki T, Matsushita M, Nakajima Y, Todo S. Indication and strategy for adult living related liver transplantation. Transplant Proc. 1999;31:1952.

53. Emond JC, Renz JF, Ferrell LD, Rosenthal P, Lim RC, Roberts JP, Lake JR, Ascher NL. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. Ann Surg. 1996;224:544–52; discussion 52–4.

54. Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA. ICAM-1 triggers liver regeneration through leuko- cyte recruitment and Kupffer cell-dependent release of TNF-al- pha/IL-6 in mice. Gastroenterology. 2003;124:692–700.

55. Akita K, Okuno M, Enya M, Imai S, Moriwaki H, Kawada N, Suzuki Y, Kojima S. Impaired liver regeneration in mice by lipo- polysaccharide via TNF-alpha/kallikrein-mediated activation of latent TGF-beta. Gastroenterology. 2002;123:352–64.

56. Rice GC, Leiberman DP, Mathie RT, Ryan CJ, Harper AM, Blumgart LH. Liver tissue blood flow measured by 85Kr clear- ance in the anaesthetized rat before and after partial hepatectomy. Br J Exp Pathol. 1977;58:243–50.

57. Golse N, Bucur PO, Adam R, Castaing D, Sa Cunha A, Vibert E. New paradigms in post-hepatectomy liver failure. J Gastrointest Surg. 2013;17:593–605.

58. Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress- induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide. 2001;5:453–64.

59. Michalopoulos GK. Liver regeneration. J Cell Physiol. 2007;213: 286–300.

60. Jin X, Zimmers TA, Perez EA, Pierce RH, Zhang Z, Koniaris LG. Paradoxical effects of short- and long-term interleukin-6 exposure on liver injury and repair. Hepatology. 2006;43:474–84.

61. Taub R. Liver regeneration: from myth to mechanism. Nat Rev Mol Cell Biol. 2004;5:836–47.

62. Wack KE, Ross MA, Zegarra V, Sysko LR, Watkins SC, Stolz DB. Sinusoidal ultrastructure evaluated during the revascular iza- tion of regenerating rat liver. Hepatology. 2001;33:363–78.

63. Nagasue N, Yukaya H, Ogawa Y, Kohno H, Nakamura T. Human liver regeneration after major hepatic resection. A study of normal liver and livers with chronic hepatitis and cirrhosis. Ann Surg. 1987;206:30–9.

64. Panis Y, McMullan DM, Emond JC. Progressive necrosis after hepatectomy and the pathophysiology of liver failure after massive resection. Surgery. 1997;121:142–9.

65. Oussoultzoglou E, Jaeck D, Addeo P, Fuchshuber P, Marzano E, Rosso E, Pessaux P, Bachellier P. Prediction of mortality rate after major hepatectomy in patients without cirrhosis. Arch Surg. 2010;145:1075–81.

66. Maeda Y, Nishida M, Takao T, Mori N, Tamesa T, Tangoku A, Oka M. Risk factors for postoperative liver failure after hepatec- tomy for hepatocellular carcinoma. Hepatogastroenterology. 2004;51:1792–6.

67. Osada S, Saji S. The clinical significance of monitoring alkaline phosphatase level to estimate postoperative liver failure after hep- atectomy. Hepatogastroenterology. 2004;51:1434–8.

68. Nanashima A, Tobinaga S, Abo T, Nonaka T, Takeshita H, Hidaka S, Sawai T, Nagayasu T. Reducing the incidence of post- hepatectomy hepatic complications by preoperatively applying parameters predictive of liver function. J Hepatobiliary Pancreat Sci. 2010;17:871–8.

69. Reissfelder C, Rahbari NN, Koch M, Kofler B, Sutedja N, Elbers H, Buchler MW, Weitz J. Postoperative course and clinical signif- icance of biochemical blood tests following hepatic resection. Br J Surg. 2011;98:836–44.

70. Du ZG, Wei YG, Chen KF, Li B. An accurate predictor of liver failure and death after hepatectomy: a single institution's experi- ence with 478 consecutive cases. World J Gastroenterol. 2014;20: 274–81.

71. Hotta T, Kobayashi Y, Taniguchi K, Johata K, Sahara M, Ochiai M, Watanabe T, Tanimura H. Liver functional analysis by total bile acid level of C-tube bile after hepatectomy. Hepatogastroenterology. 2005;52:1211–5.

72. Yokoyama Y, Ebata T, Igami T, Sugawara G, Ando M, Nagino M. Predictive power of prothrombin time and serum total bilirubin for postoperative mortality after major hepatectomy with extrahepatic bile duct resection. Surgery. 2014;155:504–11.

73. Ercolani G, Grazi GL, Calliva R, Pierangeli F, Cescon M, Cavallari A, Mazziotti A. The lidocaine (MEGX) test as an index of hepatic function: its clinical usefulness in liver surgery. Surgery. 2000;127:464–71.

74. Delis SG, Bakoyiannis A, Dervenis C, Tassopoulos N. Perioperative risk assessment for hepatocellular carcinoma by using the MELD score. J Gastrointest Surg. 2009;13:2268–75.

75. Huang L, Li J, Yan JJ, Liu CF, Wu MC, Yan YQ. Prealbumin is predictive for postoperative liver insufficiency in patients under- going liver resection. World J Gastroenterol. 2012;18:7021–5.

76. Huo TI, Lui WY, Wu JC, Huang YH, King KL, Loong CC, Lee PC, Chang FY, Lee SD. Deterioration of hepatic functional reserve in patients with hepatocellular carcinoma after resection: inci- dence, risk factors, and association with intrahepatic tumor recur- rence. World J Surg. 2004;28:258–62.

77. Wang Q, Lau WY, Zhang B, Zhang Z, Huang Z, Luo H, Chen X. Preoperative total cholesterol predicts postoperative outcomes af- ter partial hepatectomy in patients with chronic hepatitis B- or C- related hepatocellular carcinoma. Surgery. 2014;155:263–70.

78. Cucchetti A, Ercolani G, Cescon M, Ravaioli M, Zanello M, Del Gaudio M, Lauro A, Vivarelli M, Grazi GL, Pinna AD. Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease. J Am Coll Surg. 2006;203:670–6.

79. Rahbari NN, Reissfelder C, Koch M, Elbers H, Striebel F, Buchler MW, Weitz J. The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. Ann Surg Oncol. 2011;18:3640–9.

80. Hyder O, Pulitano C, Firoozmand A, Dodson R, Wolfgang CL, Choti MA, Aldrighetti L, Pawlik TM. A risk model to predict 90- day mortality among patients undergoing hepatic resection. J Am Coll Surg. 2013;216:1049–56.

81. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, Plevak DJ, Talwalkar JA, Kim WR, Kamath PS. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology. 2007;132:1261–9.

82. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR. Indocyanine green clearance as a predictor of successful he- patic resection in cirrhotic patients. Am J Surg. 1992;163:515–8.

83. Nonami T, Nakao A, Kurokawa T, Inagaki H, Matsushita Y, Sakamoto J, Takagi H. Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. Hepatogastroenterology. 1999;46:1669–72.

84. de Liguori Carino N, O'Reilly DA, Dajani K, Ghaneh P, Poston GJ, Wu AV. Perioperative use of the LiMON method of indocya- nine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure. Eur J Surg Oncol. 2009;35:957–62.

85. Ohwada S, Kawate S, Hamada K, Yamada T, Sunose Y, Tsutsumi H, Tago K, Okabe T. Perioperative real-time monitoring of indo- cyanine green clearance by pulse spectrophotometry predicts rem- nant liver functional reserve in resection of hepatocellular carci- noma. Br J Surg. 2006;93:339–46.

86. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. Br J Surg. 2010;97:1260–8.

87. Derpapas MK, Contis J, Fragulidis GP, Lykoudis PM, Polymeneas G, Ntourakis S, Voros D. Correlation of the ICG test with risk factors and postoperative outcomes following hepatic resection. J buon. 2013;18:703–7.

88. Scheingraber S, Richter S, Igna D, Flesch S, Kopp B, Schilling MK. Indocyanine green disappearance rate is the most useful marker for liver resection. Hepatogastroenterology. 2008;55: 1394–9.

89. Tralhao JG, Hoti E, Oliveiros B, Botelho MF, Sousa FC. Study of perioperative liver function by dynamic monitoring of ICG-clear- ance. Hepatogastroenterology. 2012;59:1179–83.

90. Okochi O, Kaneko T, Sugimoto H, Inoue S, Takeda S, Nakao A. ICG pulse spectrophotometry for perioperative liver function in hepatectomy. J Surg Res. 2002;103:109–13.

91. Fan ST. Liver functional reserve estimation: state of the art and relevance for local treatments: the Eastern perspective. J Hepatobiliary Pancreat Sci. 2010;17:380–4.

92. Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, Fleig WE, Dollinger MM. Incorporating indocyanin green clearance into the Model for End Stage Liver Disease (MELD-ICG) improves prognostic accuracy in interme- diate to advanced cirrhosis. Gut. 2010;59:963–8.

93. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg. 1995;130:198–203.

94. Lam CM, Fan ST, Lo CM, Wong J. Major hepatectomy for hepa- tocellular carcinoma in patients with an unsatisfactory indocya- nine green clearance test. Br J Surg. 1999;86:1012–7.

95. Zoedler T, Ebener C, Becker H, Roeher HD. Evaluation of liver function tests to predict operative risk in liver surgery. HPB Surg. 1995;9:13–8.

96. Fan ST, Wang QS, Lo CM, Tam Yu KW, Lai EC, Wong J. Evaluation of indocyanine green retention and aminopyrine breath tests in patients with malignant biliary obstruction. Aust N Z J Surg. 1994;64:759–62.

97. Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci. 1961;21:43–57.

98. Shirin H, Aeed H, Shalev T, Sorin V, Stavinski S, Shahmurov M, Ilan Y, Avni Y. Utility of a 13C-methacetin breath test in evaluating hepatic injury in rats. J Gastroenterol Hepatol. 2008;23:1762–8.

99. Yachida S, Wakabayashi H, Kokudo Y, Goda F, Okada S, Maeba T, Maeta H. Measurement of serum hyaluronate as a predictor of human liver failure after major hepatectomy. World J Surg. 2000;24:359–64.

100. Kubo S, Tsukamoto T, Hirohashi K, Tanaka H, Shuto T, Takemura S, Yamamoto T, Uenishi T, Ogawa M, Kinoshita H. Correlation between preoperative serum concentration of type IV collagen 7s domain and hepatic failure following resection of hepatocellular carcinoma. Ann Surg. 2004;239:186–93.

101. Kiuchi T, Ozawa K, Yamamoto Y, Takayasu T, Maki A, Shimahara Y, Mori K, Kobayashi N, Yamaoka Y, Kumada K. Changes in arterial ketone body ratio in the phase immediately after hepatectomy. Prognostic implications. Arch Surg. 1990;125: 655–9.

102. Yoshida M, Shiraishi S, Sakaguchi F, Utsunomiya D, Tashiro K, Tomiguchi S, Okabe H, Beppu T, Baba H, Yamashita Y. Fused 99m-Tc-GSA SPECT/CT imaging for the preoperative evaluation of postoperative liver function: can the liver uptake index predict postoperative hepatic functional reserve? Jpn J Radiol. 2012;30: 255–62.

103. Katsuramaki T, Fujimori K, Furuhata T, Kimura Y, Meguro M, Nagayama M, Honma T, Mukaiya M, Hareyama M, Hirata K. Preoperative estimation of risk in hepatectomy using technetium- 99m-

galactosyl human serum albumin receptor amount by nonlin- ear 3-compartment model. Hepatogastroenterology. 2003;50:174– 7.

104. Kwon AH, Matsui Y, Kaibori M, Ha-Kawa SK. Preoperative re- gional maximal removal rate of technetium-99m-galactosyl hu- man serum albumin (GSA-Rmax) is useful for judging the safety of hepatic resection. Surgery. 2006;140:379–86.

105. Kokudo N, Vera DR, Tada K, Koizumi M, Seki M, Matsubara T, Ohta H, Yamaguchi T, Takahashi T, Nakajima T, Muto T. Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. World J Surg. 2002;26:1342–7.

106. Kaibori M, Ha-Kawa SK, Ishizaki M, Matsui K, Saito T, Kwon AH, Kamiyama Y. HA/GSA-Rmax ratio as a predictor of postop- erative liver failure. World J Surg. 2008;32:2410–8.

107. Thian YL, Riddell AM, Koh DM. Liver-specific agents for contrast-enhanced MRI: role in oncological imaging. Cancer Imaging. 2013;13:567–79.

108. Wibmer A, Prusa AM, Nolz R, Gruenberger T, Schindl M, Ba- Ssalamah A. Liver failure after major liver resection: risk assess- ment by using preoperative Gadoxetic acid-enhanced 3-T MR imaging. Radiology. 2013;269:777–86.

109. Tsuboyama T, Onishi H, Kim T, Akita H, Hori M, Tatsumi M, Nakamoto A, Nagano H, Matsuura N, Wakasa K, Tomoda K. Hepatocellular carcinoma: hepatocyte-selective enhancement at gadoxetic acid-enhanced MR imaging–correlation with expres- sion of sinusoidal and canalicular transporters and bile accumula- tion. Radiology. 2010;255:824–33.

110. D'Onofrio M, De Robertis R, Demozzi E, Crosara S, Canestrini S, Pozzi Mucelli R. Liver volumetry: Is imaging reliable? Personal experience and review of the literature. World J Radiol. 2014;6: 62–71.

111. Kitajima K, Taboury J, Boleslawski E, Savier E, Vaillant JC, Hannoun L. Sonographic preoperative assessment of liver volume before major liver resection. Gastroenterol Clin Biol. 2008;32: 382–9.

112. Xu HX, Yin XY, Lu MD, Liu GJ, Xu ZF. Estimation of liver tumor volume using a three-dimensional ultrasound volumetric system. Ultrasound Med Biol. 2003;29:839–46.

113. Ulla M, Ardiles V, Levy-Yeyati E, Alvarez FA, Spina JC, Garcia- Monaco RD, De Santibanes E. New surgical strategy to induce liver hypertrophy: role of MDCT-volumetry to monitor and pre- dict liver growth. Hepatogastroenterology. 2013;60:337–42.

114. Yamanaka N, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E, Tanaka T, Tomoda F. A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. Ann Surg. 1994;219:342–6.

115. Uchiyama K, Mori K, Tabuse K, Ueno M, Ozawa S, Nakase T, Kawai M, Tani M, Tanimura H, Yamaue H. Assessment of liver function for successful hepatectomy in patients with hepatocellular carcinoma with impaired hepatic function. J Hepatobiliary Pancreat Surg. 2008;15:596–602.

116. Du ZG, Li B, Wei YG, Yin J, Feng X, Chen X. A new scoring system for assessment of liver function after successful hepatecto- my in patients with hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2011;10:265–9.

117. Ribero D, Chun YS, Vauthey JN. Standardized liver volumetry for portal vein embolization. Semin Intervent Radiol. 2008;25:104–9.

118. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, Hicks M, Alsfasser G, Lauwers G, Hawkins IF, Caridi J. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clini- cal associations. Surgery. 2000;127:512–9.

119. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13:1271–80.

120. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg. 2007;94:1386–94.

121. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, Curley SA, Vauthey JN. Three hundred and one consecutive ex- tended right hepatectomies: evaluation of outcome based on sys- tematic liver volumetry. Ann Surg. 2009;250:540–8.

122. Skrzypczyk C, Truant S, Duhamel A, Langlois C, Boleslawski E, Koriche D, Hebbar M, Fourrier F, Mathurin P, Pruvot FR. Relevance of the ISGLS definition of posthepatectomy liver fail- ure in early prediction of poor outcome after liver resection: study on 680 hepatectomies. Ann Surg. 2014;260:865–70; discussion 70.

123. McCormack L, Petrowsky H, Jochum W, Furrer K, Clavien PA. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case–control study. Ann Surg. 2007;245:923–30.

124. Roberts KJ, Bharathy KG, Lodge JP. Kinetics of liver function tests after a hepatectomy for colorectal liver metastases predict post-operative liver failure as defined by the International Study Group for Liver Surgery. HPB (Oxford). 2013;15:345–51.

125. Yigitler C, Farges O, Kianmanesh R, Regimbeau JM, Abdalla EK, Belghiti J. The small remnant liver after major liver resection: how common and how relevant? Liver Transpl. 2003;9:S18-25.

126. Hemming AW, Reed AI, Howard RJ, Fujita S, Hochwald SN, Caridi JG, Hawkins IF, Vauthey JN. Preoperative portal vein em- bolization for extended hepatectomy. Ann Surg. 2003;237:686– 91; discussion 91–3.

127. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S. Preoperative portal vein embolization for hepatocellular carci- noma. World J Surg. 1986;10:803–8.

128. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, Yamazaki S, Hasegawa H, Ozaki H. Preoperative por- tal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery. 1990;107:521– 7.

129. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N, Jiao LR. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg. 2008;247:49–57.

130. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two- stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg. 2000;232:777–85.

131. Tsai S, Marques HP, de Jong MC, Mira P, Ribeiro V, Choti MA, Schulick RD, Barroso E, Pawlik TM. Two-stage strategy for pa- tients with extensive bilateral colorectal liver metastases. HPB (Oxford). 2010;12:262–9.

132. Pandanaboyana S, Bell R, Hidalgo E, Toogood G, Prasad KR, Bartlett A, Lodge JP. A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. Surgery. 2015;157:690–8.

133. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Horbelt R, Kroemer A, Loss M, Rummele P, Scherer MN, Padberg W, Konigsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255:405–14.

134. Zhang GQ, Zhang ZW, Lau WY, Chen XP. Associating liver par- tition and portal vein ligation for staged hepatectomy (ALPPS): a new strategy to increase resectability in liver surgery. Int J Surg. 2014;12:437–41.

135. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369: 2525–34.

136. Singanayagam A, Bernal W. Update on acute liver failure. Curr Opin Crit Care. 2015;21:134–41.

137. Chiu A, Chan LM, Fan ST. Molecular adsorbent recirculating system treatment for patients with liver failure: the Hong Kong experience. Liver Int. 2006;26:695–702.

138. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350–electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Intern Med. 2014;174:1727–33.

139. Mas A, Rodes J, Sunyer L, Rodrigo L, Planas R, Vargas V, Castells L, Rodriguez-Martinez D, Fernandez-Rodriguez C, Coll I, Pardo A, Spanish Association for the Study of the Liver Hepatic Encephalopathy Cooperative G. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol. 2003;38:51–8.

140. Leithead JA, Ferguson JW, Bates CM, Davidson JS, Lee A, Bathgate AJ, Hayes PC, Simpson KJ. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. Gut. 2009;58: 443–9.

141. Jin S, Fu Q, Wuyun G, Wuyun T. Management of post- hepatectomy complications. World J Gastroenterol. 2013;19: 7983–91.

142. Gill RQ, Sterling RK. Acute liver failure. J Clin Gastroenterol. 2001;33:191–8.

143. Yadav K, Shrikhande S, Goel M. Post hepatectomy liver failure: concept of management. J Gastrointest Cancer. 2014;45:405–13.

144. Steiner C, Mitzner S. Experiences with MARS liver support ther- apy in liver failure: analysis of 176 patients of the International MARS Registry. Liver. 2002;22 Suppl 2:20–5.

145. van de Kerkhove MP, de Jong KP, Rijken AM, de Pont AC, van Gulik TM. MARS treatment in post-hepatectomy liver failure. Liver Int. 2003;23 Suppl 3:44–51.

146. Rittler P, Ketscher C, Inthorn D, Jauch KW, Hartl WH. Use of the molecular adsorbent recycling system in the treatment of postop- erative hepatic failure and septic multiple organ dysfunction–pre- liminary results. Liver Int. 2004;24:136–41.

147. Chan SC, Sharr WW, Chan AC, Chok KS, Lo CM. Rescue Living-donor Liver Transplantation for Liver Failure Following Hepatectomy for Hepatocellular Carcinoma. Liver Cancer. 2013;2:332–7.

148. Otsuka Y, Duffy JP, Saab S, Farmer DG, Ghobrial RM, Hiatt JR, Busuttil RW. Postresection hepatic failure: successful treatment with liver transplantation. Liver Transpl. 2007;13:672–9.

149. Nanashima A, Abo T, Arai J, Matsumoto H, Kudo T, Nagayasu T. Functional liver reserve parameters predictive for posthepatectomy complications. J Surg Res. 2013;185:127–35.

150. Kim SH, Kang DR, Lee JG, Kim do Y, Ahn SH, Han KH, Chon CY, Kim KS. Early predictor of mortality due to irreversible posthepatectomy liver failure in patients with hepatocellular car- cinoma. World J Surg. 2013;37:1028–33.

CHAPTER 3

Survival after Resection of Perihilar Cholangiocarcinoma in Patients with Lymph Node Metastases

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Abstract

Introduction: The aim of this study was to compare patients with PHC with lymph node metastases (LN+) who underwent a resection with patients who did not undergo resection because of locally advanced disease at exploratory laparotomy.

Methods: Consecutive LN+ patients who underwent a resection for PHC in 12 centers were compared with patients who did not undergo resection because of locally advanced disease at exploratory laparotomy in 2 centers.

Results: In the resected cohort of 119 patients, the median overall survival (OS) was 19 months and the estimated 1-, 3- and 5-year OS was 69%, 27% and 13%, respectively. In the non-resected cohort of 113 patients, median OS was 12 months and the estimated 1-, 3- and 5-year OS was 49%, 7%, and 3%, respectively. OS was better in the resected LN+ cohort ($p<0.001$). Positive resection margin (hazard ratio [HR]:1.54; 95%CI:0.97-2.45) and lymphovascular invasion (LVI) (HR:1.71; 95%CI:1.09-2.69) were independent poor prognostic factors in the resected cohort.

Conclusion: Patients with PHC who underwent a resection for LN+ disease had better OS than patients who did not undergo resection because of locally advanced disease at exploratory laparotomy. LN+ PHC does not preclude 5-year survival after resection.

Introduction

Perihilar cholangiocarcinoma (PHC) is the most common bile duct cancer, with an annual incidence in Western countries of around 2 per 100,000.[1,2] Patients usually present with obstructive jaundice, abdominal pain, and weight loss [2,3]. Surgical resection is the only potentially curative option for patients with PHC, resulting in a median overall survival (OS) of about 35-40 months.[4-7] At diagnosis, however, most patients are ineligible for resection because of locally advanced or metastatic disease.[8-10] Resection typically involves a right or left (extended) hemihepatectomy with an extrahepatic bile duct resection.[2] These extensive operations have considerable major postoperative morbidity and mortality of 5 to 15% in Western centers.[11,12] Patient selection is paramount to make a trade-off between the potential improved OS and quality of life (QoL) after surgery versus the substantial postoperative morbidity and mortality.

Lymph node metastases (LN+) have been reported to be the major determinant of OS.[2,13,14] In a recent study conducted in a large international cohort, patients with lymph node metastases had an estimated 100% chance of recurrence.[15] However, resection of LN+ PHC may still improve life expectancy. The aim of this multi-institutional study was to compare survival of patients with PHC with LN+ who underwent a resection with patients who did not undergo resection because of locally advanced disease at exploratory laparotomy.

Methods

In this retrospective analysis, the resected cohort consisted of patients with PHC and LN+ who underwent curative-intent surgical resection between January 1, 2000, and December 31, 2014 at one of twelve academic institutions in the United States and Western Europe (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina; Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands; Academic Medical Center, Amsterdam, the Netherlands). The non-resected cohort consisted of patients who did not undergo resection because of locally advanced disease at exploratory laparotomy from two centers (Academic Medical Center, Amsterdam, the Netherlands, and Erasmus MC University Medical Center, Rotterdam, the Netherlands). Patients with locally advanced disease

at exploratory laparotomy were found to have vascular or biliary involvement precluding a complete resection with adequate liver remnant or had lymph node metastases (N1 or N2). When the reason for discontinuation of the resection was suspicion of extensive lymph node metastases, frozen analysis was conducted to confirm the suspicion. In both cohorts, patients were excluded if they had an Eastern Cooperative Oncology Group performance status 3 or 4 at presentation, distant metastases (M1) on preoperative imaging, at staging laparoscopy, or laparotomy.

Sociodemographic and clinicopathologic data were collected, including age and sex, as well as tumor size, tumor stage, presence of nodal disease, final resection margin, and the presence of lymphovascular invasion (LVI). A major hepatectomy was defined as a hepatic resection of more than 3 Couinaud segments. According to the American Joint Committee on Cancer (AJCC) 7th edition staging, involvement of lymph nodes within the hepatoduodenal ligament was classified as N1, and lymph node involvement beyond the hepatoduodenal ligament (i.e. along the common hepatic artery and celiac trunc) as N2.[16,17] Margin status was categorized as R0 for a negative transection margin, R1 when the margin was microscopically positive, and R2 when the margin was macroscopically positive. For the patients who underwent surgical resection, postoperative complications occurring within 30 days after surgery, during index admission, or during readmission within 30 days after discharge were recorded. 90-day postoperative mortality was registered. The severity of postoperative complications was scored according to the Clavien-Dindo classification.[18] Severe postoperative complications were defined as those with a Clavien-Dindo Grade IIIa or higher (i.e. requiring re-intervention). The respective institutional review boards of each participating institution approved this study.

Statistical analysis

Categorical variables were described as whole numbers and percentages, while continuous variables were reported as medians with interquartile range (IQR). Percentages for each variable were calculated based on available data, excluding missing values. Univariable comparison of categorical variables was performed using the Pearson chi-square test. Univariable comparison of continuous variables was performed using the Mann-Whitney U-test. The primary outcome of the study was OS. OS was calculated from the date of operation to the date of death or last follow-up and estimated using the Kaplan-Meier method. Last follow-up was defined as the last contact with the treating institution. Univariate and multivariable hazard ratios were calculated using the Cox proportional hazards method.

Risk factors were included in the multivariable model if the p-value was below 0.10 in univariate analysis. All tests were 2-sided and $p < 0.05$ defined statistical significance. All analyses were performed using SPSS 22.0 (IBM, New York).

Results

Demographic and Clinicopathologic Characteristics

The resected cohort included 119 LN+ PHC patients who underwent a curative intent resection. The non-resected cohort included 113 patients who did not undergo resection because of locally advanced disease at exploratory laparotomy. The reason for aborting the procedure was the extent of LN+ in 49 patients (43%). In 64 patients, the extent of vascular and or biliary involvement precluded surgery. The two cohorts are compared in Table 1. Table 2 presents resection characteristics of the resection cohort only. A notable difference between the resected cohort and the non-resected patients was observed in the administration of chemotherapy. In the resected cohort, 56 patients (49%) went on to have adjuvant chemotherapy, whereas in the non-resected cohort only 8 patients (7%) received chemotherapy.

Table 1. Characteristics of the Treatment Groups

Variable	Lymph-Node Positive Resection (n = 119)	Non-Resected Patients (n = 113)	*P-value*
Female Gender	42 (35)	38 (34)	0.790
Age, years	65 (55-72)	65 (55-70)	0.593
BMI, kg/m²	25 (22-28)	24 (22-27)	0.054
Clinical Jaundice at Presentation	99 (85)	89 (81)	0.373
Bismuth Classification on imaging			
I	5 (5)	12 (11)	0.318
II	14 (13)	10 (9)	
IIIA	35 (32)	28 (25)	
IIIB	26 (24)	30 (27)	
IV	30 (27)	33 (29)	
Vascular Involvement (hepatic artery or portal vein, on imaging)	57 (56)	76 (69)	0.057
N2 Lymph Node Metastases, pathologically confirmed	9 (8)	7 (12)	0.364

Table 2. Resection Details and Postoperative Course After Lymph-Node Positive Resection

Variable	Lymph-Node Positive Resection (n = 119)
ASA	
I	10 (8)
II	41 (43)
III	42 (44)
IV	3 (3)
Drainage Preoperative	
None	23 (19)
Percutaneous	45 (38)
Endoscopic	22 (19)
Both	29 (24)
AJCC pT-stage	
pT1-pT2	61 (60)
pT3-pT4	40 (40)
Type of Resection	
Minor hepatectomy (< 3 Couinaud Segments)	18 (15)
Major hepatectomy (≥ 3 Couinaud Segments)	100 (85)
Margin Status	
R0	76 (64)
R1	42 (36)
Tumor Size	
≤ 2.5 cm	65 (69)
> 2.5 cm	29 (31)
Any complication	87 (75)
Clavien Dindo Grade	
I-II	32 (37)
III-V	55 (63)
Length of Stay (days)	12 (8-19)
Readmission within 30 days	16 (27)
Postoperative 90-day mortality	8 (7)
Adjuvant Therapy	
Adjuvant Chemotherapy	56 (49)
Adjuvant Radiotherapy	37 (34)

Factors Associated with Overall Survival

Ninety-day postoperative mortality in the resected cohort was 7% (n = 8), which did not differ significantly from the ninety-day mortality in the non-resected patients (n = 15, 13%; p = 0.09). In the resected cohort, the median OS was 19.2 months and the estimated 1-, 3- and 5-year OS was 69%, 27% and 13%, respectively. Only 7 patients were alive at last follow-up with a median follow-up of 60 months. Three out of 7 patients (43%) were alive with recurrent disease, while 4 patients had no evidence of disease at a follow-up of 62, 68, 76, and 98 months. In the non-resected cohort, the median OS was 12 months and the estimated 1-, 3- and 5-year OS was 49%, 7%, and 3%, respectively, which was significantly worse compared with the resected cohort (p < 0.001; figure 1).

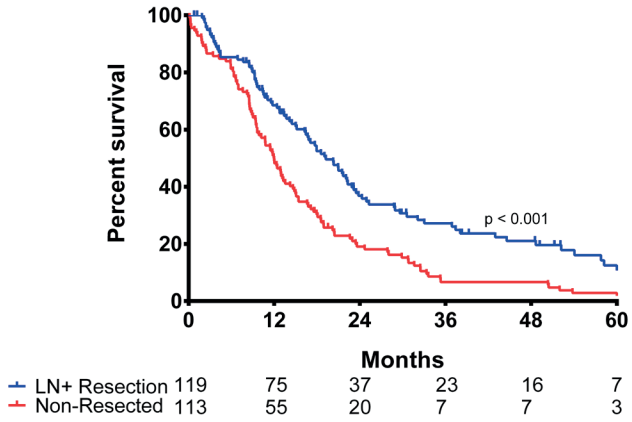

Figure 1. Overall survival stratified for treatment group (p < 0.001)

In Cox regression analyses, several patient and disease specific characteristics were assessed for their correlation with OS in the resected LN+ cohort (Table 3). Positive margin and LVI were associated with OS in univariate analysis, and remained associated with OS in multivariable analysis (HR 1.54, 95%CI 0.97 – 2.45, p = 0.067; HR 1.71, 95%CI 1.09 – 2.69, p = 0.019). When patients with R1 resection margins were compared with the non-resected patients, no difference in median OS was found (17 months vs. 12 months; p = 0.086; figure 2). Median OS was also comparable between resected patients with LVI and non-resected patients (16 months vs. 12 months; p = 0.073; figure 3).

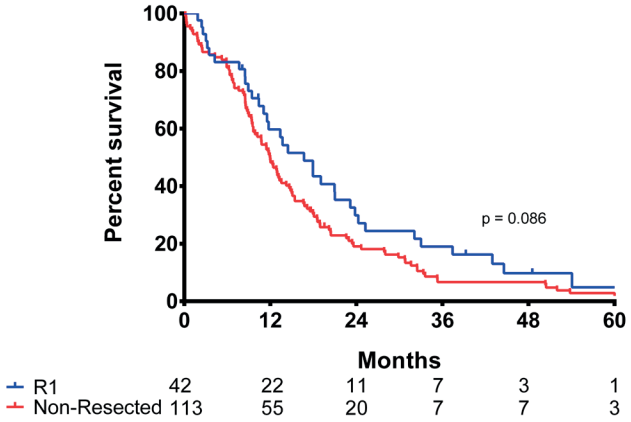

Figure 2. Overall Survival of Resected R1 Patients versus Non-Resected Patients (p = 0.086)

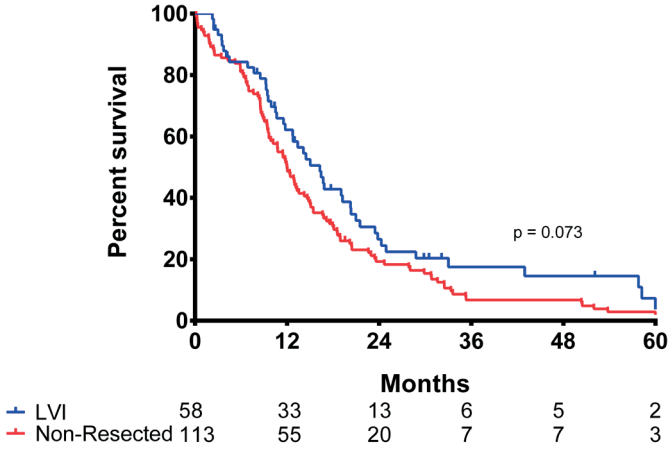

Figure 3. Overall Survival of Resected Lymphovascular Invasion Patients versus Non-Resected Patients (p = 0.073)

Table 3. Univariable and Multivariable Proportional Hazards Regression Models in Patients with LN+ Disease Undergoing Resection.

	Univariable Analysis			Multivariable Analysis		
Variable Name	HR	95%CI	P-value	HR	95%CI	P-value
Sex (male)	1.01	0.66-1.55	0.959			
Age	1.01	0.99-1.02	0.595			
BMI	0.99	0.95-1.04	0.729			
Clinical Jaundice	1.29	0.70-2.38	0.410			
ASA						
I-II	Ref	-	-			
III-IV	0.90	0.50-1.62	0.731			
Drainage Preoperative						
None	Ref	-	-			
Endoscopic	0.97	0.54-1.72	0.905			
Percutaneous	1.52	0.79-2.90	0.208			
Both	1.17	0.63-2.20	0.618			
Major Resection (≥3 segments)	1.22	0.69-2.16	0.503			
Margin Status						
R0	Ref.	-	-	Ref	-	-
R1	1.48	0.96-2.27	0.075	1.54	0.97-2.45	0.067
N2 Lymph Node metastases	0.83	0.36-1.90	0.653			
Tumor size (mm)	1.00	0.99-1.02	0.804			
Bismuth Classification						
I	Ref.	-	-			
II	0.56	0.17-1.82	0.332			
IIIA	1.13	0.40-3.25	0.816			
IIIB	0.91	0.31-2.68	0.862			
IV	0.94	0.33-2.69	0.906			
AJCC T-stage						
T1-T2	Ref.	-	-			
T3-T4	1.45	0.78-2.67	0.238			
Lymphovascular Invasion	1.64	1.05-2.58	0.030	1.71	1.09-2.69	0.019
Adjuvant Chemotherapy	1.08	0.70-1.66	0.725			
Adjuvant Radiotherapy	1.04	0.67-1.63	0.856			

Discussion

In an international cohort of 12 centers, LN+ patients had a median OS of 19 months after resection of PHC. These data confirm that LN+ PHC has a poor prognosis.[2,13-15] However, resection of LN+ PHC did not preclude 5-year OS (13%). A recent study reported that LN+ disease is virtually incurable, with an estimated disease-free survival of 0% after seven years.[15] In the current study, 7 patients who were alive at last follow-up were identified, of whom 4 had no evidence of disease after more than 5 years follow-up.

OS after resection for LN+ PHC compared favorably with a 12 months median OS in patients who did not undergo resection because of locally advanced disease at exploratory laparotomy. Patients who underwent exploratory laparotomy were chosen, because of their relative comparability to the resected cohort. In contrast, median OS for non-operated patients has been reported as less than 6 months.[19] These patients were found to have vascular or biliary involvement precluding a complete resection with adequate liver remnant or had positive lymph nodes (N1 or N2). The difference of 7 months between the resected and the non-resected cohorts may be attributable to both the resection in the resection cohort and more advanced disease in the non-resected cohort. Therefore, the actual benefit of resection for LN+ PHC patients is likely smaller than 7 months.

The potential survival benefit of surgery must be weighed against the potential harm of surgery with a mortality of 5 to 15% in published Western series.[11,12] A risk score by Wiggers et al. identified a high-risk subgroup of PHC patients with a 37% postoperative mortality risk based on age, preoperative cholangitis, future liver remnant, portal vein reconstruction, and incomplete drainage of the future liver remnant.[20]

Recent advances in imaging techniques have made it possible to identify lymph node metastases preoperatively with an acceptable accuracy, with a positive predictive value of 80% and a negative predictive value of 84% using computed tomography and a short axis diameter of 10 mm.[21,22] EUS/FNA can confirm nodal metastases in suspicious lymph nodes on imaging. This is recommended in most patients for N2 nodes (beyond the hepatoduodenal ligament, stage IVb) because of poor prognosis after resection. Biopsy of N1 nodes should be considered in patients with a high postoperative mortality risk because of advanced age (>70 years), small future liver remnant (<30%), or preoperative cholangitis. When positive N2 nodes are found during exploratory laparotomy the surgeon should also consider to withhold resection. In addition, withholding resection

can be considered in high-risk patients with positive N1 nodes during exploratory laparotomy; the small potential survival benefit of resection may not justify the risk of surgery.

In addition to the above, LVI and positive resection margin were independent poor prognostic factors after resection of LN+ PHC. Both LVI and R1 resection have previously been identified as poor prognostic factors after PHC resection.[14,23] Unfortunately, LVI and margin status are more difficult to guide decision making because they are typically known only after resection.

Patients in the resected cohort were much more likely to receive postoperative chemotherapy than patients in the non-resected cohort. The explanation for this difference is likely a combination of better postoperative performance status after resection and the willingness of both patients and physicians to administer adjuvant chemotherapy. This is contrary to phase III trials that support palliative chemotherapy more than adjuvant chemotherapy.[24,25]

This study has several limitations. Because of the retrospective nature of the study, the two cohorts differed in baseline tumor characteristics and the actual difference in OS between the resected and the non-resected cohort may be smaller than 7 months. Secondly, work-up and decision-making differed across centers and over time. Finally, because of the small sample size of N2 disease in the observed cohort, definitive conclusions could not be drawn in the present study. The preoperative decision to perform an exploratory laparotomy and the intraoperative decision to perform or withhold a resection are influenced by many known and unknown factors. However, the presented data from 12 centers may be some of the best available data to guide decision making for patients with LN+ PHC.

In conclusion, patients with PHC who underwent a resection for LN+ disease had better OS than patients who did not undergo resection because of locally advanced disease at exploratory laparotomy. The actual benefit of resection in patients with LN+ PHC may be smaller than 7 months and should be weighed against considerable postoperative morbidity and mortality.

References

1. Hartog H, Ijzermans JN, van Gulik TM, Groot Koerkamp B. Resection of Perihilar Cholangiocarcinoma. *Surg Clin North Am* 2016; **96**(2): 247-67.
2. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. *J Surg Oncol* 2014; **110**(5): 585-91.
3. Jarnagin W, Winston C. Hilar cholangiocarcinoma: diagnosis and staging. *HPB (Oxford)* 2005; **7**(4): 244-51.
4. Pichlmayr R, Lamesch P, Weimann A, Tusch G, Ringe B. Surgical treatment of cholangiocellular carcinoma. *World J Surg* 1995; **19**(1): 83-8.
5. Matsuo K, Rocha FG, Ito K, et al. The blumgart preoperative staging system for hilar cholangiocarcinoma: Analysis of resectability and outcomes in 380 patients. *J Am Coll Surg* 2012; **215**(3): 343-55.
6. Groot Koerkamp B, Wiggers JK, Allen PJ, et al. American Joint Committee on Cancer staging for resected perihilar cholangiocarcinoma: a comparison of the 6th and 7th editions. *HPB (Oxford)* 2014; **16**(12): 1074-82.
7. Igami T, Nishio H, Ebata T, et al. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. *J Hepatobiliary Pancreat Sci* 2010; **17**(4): 449-54.
8. Dodson RM, Weiss MJ, Cosgrove D, et al. Intrahepatic cholangiocarcinoma: management options and emerging therapies. *J Am Coll Surg* 2013; **217**(4): 736-50 e4.
9. Brito AF, Abrantes AM, Encarnacao JC, Tralhao JG, Botelho MF. Cholangiocarcinoma: from molecular biology to treatment. *Med Oncol* 2015; **32**(11): 245.
10. Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; **383**(9935): 2168-79.
11. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)* 2013; **15**(7): 492-503.
12. Lafaro K, Buettner S, Maqsood H, et al. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? *J Gastrointest Surg* 2015; **19**(11): 2079-92.
13. Buettner S, van Vugt JL, Gani F, et al. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. *J Gastrointest Surg* 2016.
14. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.
15. Groot Koerkamp B, Wiggers JK, Allen PJ, et al. Recurrence Rate and Pattern of Perihilar Cholangiocarcinoma after Curative Intent Resection. *J Am Coll Surg* 2015; **221**(6): 1041-9.
16. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. Chicago, IL: Springer; 2009.
17. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975; **140**(2): 170-8.
18. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**(2): 187-96.

19. Chaiteerakij R, Harmsen WS, Marrero CR, et al. A new clinically based staging system for perihilar cholangiocarcinoma. *Am J Gastroenterol* 2014; **109**(12): 1881-90.

20. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. *J Am Coll Surg* 2016; **223**(2): 321-31 e1.

21. Lee HY, Kim SH, Lee JM, et al. Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. *Radiology* 2006; **239**(1): 113-21.

22. Engelbrecht MR, Katz SS, van Gulik TM, Lameris JS, van Delden OM. Imaging of perihilar cholangiocarcinoma. *AJR Am J Roentgenol* 2015; **204**(4): 782-91.

23. Soares KC, Kamel I, Cosgrove DP, Herman JM, Pawlik TM. Hilar cholangiocarcinoma: diagnosis, treatment options, and management. *Hepatobiliary Surg Nutr* 2014; **3**(1): 18-34.

24. Stein A, Arnold D, Bridgewater J, et al. Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 trial) - a randomized, multidisciplinary, multinational phase III trial. *BMC Cancer* 2015; **15**(1): 564.

25. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**(14): 1273-81.

CHAPTER 4

Inclusion of Sarcopenia Outperforms the Modified Frailty Index in Predicting 1- Year Mortality among 1,326 Patients Undergoing Gastrointestinal Surgery for a Malignant Indication

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Abstract

Background: Although a useful metric for preoperative risk-stratification, frailty can be difficult to identify in patients prior to surgery. We sought to develop a preoperative frailty-risk model combining sarcopenia with clinical parameters to predict 1-year mortality using a cohort of patients undergoing gastrointestinal cancer surgery.

Methods: 1,326 patients undergoing a hepatobiliary, pancreatic or colorectal surgery between 2011 and 2014 were identified. Sarcopenia defined by psoas density was measured using preoperative cross-sectional imaging. Multivariable Cox regression analysis was performed to identify preoperative risk-factors associated with 1-year mortality and used to develop a preoperative risk-stratification score.

Results: Among all patients identified, 640 (48.3%) patients underwent pancreatic surgery, 347 (26.2%) underwent a hepatobiliary procedure and 339 (25.5%) a colorectal procedure. Using sex-specific cut-offs, 398 (30.0%) patients were categorized as sarcopenic. Sarcopenic patients were more likely to develop postoperative complications versus non-sarcopenic patients (OR=1.80, 95% CI 1.42-2.29; p<0.001). Overall 1-year mortality was 9.4%. On multivariable analysis, independent risk factors for 1-year mortality included increasing age (65-75 years: [Hazard Ratio; HR 1.81, 95%CI 1.05- 3.14) >75 years [HR 2.79, 95%CI 1.55-5.02]), preoperative anemia Hb<12.5g/dL (HR 1.68, 95%CI 1.17-2.40), and preoperative sarcopenia (HR 1.98, 95%CI 1.36-2.88 all p<0.05). Using these variables, a 28-point weighed composite score was able to stratify patient by their risk for mortality 1-year following surgery (c-statistic=0.70). The proposed score outperformed other indices of frailty including the modified Frailty Index (c-statistic=0.55) and the Eastern Cooperative Oncology Group (ECOG) performance score (c-statistic=0.57)(both p<0.05).

Conclusion: Sarcopenia was combined with clinical factors to generate a composite risk- score that can be used to identify frail patients at greatest risk for 1-year mortality following gastrointestinal cancer surgery.

Introduction

Given advances in surgical technique and medical therapy, an increasing number of patients are being considered as surgical candidates for a wide array of gastrointestinal cancers.[1-4] While perioperative mortality is relatively low, many patients are at risk for adverse postoperative outcomes due to the often complex nature of these procedures.[4- 6] Furthermore, with an estimated 70 million patients expected to be 65 years or older by 2030, preoperative risk assessment and appropriate patient selection for these complex procedures has taken on increased importance.[7] Several studies have noted that physiological, rather than chronological, age is more strongly associated with perioperative outcomes.[8-10] Specifically, the evaluation of patient frailty – a physiological syndrome characterized by a cumulative decline across multiple physiological systems – has been proposed as an important metric to assess perioperative risk.[11-14]

A standard objective assessment of frailty to measure a patient's physiological reserve can be difficult to define.[15] Frailty can be measured by combining information from a patient's medical history, physical examination and assessment of physical / functional status.[16] These proposed composite measures are, however, often time- consuming, cumbersome to record and rely on multiple subjective measurements.[17,18] For example, the Frailty Index (FI) developed by the Canadian Study of Health and Aging (CSHA) consists of a 70-item scale derived from patient history and physical examination.[19,20] A more recent modified iteration of the frailty index proposed by Obeid et al. maps 11 characteristics from the FI to data from the National Surgical Quality Improvement Program (NSQIP).[21] Other groups, including our own, have proposed the use of sarcopenia (muscle wasting) as an alternative, objective, and easy to measure marker for patient frailty.[22-25]

To date, most data on patient physiological reserve, frailty, and sarcopenia have focused exclusively on short-term outcomes.[13,14,26] Specifically, data on the use of the modified frailty index (mFI), as well as sarcopenia, to determine patient outcomes have been limited to reports on perioperative morbidity and mortality within the first 30- to 90-days following surgery.[21,23] While information on immediate short-term outcomes is important, data to predict death within 1-year of surgery are also relevant to patients and providers. Given that major gastrointestinal surgery can be associated with some degree of morbidity and loss of quality of life, accurate identification of patients who are the least likely to benefit from surgery would be valuable.[27] Therefore, the objective of the current study was to identify factors, as well as assess the prognostic accuracy of the mFI,

in predicting 1-year mortality following hepato-pancreatico-biliary and colorectal surgery. Specifically, we sought to develop a preoperative frailty-risk model using both clinical and morphometric parameters to predict 1-year outcomes of patients following major surgery.

Methods

Data Sources and Patient Population

Patients undergoing a hepatobiliary, pancreatic or colorectal resection for malignant disease between January1, 2011 and December 31, 2014 at the Johns Hopkins Hospital were identified using relevant International Classification of Disease – Clinical Modification (ICD-9-CM) procedure and diagnosis codes. Patients aged less than 18 years and patients undergoing emergent procedures were excluded from the study. For each patient record, detailed sociodemographic, clinicopathologic and laboratory data were extracted from hospital records. Specifically, sociodemographic and clinicopathologic data were collected including age, sex and race, as well as preoperative comorbidity, preoperative functional and performance status, body mass index (BMI), smoking status, procedure type, year of procedure, duration of intensive care unit (ICU) stay, length-of-stay for the index admission, and development of postoperative complications. Preoperative comorbidity was classified according to the Charlson Comorbidity Index (CCI) (CCI=0-2 and CCI≥3).[28] Functional and performance status were categorized according to the American Society of Anesthesiologists (ASA) physical classification grade and the Eastern Cooperative Oncology Group (ECOG) performance score, respectively.[29,30] To assess preoperative frailty, the mFI score was calculated for each patient using a composite score derived from 11 conditions identified by the CSHA mapped to the ACS-NSQIP database.[21] Conditions included diabetes mellitus, chronic obstructive pulmonary disease (COPD), active pneumonia infection, heart disease (defined as either a history of congestive heart failure within 30 days before surgery or a history of myocardial infarction within the 6 months preceding surgery), hypertension requiring medical treatment, peripheral vascular disease, altered sensorium, cerebrovascular disease (with and without neurological impairment) and impaired functional status.[21] Using previously described methodology, an mFI score was calculated for each patient as the proportion of the total number of conditions present from the 11 conditions that were measured.[21] For example, if a patient presented with a history of diabetes mellitus and a history of congestive heart failure within 30 days prior to surgery, their calculated mFI would be 0.18 (2 out of 11).[21] To limit spurious analysis with low numbers,

patients with a mFI>0.36 were grouped together and represented a high mFI score.[21]

Image Analysis and Calculating Sarcopenia

For all patients who met inclusion criteria, preoperative abdominal computed tomography (CT) images within 90-days of surgery were reviewed and morphometric measurements of sarcopenia, including TPA, TPV and HUAC were calculated. Using the Ultravisual software package (Merge Emageon, Birmingham, AL, USA), TPA was measured in a semi-automated fashion with a manual outlining of the psoas muscle borders at the level of the third lumbar vertebra (L3) where both iliac crests were clearly visible.[24,25] Similarly, TPV was calculated using the AW Workstation Volume Viewer Software (GE Healthcare, Little Chalfont, UK) by three manual measurements at the level of the L3 vertebra on the first image where both iliac crests are clearly visible.[22,31] To reduce potential bias due to vascular and / or fatty infiltration, all measurements were performed with a density threshold setting between -30 and 110 Hounsfield Units (HU). For greater comparability, all measurements for TPA and TPV were normalized for height calculated as (height [m] x height [m]). HUAC, a measure of muscle density and fatty infiltration, was calculated for both right and left psoas muscles using the methodology described by Joglekar et al.[23] Right and left psoas muscles were evaluated and the average psoas density was used to calculate the final HUAC: right Hounsfield unit calculation (RHUC) = (right Hounsfield unit*right psoas area) / (total psoas area); left Hounsfield unit calculation (LHUC) = (left Hounsfield unit*left psoas area) / (total psoas area); and final HUAC = (right Hounsfield unit calculation + left Hounsfield unit calculation) / 2.[23] Optimum stratification based on sensitivity analyses was performed using log-rank statistics to define the optimal sex-specific cut-offs for TPA, TPV and HUAC associated with the primary outcome of interest (1-year mortality).

Statistical Analysis

Continuous variables were reported as medians with interquartile range (IQR), while categorical variables were reported as whole numbers and percentages. Univariable comparisons for continuous variables were performed using the Kruskal-Wallis test, and for categorical variables using the Pearson χ^2 test. Multiple imputations were performed using the MICE package for R version 3.0.3 (www.r-project.net) to account for missing data for preoperative Hb (14.8%), ECOG score (16.9%), CCI (1.3%) and ASA (3.8%).

The primary outcome of the study was 1-year mortality, calculated from the date of surgery to the date of death or last available follow-up, as appropriate. 1-year mortality was estimated using the Kaplan-Meier method and differences in survival between patient groups were compared using the log-rank test. To identify preoperative risk factors for 1-year mortality, multivariable Cox-proportional hazards regression analysis was performed using a backward stepwise selection based on Akaike Information Criterion (AIC). Model performance was assessed using Harrell's concordance index (C- index) and bootstrap resampling was performed to quantify model overfit. Regression coefficients from multivariable regression analysis were reported as hazard ratios (HR) with 95% confidence intervals (95% CI); beta coefficients from the multivariable model were subsequently used to develop a nomogram to predict the probability of 1-year mortality following surgery. All statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX) or R version 3.0.3 (http://www.r-project.org). Statistical significance was defined as $p<0.05$. The study was approved by the Johns Hopkins University Institutional Review Board.

Results

Baseline Demographic and Clinicopathologic Characteristics

A total of 1,326 patients were identified who met inclusion criteria (Table 1). The median age of the study cohort was 62.5 years (IQR 53-70) with a majority of patients being male (n=730, 55.1%) and Caucasian (n=1,115, 84.1%). The median BMI for all patients was 26.1 kg/m2 (IQR 23.1-29.9); 9.8% (n=111) of the cohort were either active smokers or had a previous smoking history. Comorbidity was common as 42.7% (n=559) of patients presented with an age-adjusted CCI of ≥3. All patients had a malignant indication for surgery and were operated on with curative intent. At the time of surgery, 347 (26.2%) patients underwent a hepatectomy, while 640 (48.3%) had a pancreatic resection, and 339 (25.5%) a colorectal resection (Table 2).

Over a third of patients presented with an mFI score of 0 (n=501, 37.8%) with approximately 29.1% of patients presenting with an mFI score of ≥0.18. Among all patients, the median TPA, TPV and HUAC was 7.8 cm2/m2 (IQR 6.4-9.5), 27.8 cm3/m2 (IQR 21.8-34.3), and 45.0 HU (IQR 36.7-51.0), respectively (Supplemental Figure 1). Given that HUAC performed slightly better on sensitivity analyses, as well as its relative clinical ease to measure compared with TPV or TPA, HUAC measurements were utilized for subsequent morphometric

Table 1. Clinicopathologic and Operative Characteristics of the Cohort by Sarcopenia

Characteristic	All patients (n=1,326)	Patients without sarcopenia* (n=928)	Patients with sarcopenia* (n=398)	p Value
Age, yr, median (IQR)	62.5 (53.0-70.0)	59.0(51.0-68.0)	68.0(61.0-75.0)	<0.001
Sex, n (%)				0.99
Female	596 (44.9)	417 (44.9)	179 (45.0)	
Male	730 (55.1)	511 (55.1)	219 (55.0)	
Race, n (%)				0.006
White	1115 (84.1)	761 (82.0)	354 (88.9)	
Black	104 (7.8)	84 (9.1)	20 (5.0)	
Others	107 (8.1)	83 (8.9)	24 (6.0)	
BMI, kg/m2, median (IQR)	26.1 (23.1-29.9)	26.0 (22.9-29.9)	26.5 (23.5-30.3)	0.08
Smoking status (n=1,138), n (%)				0.05
Nonsmoker	1027 (90.2)	723 (91.4)	304 (87.6)	
Smoker	111 (9.8)	68 (8.6)	43 (12.4)	
Charlson Index (n=1,309)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	<0.001
0-2	750 (57.3)	610 (66.5)	140 (35.7)	
≥ 3	559 (42.7)	307 (33.5)	252 (64.3)	
ASA (n=1,275), n (%)				<0.001
1	8 (0.6)	6 (0.7)	2 (0.5)	
2	366 (28.7)	299 (33.8)	67 (17.2)	
3	866 (67.9)	566 (64.0)	300 (76.9)	
4	34 (2.7)	14 (1.6)	20 (5.1)	
5	1 (0.1)	0	1 (0.3)	
Modified Frailty Score, n (%)				<0.001
0.00	501 (37.8)	398 (42.9)	103 (25.9)	
0.09	439 (33.1)	306 (33.0)	133 (33.4)	
0.18	270 (20.4)	169 (18.2)	101 (25.4)	
0.27	82 (6.2)	38 (4.1)	44 (11.1)	
0.36	23 (1.7)	13 (1.4)	10 (2.5)	
≥0.45	11 (0.8)	4 (0.4)	7 (1.8)	
ECOG functional status (n=1,102), n (%)				<0.001
0	587 (53.3)	433 (55.7)	154 (47.4)	
1	491 (44.6)	336 (43.2)	155 (47.7)	
2	21 (1.9)	7 (0.9)	14 (4.3)	
3	2 (0.2)	0 (0.0)	2 (0.6)	
4	1 (0.1)	1 (0.1)	0 (0.0)	

Table 1. Clinicopathologic and Operative Characteristics of the Cohort by Sarcopenia (*continued*)

Characteristic	All patients (n=1,326)	Patients without sarcopenia* (n=928)	Patients with sarcopenia* (n=398)	p Value
TPA, cm2/m2, median (IQR)	7.8 (6.4-9.5)	8.0 (6.6-9.8)	7.3 (6.0-9.0)	<0.001
TPV, cm3/m2, median (IQR)	27.8 (21.8-34.3)	29.1 (22.8-35.7)	24.3 (20.2-30.5)	<0.001
HUAC, HU, median (IQR)	45.0 (36.7-51.0)	48.3 (44.4-53.4)	32.7 (27.2-35.9)	<0.001
Metastasis, n (%)				<0.001
M0	1050 (79.2)	705 (76.0)	345 (86.7)	
M1	276 (20.8)	223 (24.0)	53 (13.3)	

*Sarcopenia was quantified using the Hounsfield Unit Average Calculation (HUAC). Sex-specific cut-offs (male: 39.9 HU, female: 38.1 HU) that defined a significant association between low HUAC with 1-year mortality were ascertained by stratification analyses and patients who were below these cut-offs were classified as having sarcopenia.

assessments of sarcopenia. Sensitivity analyses were performed to determine sex-specific cut-offs to define sarcopenia (HUAC <39.9 HU for male patients and HUAC < 38.1 HU for female patients). Using these sex-specific cut- offs for HUAC, 398 (30.0%) patients were categorized as sarcopenic (male: n=219, 55.0% vs. female: n=179, 45.0%).

Frailty and Sarcopenia

Patients with sarcopenia were more likely to present with a poor functional / performance status, as well as be classified as frail according to the mFI. Specifically, compared with patients without sarcopenia, patients presenting with sarcopenia were more likely to have a CCI score ≥3 (sarcopenia vs. no sarcopenia: 64.3% [n=252] vs. 33.5% [n=307], p<0.001), as well as present with a worse preoperative ECOG functional status score (ECOG ≥1: 52.6% [n=171] vs. 44.3% [n=344], p=0.01). Similarly, while only 5.9% (n=55) of non-sarcopenic patients presented with an mFI score ≥0.27, roughly 1 in 6 sarcopenic patients presented with an mFI ≥0.27 (15.3% [n=61], p<0.001).

Sarcopenic patients were more likely to develop postoperative complications versus non-sarcopenic patients (49.5% [n=197] vs. 35.2% [n=327]; OR=1.80, 95% CI 1.42-2.29; p<0.001). In addition, sarcopenic patients had a higher risk of suffering a severe, high-grade postoperative complication (Clavien-Dindo grade III-V: sarcopenic, 29.2% [n=116] vs. non-sarcopenic, 15.3% [n=142]; OR=2.28, 95% CI 1.72-3.01; p<0.001). Of note, a decreasing HUAC (i.e. increasing sarcopenia) was associated with worse postoperative outcomes as patients in the lowest

sex specific percentiles for HUAC were the most likely to develop postoperative complications, as well as have a longer ICU and overall LOS (Figure 1a). Interestingly, the correlation of mFI with short-term perioperative clinical outcomes was less pronounced (Figure 1b and Supplemental Table 1).

Table 2. Operative details and outcomes of the cohort by sarcopenia

Characteristic	All patients (n=1,326)	Patients without sarcopenia (n=928)	Patients with sarcopenia (n=398)	p Value
Preoperative Hb, g/dL, median (IQR)	12.9 (11.6-14.1)	13.0 (11.8-14.1)	12.7 (11.1-13.9)	0.005
Preoperative Cr, median (IQR)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.72
Preoperative chemotherapy, n (%)	404 (30.5)	312 (33.6)	92 (23.1)	<0.001
Preoperative radiotherapy, n (%)	191 (14.4)	149 (16.1)	42 (10.6)	0.04
Procedure type, n (%)				<0.001
Hepatectomy	347 (26.2)	266 (28.7)	81 (20.4)	
Pancreatectomy	640 (48.3)	408 (44.0)	232 (58.3)	
Colorectal resection	339 (25.6)	254 (27.4)	85 (21.4)	
Year of procedure, n (%)				0.09
2011	204 (15.4)	138 (14.9)	66 (16.6)	
2012	474 (35.8)	319 (34.4)	155 (38.9)	
2013	436 (32.9)	309 (33.3)	127 (31.9)	
2014	212 (16.0)	162 (17.5)	50 (12.6)	
LOS, days, median (IQR)	7.0(5.0-12.0)	7.0(5.0-11.0)	9.0(6.0-14.0)	<0.001
ICU days, days, median (IQR)	1.0(0.0 -1.0)	1.0(0.0-1.0)	1.0(1.0-2.0)	<0.001
Complication, n (%)	524 (39.5)	327 (35.2)	197 (49.5)	<0.001
I	108 (20.6)	80 (24.5)	28 (14.2)	
II	158 (30.2)	105 (32.1)	53 (26.9)	
III	178 (34.0)	102 (31.2)	76 (38.6)	
IV	67 (12.8)	35 (10.7)	32 (16.2)	
V	13 (2.5)	5 (1.5)	8 (4.1)	
Readmission, n (%)	211 (15.9)	138 (14.9)	73 (18.3)	0.11
1-year mortality, n (%)	125 (9.4)	60 (6.5)	65 (16.3)	<0.001

LOS, length of stay

Factors Associated with 1-Year Mortality

Among all patients, overall mortality within 1-year of surgery was 9.4% (n=125) (pancreatectomy: 12.0% vs. hepato-biliary: 9.8% vs. colorectal: 4.1%; p<0.001).

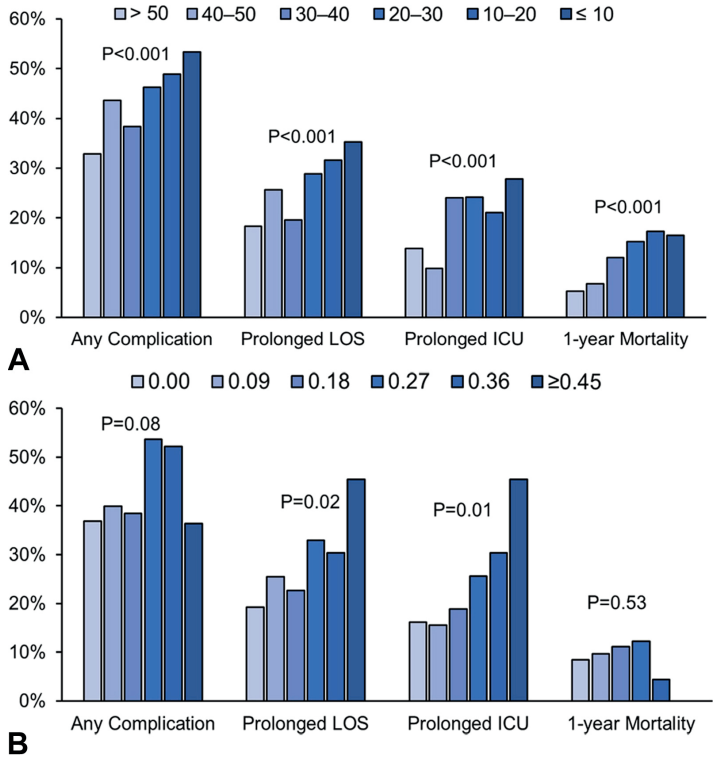

Figure 1: Postoperative clinical outcomes including the development of postoperative complications, prolonged length-of-stay, prolonged intensive care unit stay, and 1-year mortality by (A) Lean muscle mass percentile (sarcopenia) measured by Hounsfield units average calculation (B) modified Frailty Index score.

While 1-year mortality was not associated with sex or race, patients older than 65 years demonstrated an increased risk of death within 1-year (referent 55 years; 65-75 years: HR 2.57, 95% CI 1.52-4.33; >75 years: HR 4.61, 95% CI 2.67-7.97; both p<0.001)(Table 3). Similarly, patients presenting with a preoperative Hb <12.5 g/dL demonstrated a two-fold increased risk of mortality at 1-year following surgery (HR 2.34, 95% CI 1.60-3.44, p<0.001). On univariable analysis, patients presenting with an ECOG performance score of ≥1 demonstrated a 72% increased risk for mortality within 1-year of surgery (HR 1.72, 95% CI 1.13-2.59 p=0.01). Of note, mFI score assessed at the time of initial surgery was not associated with 1-year mortality (HR 1.73, 95% CI 0.31-9.60, p=0.53). In contrast, patients with sarcopenia demonstrated a 2.6 times greater risk for mortality within 1-year of surgery (HR 2.61, 95% CI 1.83-3.71, p< 0.001).

Table 3.

	Total No.	n (%)	Univariable			Multivariable		
			HR (95% CI)	p Value	C index*	HR (95% CI)	p Value	C index**
Age					0.64			0.70
≤55 years	421	21 (5.0)	Ref			Ref		
55-65 years	376	29 (7.7)	1.55 (0.89-2.73)	0.12		1.30 (0.74-2.31)	0.36	
65-75 years	368	42 (11.4)	2.57 (1.52-4.33)	<0.001		1.81 (1.05-3.14)	0.03	
>75 years	161	33 (20.5)	4.61 (2.67-7.97)	<0.001		2.79 (1.55-5.02)	0.001	
Preoperative Hemoglobin					0.60			
≥12.5 g/dL	663	43 (6.5)	Ref			Ref		
<12.5 g/dL	466	67 (14.4)	2.34 (1.60-3.44)	<0.001		1.68 (1.17-2.40)	0.01	
ECOG functional status †					0.57			
0	587	38 (6.5)	Ref			Ref		
≥1	515	55 (10.7)	1.72 (1.13-2.59)	0.01		1.44 (1.01-2.07)	0.05	
Sarcopenia					0.62			
Non-sarcopenic	928	60 (6.5)	Ref			Ref		
Sarcopenic	398	65 (16.3)	2.61 (1.83-3.71)	<0.001		1.98 (1.36-2.88)	<0.001	
Sex					0.52			
Female	596	52 (8.7)	Ref					
Male	730	73 (10.0)	1.11 (0.77-1.58)	0.58				
Race					0.52			
White	1115	100 (9.0)	Ref					
Black	104	11 (10.6)	1.14 (0.61-2.12)	0.68				
Others	107	14 (13.1)	1.53 (0.87-2.67)	0.14				

Table 3. (*continued*)

	Total No.	n (%)	Univariable			Multivariable		
			HR (95% CI)	p Value	C index*	HR (95% CI)	p Value	C index**
Charlson Index ‡					0.59			
0-2	750	50 (6.7)	Ref					
≥ 3	559	71 (12.7)	2.07 (1.44-2.98)	<0.001				
ASA §					0.55			
1-2	374	26 (6.9)	Ref					
≥3	901	90 (10.0)	1.52 (0.98-2.35)	0.06				
Modified Frailty Index					0.55			
0.00	501	42 (8.4)	Ref					
0.09	439	42 (9.6)	1.15 (0.75-1.77)	0.52				
0.18	270	30 (11.1)	1.43 (0.90-2.29)	0.13				
0.27	82	10 (12.2)	1.53 (0.77-3.05)	0.23				
0.36	23	1 (4.4)	0.48 (0.07-3.52)	0.47				
≥0.45	11	0	-	-				
Metastatic disease	276	24 (8.7)	0.86 (0.53-1.39)	0.53	0.51			

*C-statistic for model fit of each variable; ** C-statistic for the multivariable model; † n=1,129; ‡ n=1,309; § n=1,275 HR, Hazard ratio

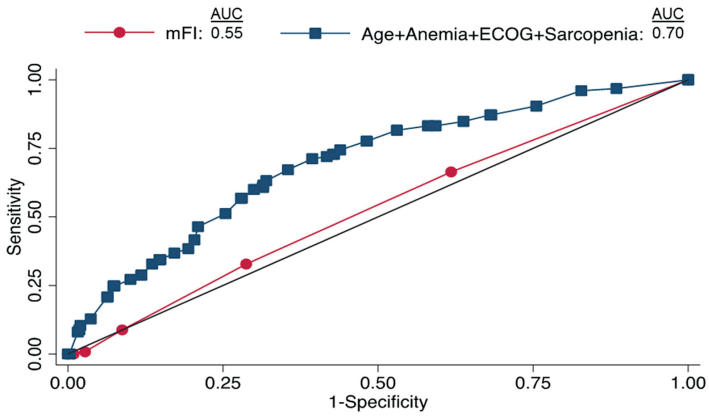

Figure 2: Area under the receiver operating characteristic (ROC) curve demonstrating improved discrimination with inclusion of sarcopenia measured by Hounsfield unit average calculation (HUAC).

On multivariable analysis, after controlling for competing risk factors, several factors remained associated with 1-year mortality. On multivariable analysis, while patients aged 55-65 years did not have an increased risk of 1-year mortality, patients 65- 75 years had an 80% increased risk (HR 1.81, 95% CI 1.05-3.14,p=0.03), while patients >75 years demonstrated an almost 3 times greater risk (HR 2.79, 95% CI 1.55-5.02, p=0.001). Preoperative anemia, defined as Hb level<12.5 g/dL prior to the initial surgery, was also associated with an increased risk of death within 1-year (HR 1.68, 95% CI 1.17- 2.40, p=0.01). In addition, sarcopenia was independently associated with higher risk of 1-year mortality (HR 1.98, 95% CI 1.36-2.88, p<0.001). Model diagnostics demonstrated good discriminatory ability of the multivariable model with an AUC of 0.70 and no overfit was noted upon bootstrap resampling. When compared with mFI (0.55) and ECOG alone

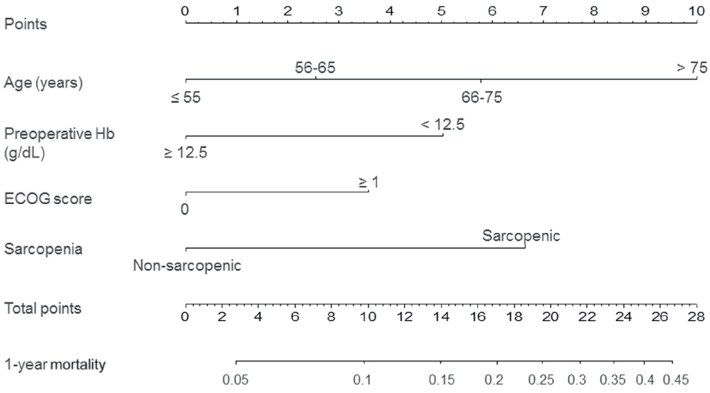

Figure 3: Nomogram to calculate the 1-year mortality of patients undergoing complex gastrointestinal surgery.

(0.57), the multivariable model demonstrated an improved discrimination with the inclusion of sarcopenia (Figure 2).

Development of Nomogram and Risk-stratification of Patients

Regression coefficients from the multivariable analysis were used to assign each independent parameter associated with 1-year mortality (age, preoperative Hb, ECOG and sarcopenia) a specific weighted score (Figure 3). A higher total points based on the sum of the assigned number of points for each factor in the nomogram was associated with a worse 1-year prognosis. For example, a 65-year-old male patient with a preoperative Hb 13 g/dL, ECOG 1, and HUAC 30 HU would have a total of 17 points (age= 6 points, Hb=0 points, EGOC=4 points, sarcopenia=7) for a predicted 1-year mortality of 20%. Similarly, a 55-year old

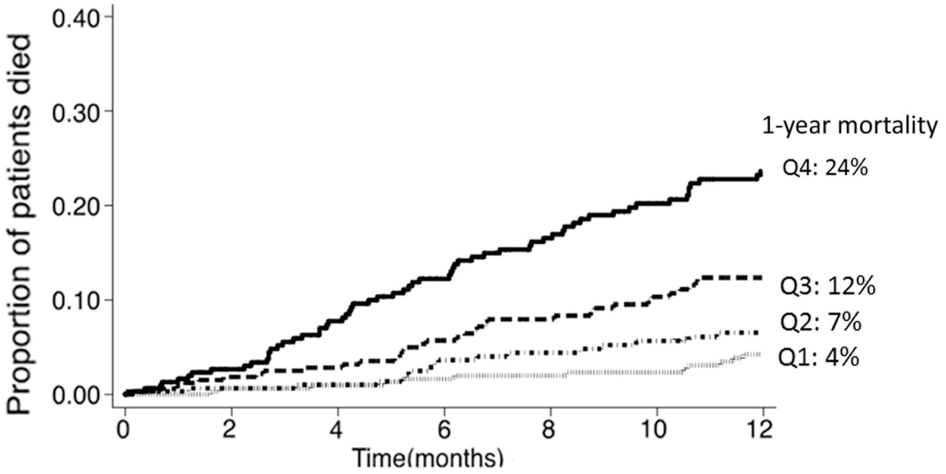

Figure 4: One-year mortality stratified by quartile of predicted probability as calculated by the proposed nomogram.

female patient who presented with a Hb 9 g/dL, ECOG 0, and HUAC 40 HU would have a total of 8 points (age=3 points, Hb=5 points, EGOC=0 points, sarcopenia=0) for a predicted 1-year mortality of 9%.

To further assess the discriminative ability of the model, the predicted probability of 1-year mortality was plotted as Kaplan-Meier curves stratified by quartiles of predicted probability calculated from the nomogram (Figure 4). Patients with the lowest predicted 1-year mortality (quartile 4) did substantially worse (1-year mortality 23.6%) compared with patients in other quartiles (1-year mortality: quartile 1, 4.2% vs. quartile 2, 6.5% vs. quartile 3, 12.3%, all $p<0.001$). Discrimination

ability of the final model for 1-year mortality was also assessed using the C-statistic (overall C-index: 0.70) and was comparable among the different procedures (C-index: pancreatectomy, 0.70 vs. hepato- biliary, 0.70 vs. colorectal 0.79). The accuracy of the model and potential model overfit were assessed by bootstrap validation with 1,000 resampling. The bootstrapped calibration plot for the prediction of 1-year mortality did not demonstrate overfit (Supplemental Figure 2).

Discussion

While surgery remains the cornerstone of curative-intent therapy for cancer, morbidity, long length-of-stay, and an increased risk of mortality can offset any potential oncological benefit of surgery.[4,32,33] In addition, expanding indications for surgical resection coupled with an aging population make preoperative patient selection and risk assessment an increasingly important topic.[34] As such, there has been a growing interest in developing preoperative tools to identify patients who may be the most vulnerable to poor postoperative outcomes.[27] Commonly used tools including ASA score and ECOG status have been criticized for focusing only on a limited number of organ systems, being subjective and failing to measure "true" physiologic reserve.[9,17] More recently, frailty has been proposed as a more comprehensive metric of physiologic reserve.[35] Assessing frailty can, however, be cumbersome and lack objectivity, thereby limiting its implementation into the clinical setting.[14] In an attempt to make frailty more clinically applicable, Obeid et al. proposed an mFI with a more limited number of factors that were available in the NSQIP dataset.[21] In addition, our group and others, have proposed the assessment of sarcopenia as a more objective measurement of physiologic reserve.[23,25,31] Past studies have, however, largely investigated only short-term outcomes within 30- or 90-days of surgery.[23,25,31] When determining the benefit or "success" of an operation, 1-year survival may be an important metric for patients and providers.[36,37] In the current study, using a cohort of 1,326 patients undergoing complex gastrointestinal surgery for hepato-biliary, pancreatic and colorectal cancer, we assessed the role of clinical and morphometric data to predict 1-year mortality. Sarcopenia, as measured by psoas density / HUAC, was a strong independent predictor of 1-year mortality risk (HR 2.61 95%CI 1.83-3.71). In fact, sarcopenia outperformed other measures of frailty/physiological reserve including ECOG functional status and the mFI in predicting 1-year mortality (AUC: sarcopenia: 0.62 vs. ECOG: 0.57 vs. mFI: 0.55). Using both clinical (age, Hb level, ECOG status) and morphometric (sarcopenia) parameters, a parsimonious and clinically applicable risk-stratification tool was developed to identify patients at greatest risk

for 1-year mortality following gastrointestinal surgery. The proposed nomogram performed well on internal validation (AUC 0.70).

Most frailty tools are based on cumbersome and exhaustive measurements of largely subjective data, thereby limiting the widespread applicability of frailty assessment in the preoperative setting.[14,26] In addition, outcome prediction following oncological surgery may be confounded by potential physiological decline associated with tumor burden and adjuvant therapies.[10,35] Given this, any definition of frailty should account for changes over time and remain clinically relevant independent of the underlying disease process.[20,38] Given the complexity of assessing frailty, several proposed definitions have included many variables, with some having up to 70 different factors.[39] While exhaustive and comprehensive, these definitions may be limited due to computational tractability.[35,40,41] For example, as the number of variables increases, the interactions between variables also increases exponentially resulting in an overall low predictive power.[35] As such, other authors have proposed modified frailty scores such as the mFI.[21,39] The mFI has only 11 factors, yet suffers from some of the same problems with definition (e.g. "altered" sensorium). In addition, while some studies have demonstrated that mFI was associated with short-term outcomes, no previous study had assessed whether mFI could predict mortality at 1-year.[21,39] Rather, in the current study, mFI was in fact a very poor predictor of 1-year mortality with an AUC of only 0.55 (Figure 2).

Rather than using clinical scores such as the mFI or measures of functional reserve such as hand-grip strength or walking speed, measurement of lean muscle mass has been proposed as a more objective measure of physiological reserve.[22,25,31,42] Sarcopenia, defined as lean muscle mass wasting, can be assessed in several ways (i.e. TPA, TPV, HUAC).[23,31,42,43] In the present study, each of these methods was used to calculate sarcopenia from preoperative cross-sectional imaging. Psoas density, which perhaps is the easiest means to calculate sarcopenia, was utilized. Consistent with previous reports that assessed short-term postoperative clinical outcomes, we noted that sarcopenia was associated with an increased risk of adverse perioperative outcomes.[25,42] In fact, as the severity of sarcopenia increased, there was a higher incidence of postoperative complications, as well as a greater likelihood for a longer ICU and overall LOS. Perhaps of more interest, sarcopenia was also a strong predictor of 1- year mortality. Patients who were sarcopenic had over a 2.5-fold increased risk of mortality within the first year following surgery. Of note, sarcopenia demonstrated the best ability to predict 1-year mortality compared with the mFI, ASA grade, CCI, as well ECOG performance score.

A particular strength of the study was that it took into account both clinical and morphometric variables when determining risk of 1-year mortality. On multivariable analysis, several clinic factors including age, anemia, and ECOG status were each independently associated with 1-year mortality. Combining these clinical factors with sarcopenic morphometric data, a parsimonious nomogram based on a 28-point composite score was proposed to identify patients at greatest risk of 1-year mortality. When stratified into quartiles, the proposed nomogram was able to categorize patients into distinct groups at variable risk of 1-year mortality. In fact, when patients were stratified according to their calculated score, the 1-year mortality varied widely from 4.3% to 23.6% among low and high risk patients, respectively (Figure 4). The nomogram demonstrated good discrimination with a C-statistic of 0.70 for predicting 1-year mortality. Taken together, the data strongly suggest that the proposed nomogram can be used in the preoperative setting to identify patients at high risk of 1-year mortality. Such information may be helpful to patients and providers when discussing the anticipated relative benefits and risks of major gastrointestinal surgery.

Several limitations should be considered when interpreting data from the current study. Despite a large sample size of over 1,000 patients, data were derived from a single institutional experience. In addition, while the nomogram was internally validated, external validation in an independent cohort of patients is required. We were also unable to comment on and account for other important patient outcomes such as postoperative quality of life, loss of productivity and return to function. Each of these outcomes are important patient-centered factors that warrant future examination.

In conclusion, using a large, single center cohort of patients who underwent gastrointestinal surgery, several clinical and morphometric variables predicted 1-year mortality. When predicting 1-year mortality, sarcopenia outperformed other metrics of physiological reserve such as mFI, ASA, and ECOG. A limited number of easy and readily available clinical parameters combined with an objective measurement of sarcopenia resulted in a nomogram that accurately predicted 1-year mortality and performed well on internal validation. Future studies will need to externally validate the proposed nomogram, as well as examine other important metrics of surgical "success" such as patient quality of life.

Acknowledgements:

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References:

1 Mayo SC, Heckman JE, Shore AD, Nathan H, Parikh AA, Bridges JFP, et al. Shifting trends in liver-directed management of patients with colorectal liver metastasis: a population-based analysis. Surgery 2011;150:204–16. doi:10.1016/j.surg.2011.06.013.

2 Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485–91. doi:10.1200/JCO.2008.20.7753.

3 Chapman WC, Klintmalm G, Hemming A, Vachharajani N, Majella Doyle MB, DeMatteo R, et al. Surgical treatment of hepatocellular carcinoma in North America: can hepatic resection still be justified? J Am Coll Surg 2015;220:628–37. doi:10.1016/j.jamcollsurg.2014.12.030.

4 Sukumar S, Roghmann F, Trinh VQ, Sammon JD, Gervais M-K, Tan H-J, et al. National trends in hospital-acquired preventable adverse events after major cancer surgery in the USA. BMJ Open 2013;3. doi:10.1136/bmjopen-2013-002843.

5 Mayo SC, Pulitano C, Marques H, Lamelas J, Wolfgang CL, de Saussure W, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. J Am Coll Surg 2013;216:707–16; discussion 716–8. doi:10.1016/j.jamcollsurg.2012.12.029.

6 Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in Hospital Volume and Failure to Rescue for Pancreatic Surgery. J Gastrointest Surg 2015;19:1581–92. doi:10.1007/s11605-015-2800-9.

7 Berger NA, Savvides P, Koroukian SM, Kahana EF, Deimling GT, Rose JH, et al. Cancer in the elderly. Trans Am Clin Climatol Assoc 2006;117:147–55; discussion 155–6.

8 Farquharson SM, Gupta R, Heald RJ, Moran BJ. Surgical decisions in the elderly: the importance of biological age. J R Soc Med 2001;94:232–5.

9 Afilalo J, Mottillo S, Eisenberg MJ, Alexander KP, Noiseux N, Perrault LP, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circ Cardiovasc Qual Outcomes 2012;5:222–8. doi:10.1161/CIRCOUTCOMES.111.963157.

10 Sawhney R, Sehl M, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part I. Cancer J 11:449–60.

11 Robinson TN, Wu DS, Stiegmann G V, Moss M. Frailty predicts increased hospital and six-month healthcare cost following colorectal surgery in older adults. Am J Surg 2011;202:511–4. doi:10.1016/j.amjsurg.2011.06.017.

12 Lee DH, Buth KJ, Martin B-J, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 2010;121:973–8. doi:10.1161/CIRCULATIONAHA.108.841437.

13 Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Hashmi A, Green DJ, et al. Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. JAMA Surg 2014;149:766–72. doi:10.1001/jamasurg.2014.296.

14 Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg 2010;210:901–8. doi:10.1016/j.jamcollsurg.2010.01.028.

15 Hubbard RE, Story DA. Patient frailty: the elephant in the operating room. Anaesthesia 2014;69 Suppl 1:26–34. doi:10.1111/anae.12490.

16 Amrock LG, Neuman MD, Lin H-M, Deiner S. Can routine preoperative data predict adverse outcomes in the elderly? Development and validation of a simple risk model incorporating a chart-derived frailty score. J Am Coll Surg 2014;219:684–94. doi:10.1016/j.jamcollsurg.2014.04.018.

17 Yano Y, Inokuchi T, Kario K. Walking Speed Is a Useful Marker of Frailty in Older Persons. JAMA Intern Med 2013;173:325. doi:10.1001/jamainternmed.2013.1629.

18 Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying Frailty in Hospitalized Older Adults with Significant Coronary Artery Disease. J Am Geriatr Soc 2006;54: 1674–81. doi:10.1111/j.1532-5415.2006.00914.x.

19 Saxton A, Velanovich V. Preoperative frailty and quality of life as predictors of postoperative complications. Ann Surg 2011;253:1223–9. doi:10.1097/SLA.0b013e318214bce7.

20 Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95. doi:10.1503/cmaj.050051.

21 Obeid NM, Azuh O, Reddy S, Webb S, Reickert C, Velanovich V, et al. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. J Trauma Acute Care Surg 2012;72:878–83. doi: 10.1097/TA.0b013e31824d0f70.

22 Amini N, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, et al. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. J Gastrointest Surg 2015;19:1593–602. doi:10.1007/s11605-015-2835-y.

23 Joglekar S, Asghar A, Mott SL, Johnson BE, Button AM, Clark E, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol 2015;111: 771–5. doi:10.1002/jso.23862.

24 Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg 2012;16:1478–86. doi: 10.1007/s11605-012-1923-5.

25 Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB (Oxford) 2011;13:439–46. doi:10.1111/j.1477- 2574.2011.00301.x.

26 Kim S, Han H-S, Jung H, Kim K, Hwang DW, Kang S-B, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg 2014;149:633–40. doi:10.1001/jamasurg.2014.241.

27 Bagnall NM, Faiz O, Darzi A, Athanasiou T. What is the utility of preoperative frailty assessment for risk stratification in cardiac surgery? Interact Cardiovasc Thorac Surg 2013;17:398–402. doi:10.1093/icvts/ivt197.

28 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

29 American Society of Anesthesiologists - American Society of Anesthesiologists n.d. http://www.asahq.org/ (accessed May 1, 2015).

30 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

31 Valero V, Amini N, Spolverato G, Weiss MJ, Hirose K, Dagher NN, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. J Gastrointest Surg 2015;19:272–81. doi:10.1007/s11605-014-2680-4.

32 Schneider EB, Hyder O, Brooke BS, Efron J, Cameron JL, Edil BH, et al. Patient readmission and mortality after colorectal surgery for colon cancer: impact of length of stay relative to other clinical factors. J Am Coll Surg 2012;214:390–8; discussion 398–9. doi:10.1016/j.jamcollsurg.2011.12.025.

33 Ghaferi AA, Dimick JB. Variation in mortality after high-risk cancer surgery: failure to rescue. Surg Oncol Clin N Am 2012;21:389–95, vii. doi:10.1016/j.soc.2012.03.006.

34 Mohile SG, Xian Y, Dale W, Fisher SG, Rodin M, Morrow GR, et al. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. J Natl Cancer Inst 2009;101:1206–15. doi:10.1093/jnci/djp239.

35 Rockwood K. Frailty and its definition: a worthy challenge. J Am Geriatr Soc 2005;53:1069–70. doi:10.1111/j.1532-5415.2005.53312.x.

36 Sündermann SH, Dademasch A, Seifert B, Rodriguez Cetina Biefer H, Emmert MY, Walther T, et al. Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age. Interact Cardiovasc Thorac Surg 2014;18:580–5. doi:10.1093/icvts/ivu006.

37 Eklund K, Wilhelmson K, Gustafsson H, Landahl S, Dahlin-Ivanoff S. One-year outcome of frailty indicators and activities of daily living following the randomised controlled trial: "Continuum of care for frail older people". BMC Geriatr 2013;13:76. doi:10.1186/1471- 2318-13-76.

38 McAdams-DeMarco MA, Law A, Salter ML, Chow E, Grams M, Walston J, et al. Frailty and early hospital readmission after kidney transplantation. Am J Transplant 2013;13:2091–5. doi:10.1111/ajt.12300.

39 Hodari A, Hammoud ZT, Borgi JF, Tsiouris A, Rubinfeld IS. Assessment of morbidity and mortality after esophagectomy using a modified frailty index. Ann Thorac Surg 2013;96:1240–5. doi:10.1016/j.athoracsur.2013.05.051.

40 Rønning B, Wyller TB, Jordhøy MS, Nesbakken A, Bakka A, Seljeflot I, et al. Frailty indicators and functional status in older patients after colorectal cancer surgery. J Geriatr Oncol 2014;5:26–32. doi:10.1016/j.jgo.2013.08.001.

41 Xue Q-L. The frailty syndrome: definition and natural history. Clin Geriatr Med 2011;27:1–15. doi:10.1016/j.cger.2010.08.009.

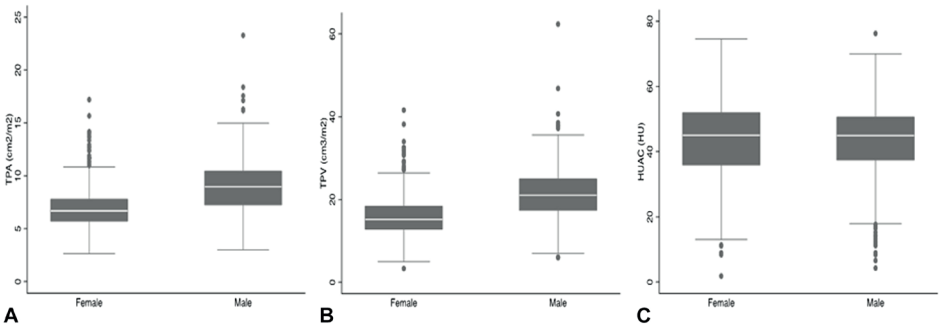
42 Dodson RM, Firoozmand A, Hyder O, Tacher V, Cosgrove DP, Bhagat N, et al. Impact of sarcopenia on outcomes following intra-arterial therapy of hepatic malignancies. J Gastrointest Surg 2013;17:2123–32. doi:10.1007/s11605-013-2348-5.

43 Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–35. doi:10.1016/S1470-2045(08)70153-0.

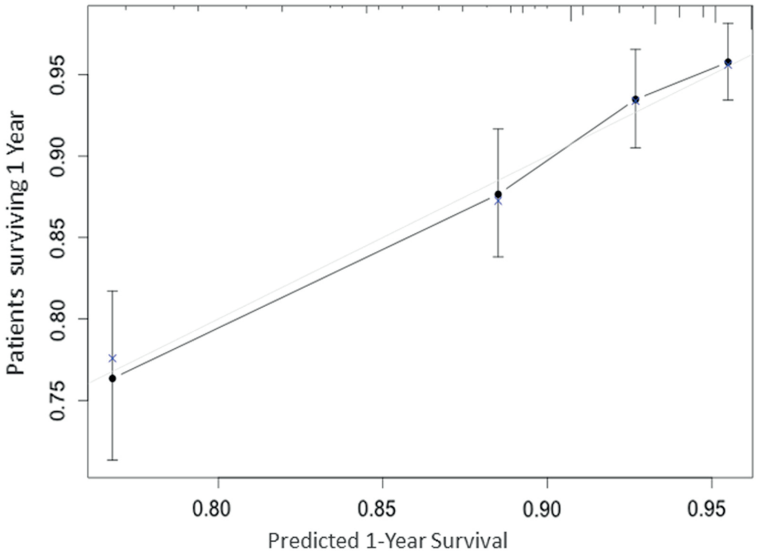
Supplemental Table 1. Clinical Outcomes According to Modified Frailty Index and HUAC (HU) Categories

Frailty Index	No. of events (%)	Total (n=1,326)						p Value
		0.00 (n=501)	0.09 (n=441)	0.18 (n=271)	0.27 (n=82)	0.36 (n=23)	≥0.45 (n=11)	
Complication, n (%)	524 (39.5)	185 (36.9)	175 (39.9)	104 (38.5)	44 (53.7)	12 (52.2)	4 (36.4)	0.08
Major complication, n (%)	258 (19.5)	85 (17.0)	92 (21.0)	47 (17.3)	24 (29.3)	8 (34.8)	2 (18.2)	0.04
Grade IV complication / death, n (%)	80 (6.0)	23 (4.6)	31 (7.0)	13 (4.8)	9 (11.0)	4 (17.4)	0	0.03
Readmission, n (%)	211 (15.9)	76 (15.2)	75 (17.1)	36 (13.3)	16 (19.5)	6 (26.1)	2 (18.2)	0.47
Prolonged LOS, n (%)	308 (23.2)	96 (19.2)	112 (25.5)	61 (22.6)	27 (32.9)	7 (30.4)	5 (45.5)	0.02
Prolonged ICU, n (%)	233 (17.6)	81 (16.2)	68 (15.5)	51 (18.9)	21 (25.6)	7 (30.4)	5 (45.5)	0.01
1-year Mortality, n (%)	125 (9.4)	42 (8.4)	42 (9.6)	30 (11.1)	10 (12.2)	1 (4.4)	0	0.53

HUAC	No. of events (%)	Total (n=1,326)						p Value
		> 50 percentile	40-50 percentile	30-40 percentile	20-30 percentile	10-20 percentile	≤ 10 percentile	
Complication, n (%)	524 (39.5)	218 (32.9)	58 (43.6)	51 (38.4)	61 (46.2)	65 (48.9)	71 (53.4)	<0.001
Major complication, n (%)	258 (19.5)	88 (13.3)	30 (22.6)	24 (18.1)	36 (27.3)	37 (27.8)	43 (32.3)	<0.001
Grade IV complication / death, n (%)	80 (6.0)	26 (3.9)	9 (6.8)	5 (3.8)	12 (9.1)	11 (8.3)	17 (12.8)	0.001
Readmission, n (%)	211 (15.9)	99 (14.9)	22 (16.5)	17 (12.8)	26 (19.7)	24 (18.1)	23 (17.3)	0.62
Prolonged LOS, n (%)	308 (23.2)	121 (18.3)	34 (25.6)	26 (19.6)	38 (28.8)	42 (31.6)	47 (35.3)	<0.001
Prolonged ICU, n (%)	233 (17.6)	91 (13.8)	13 (9.8)	32 (24.1)	32 (24.2)	28 (21.1)	37 (27.8)	<0.001
1-year Mortality, n (%)	125 (9.4)	35 (5.3)	9 (6.8)	16 (12.0)	20 (15.2)	23 (17.3)	22 (16.5)	<0.001



Supplemental Figure 1: Sex-specific distributions for **(a)** total psoas area **(b)** total psoas volume **(c)** Hounsfield units average calculation.



Supplemental Figure 2: Calibration plot for calculated nomogram to assess patient frailty.

CHAPTER 5

Clinical and Morphometric Parameters of Frailty to Predict Mortality following Hepato-Pancreatico-Biliary Surgery in the Elderly

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Abstract

Introduction: While a known determinant of poor postoperative outcomes, frailty can be difficult to identify in patients prior to surgery. We sought to develop a preoperative frailty-risk model to predict mortality among patients≥65 years.

Methods: Clinical and morphometric data including total psoas area (TPA), total psoas volume (TPV) and psoas density (Hounsfield Unit Average Calculation [HUAC]) were collected for 518 patients undergoing HPB surgery between 2012-2014. Multivariable Cox-proportional hazards regression was used to identify preoperative risk factors associated with 1-year mortality.

Results: Median patient age was 72 (i.q.r. 68-76) years, 55.6% patients were men, and half the cohort had multiple comorbidities (Charlson Comorbidity Index [CCI] ≥4, 55.6%). TPA cut offs to define sarcopenia were 552.7mm^2/m^2 in women and 702.9mm^2/m^2 in men; cut offs for TPV were 18.2cm^3/m^2 in women and 26.2cm^3/m^2 in men while HUAC cut offs were 31.1 HU in women and 33.3 HU in men. Overall 1-year mortality was 14.1%. On multivariable analysis, risk factors associated with 1-year mortality included CCI≥4 (HR 4.58, 95%CI 2.47-8.52, p<0.001), malignant disease (HR 6.4, 95%CI 2.33-17.53, p<0.001) and sarcopenia (HR 1.92, 95%CI 1.15-3.22, p=0.01). A weighed 25-point composite score was developed to stratify patients at risk of 1-year postoperative mortality. One-year mortality was noted to be 2.2% among patients scoring 0-10 (low-risk), 14.4% among patients scoring 11-20 (intermediate-risk) and 23.3% among patients scoring between 21 and 25 (high-risk, p<0.001).

Conclusion: Clinical and morphometric measures of frailty accurately predict the risk of 1-year mortality following HPB surgery among elderly patients and can be used to appropriately risk- stratify patients.

Introduction

Each year over 30,000 patients aged ≥65 years undergo hepato-pancreatico-biliary (HPB) surgery in the United States.[1] Although surgery is the cornerstone of multimodality therapy for many HPB disease processes, postoperative outcomes can be compromised by the high morbidity associated with surgery.[2,3] In particular, a subset of elderly patients may be at higher risk to develop postoperative complications as well as mortality due to loss of physiological functional and physical reserves.[4] Given the potential heterogeneity in the aging surgical population with regard to postoperative outcomes, there is great interest in developing more robust methodologies for risk-stratification prior to surgery.[4] Accurate identification of elderly patients at risk for perioperative morbidity and mortality may identify appropriate patients for prehabilitation, as well as better inform patient and provider decisions regarding the potential benefits of surgery.[5]

Frailty, defined as decreased physiologic reserve, has been proposed as a potential means to assess a patient's overall health status.[6,7] The concept of frailty has, however, only largely been applied to nonsurgical patients.[8-10] The small number of studies examining frailty among surgical patients have noted an association with postoperative complications, as well as longer length of stay, and additional interventional procedures.[4,11-13] Many of these studies were limited in using subjective measures / indices, as well as cumbersome clinical measurements to assess frailty.[4,12,13] These proposed parameters are time consuming and therefore may be impractical for use in the preoperative surgical setting.[4,12,13] Furthermore, the lack of standardized practices and external validation has limited the widespread use of frailty to quantify and assess patients undergoing complex surgery.[4]

Recently sarcopenia, or muscle wasting has been identified as an objective, easy to measure surrogate for frailty.[14-19] Sarcopenia may be associated with outcomes among patients undergoing several different surgical procedures.[14-19] Most often sarcopenia has been defined by measuring total psoas area (TPA) or, less commonly, total psoas volume (TPV) or Hounsfield Units Average Calculation (HUAC).[15-20] There is debate, however, regarding which parameter is most appropriate to measure sarcopenia, with conflicting results among several studies.[15-20] Furthermore, previous studies have not examined frailty using a combination of clinical and morphometric parameters.[4,12,15-20] As such, there is a dearth of information on the assessment of frailty in elderly patients using conventional clinical risk-stratification factors combined with more objective measurements of sarcopenia.[21] Given this, the objective of the current study was to evaluate the ability of TPA, TPV and HUAC to predict 1-year mortality among a cohort of

elderly patients undergoing HBP surgery. In addition, we sought to develop a preoperative risk- stratification tool that combined clinical and morphometric factors to predict and identify elderly patients at greatest risk for early mortality following HPB surgery.

Methods

Data Sources and Patient Population

This cross-sectional study was performed using data from a prospectively maintained database of patients undergoing abdominal surgery at the Johns Hopkins Hospital. As previously described, information within this database is updated monthly, and verified by institutional quality review.[22,23] Patients undergoing liver or pancreatic surgery were identified using International Classification of Disease – Ninth Revision – Clinical Manifestation (ICD-9-CM) procedure codes "50.22," "50.3," "52.51," "52.52," "52.53," "52.59," "52.6," and "52.7." To limit the analysis to elderly patients, only patients 65 years or older were included in the analyses. Additionally, to enhance the homogeneity of the patient population, only patients undergoing surgery on an elective basis were included in the study cohort. Further, as the primary outcome of the study was 1-year postoperative mortality, only patients undergoing surgery prior to July 1, 2014 were included in the analysis.

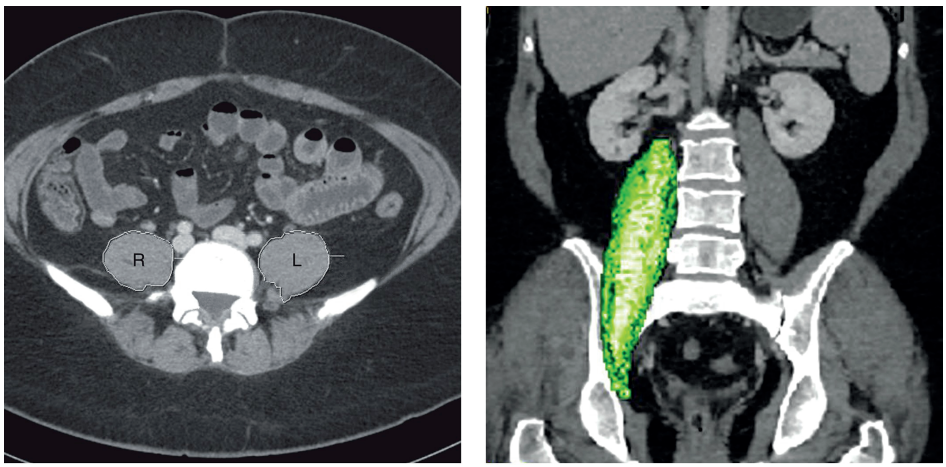
Sociodemographic and pathological data including age, sex, race, body mass index (BMI), American Society of Anesthesiologists (ASA) physical classification grade and preoperative comorbidity were collected for each patient.[24] Preoperative comorbidity was defined according to the Charlson Comorbidity Index (CCI); categorizing patients presenting with a CCI score ≥4 with "severe comorbidity."[25] Similarly, BMI was categorized according to the World Health Organization classification of BMI (normal; <25 kg/m^2, overweight; 25-30 kg/m^2 and obese; >30 kg/m^2) while preoperative anemia was defined by gender specific cut offs of hemoglobin<13.5 g/dL for men and hemoglobin<12.0 g/dL among women.[26] The study was approved by the Johns Hopkins University Institutional Review Board.

Image Analysis

Preoperative (≤90 days) abdominal CT images were reviewed for the 518 patients who met inclusion criteria. Using the Ultravisual software package (Merge Emageon, Birmingham, AL, USA), sarcopenia was initially assessed by measuring TPA at the level of L3 where both iliac crests were clearly visible.[16,17] As previously

described, measurements were performed in a semi-automated fashion with manual outlining of the psoas muscle borders (Figure 1a).[15-17]

Similarly, TPV was assessed using AW Workstation Volume Viewer Software (GE Healthcare, Little Chalfont, United Kingdom).[15,19] Specifically, TPV was calculated using three manual measurements at the level of L3 on the first image where both iliac crests were visible by hand-tracing the borders of the entire psoas muscle (Figure 1b).[15,19] Three measurements were performed to assess the total psoas length. All measurements were performed in a semi- automated fashion with the density threshold setting between –30 and 110 Hounsfield Units (HU) to exclude vascular and fatty infiltration areas from the volumetric calculations.[15,19] TPA was normalized for height (height [cm] x height [cm]) while TPV was normalized for height calculated as (height [cm] x weight [kg]) / 3600).[15,19] HUAC, a measure of muscle density and fatty infiltration, of the psoas muscle was calculated using the methodology described by Joglekar et al.[20] Specifically, right and left psoas muscles were evaluated and the average calculation was used for the final HUAC calculation; Right Hounsfield Unit Calculation (RHUC) = (Right Hounsfield Unit*Right Psoas Area) / (Total Psoas Area), Left Hounsfield Unit Calculation (LHUC) = (Left Hounsfield Unit*Left Psoas Area) / (Total Psoas Area), and HUAC = (Right Hounsfield Unit Calculation +Left Hounsfield Unit Calculation) / 2 (Figure 1a).[20]



a Measurement using TPA and HUAC **b** Measurement using TPV

Figure 1. Sarcopenia measurement at level L3 using (a) total psoas area (TPA) and Hounsfield Units density measurement (HUAC) and (b) total psoas volume (TPV).

Statistical Analysis

Continuous variables were reported as medians with interquartile range while categorical variables reported as whole numbers and percentages. As previously reported and validated, to obtain sex-specific categorical cut offs for sarcopenia, optimum stratification was assessed through a series of sensitivity analyses and sarcopenia was defined in categorical analyses as the lowest quartile.[14,15,27] TPA cut offs used to define sarcopenia were 702.9 mm^2/m^2 and 552.7 mm^2/m^2 among males and females, respectively. Similarly, sarcopenia was defined as TPV<26.2 cm^3/m^2 in male patients and TPV<18.2 cm^3/m^2 among females, while HUAC<33.3 HU in males and HUAC<31.1 HU in females were used to defined sarcopenia according to HUAC. Overall survival was analysed using the Kaplan-Meier method, and differences in survival assessed by the log-rank test.

To identify preoperative factors predictive of 1-year all-cause mortality a multivariable Cox proportional hazards model was built. The inclusion of clinicopathologic risk factors into the multivariable model was assessed using results from a stepwise backward selection methodology based on the Akaike Information Criterion (AIC) as well as using results from the Lasso regression (Supplemental Table). As similar variables were selected according to each methodology, the final multivariable model was built to include all clinically relevant, preoperative variables to generate the most parsimonious as well as the most clinically applicable prediction model.[28] Model calibration was evaluated by Harrell's concordance index (C-index). Bootstrap validation was performed by drawing random samples from the original data set with replacement; specifically, 150 iterations were performed to assess for model overfitting.[29,30] Point estimates were reported as hazard ratios (HR) with 95% confidence intervals (95 % CI) as appropriate. Regression coefficients obtained from the multivariable model were subsequently used to generate a weighted score to predict the probability of 1-year mortality. All tests were two-sided and P<0.05 was used to define statistical significance. Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX) and R version 3.0.3 (http://www.r-project.org).

Results

Patient characteristics

Among the 518 patients who met inclusion criteria, the median age was 72 (i.q.r. 68-76) years with a majority of patients being men (n=288, 55.6%) and Caucasian (n=435, 84.0%). A pancreatic resection was performed in 424patients

(81.8%) and 94 patients underwent a hepato- biliary resection (18.2%). Baseline characteristics of the patients are shown in table 1.

Table 1. Baseline characteristics of patients undergoing hepato-pancreatico-biliary surgery

Characteristic	Total (n=518)	Hepato-biliary (n=94)	Pancreatic (n=424)	P
Age, years, median (IQR)	72.0 (68.0-76.0)	72.5 (68.0-77.0)	71.0 (68.0-76.0)	0.517
Sex				
Female	230 (44.4)	31 (33.0)	199 (46.9)	0.014
Male	288 (55.6)	63 (67.0)	225 (53.1)	
Race				0.235
White	435 (84.0)	75 (79.8)	360 (84.9)	
Black	39 (7.5)	11 (11.7)	28 (6.6)	
Others	44 (8.5)	8 (8.5)	36 (8.5)	
CCI, n (%)				<0.001
0-3	230 (44.4)	23 (24.5)	207 (48.8)	
≥ 4	288 (55.6)	71 (75.5)	217 (51.2)	
BMI, Kg/m², median (IQR)	25.8 (23.4-28.8)	26.0 (23.8-28.4)	25.7 (23.2-28.8)	0.56 0.381
ASA (n=471)				
1-2	105 (20.3)	16 (17.0)	89 (21.0)	
3-4	412 (79.7)	78 (83.0)	334 (79.0)	
Coexisting Condition, n (%) CHF	7 (1.6)	0 (0.0)	7 (1.9)	0.198
Pulmonary	51 (11.5)	3 (3.6)	48 (13.3)	0.012
PVD	36 (8.1)	8 (9.5)	28 (7.8)	0.593
HTN	268 (60.2)	53 (63.1)	215 (59.6)	0.551
DM	114 (25.6)	23 (27.4)	91 (25.2)	0.681
Renal	18 (4.0)	4 (4.8)	14 (3.9)	0.711
Primary Diagnosis				<0.001
Benign	130 (25.1)	10 (10.6)	120 (28.3)	
Malignant	388 (74.9)	84 (89.4)	304 (71.7)	
Preoperative Hemoglobin, g/dL, median (IQR)	12.9 (11.8-14.2)	12.8 (11.8-14.3)	13.0 (11.8-14.2)	0.654
1-year mortality	73 (14.1)	19 (20.2)	54 (12.7)	0.059

CCI, Charlson comorbidity index ASA, American Society of Anesthesiologist; CHF, congestive heart failure; PVD, peripheral vascular disease; HTN, hypertension; DM, diabetes mellitus; Hb, Hemoglobin; EBL, Estimated Blood Loss

TPV, TPA, HUAC and Sarcopenia

Preoperative imaging was used to calculate morphometric parameters for sarcopenia among patients undergoing HPB surgery. Among the study cohort, the median TPA and TPV corrected for height were noted to be 723.0 (i.q.r. 618.5-891.8) mm^2/m^2 and 25.8 (i.q.r. 20.9- 31.7)cm^3/m^2, respectively. When stratified by sex, the median TPA and TPV were both noted to be higher among men compared with women (TPA; 852.6 [i.q.r. 702.9-971.0] mm^2/m^2 vs. 635.3 [i.q.r. 552.7-722.1] mm^2/m^2, TPV; 30.5 [i.q.r. 26.2-35.5] cm^3/m^2 vs. 21.0 [i.q.r. 18.2-24.1] cm^3/m^2, $p<0.001$). Similarly, the median HUAC was noted be 40.9 (i.q.r. 32.5-47.3) HU; the median HUAC was also noted to be higher among males (41.1 [i.q.r. 33.3-47.5] HU vs. 40.5 [i.q.r. 31.1-46.3] HU, p=0.29). Due to this potential confounding by sex, sex-specific quartiles for each parameter were developed that categorized patients in the lowest sex-specific quartile as sarcopenic. Examining the entire cohort, 112 (25.3%) patients were sarcopenic defined by TPA, 117 patients (25.0%) had sarcopenia defined by TPV and 112 (25.3%) patients presented with sarcopenia defined by the HUAC. Using all 3 parameters, the proportion of patients categorized preoperatively as sarcopenic did not vary between patients undergoing hepato-biliary or pancreatic surgery.

Preoperative Risk Factors Associated with 1-year all-cause Mortality

Among all patients included in the study cohort, the all-cause 1-year mortality was 14.1%. Of note, patients undergoing pancreatic or hepato-biliary procedures demonstrated a similar risk of mortality ($p>0.05$). Patients categorized as sarcopenic using the measurements for TPV and HUAC demonstrated a 78% and 92% greater risk of mortality, respectively (TPV; HR 1.78, CI 95% 1.05-3.0, p=0.03, HUAC; HR 1.92, CI 95% 1.15-3.22, p=0.01). In contrast, sarcopenia defined by TPA tended to be associated with 1-year survival (HR 1.62, CI 95% 0.96- 2.75, p=0.07, Table 2).

To further identify factors predictive of 1-year mortality following HPB surgery, a multivariable Cox proportional hazards regression model was built adjusting for patient and disease characteristics. A stepwise backward selection model based on AIC was used to select for the most parsimonious model that included preoperative comorbidity as defined by the CCI, indication for surgery (benign vs. malignant) and sex (Table 3). To further evaluate the predictive effect of sarcopenia, TPV, TPA and HUAC were each subsequently added to the model. Selection of the final model was based on comparisons of discrimination via Harrell's c- statistics (Table 3). On multivariable analysis after adjusting for patient and disease characteristics, patients with severe preoperative comorbidity classified as CCI≥4

Table 2. Univariable analysis for factors associated with 1-year mortality following Hepato-Pancreatico-Biliary Surgery in the Elderly

	1-year mortality		Univariable	
Factors selected	(%)	HR	95% CI	P value
Sex				
Female	**26 (11.3)**	Ref	-	-
Male	**47 (16.3)**	1.41	0.87-2.28	0.16
CCI				
≤3	**12 (5.2)**	Ref	-	-
>3	**61 (21.2)**	4.58	2.47-8.52	<0.001
Diagnosis				
Benign	**4 (3.1)**	Ref	-	-
Malignant	**69 (17.8)**	6.40	2.33-17.53	<0.001
Sarcopenia by TPA				
No	**40 (12.0)**	Ref	-	-
Sarcopenic	**21 (18.8)**	1.62	0.96-2.75	0.07
Sarcopenia by TPV				
No	**43 (12.3)**	Ref	-	-
Sarcopenic	**21 (18.0)**	1.78	1.05-3.00	0.03
Sarcopenia by HUAC				
No	**38 (11.5)**	Ref	-	-
Sarcopenic	**23 (20.5)**	1.92	1.15-3.22	0.01
Factors not selected				
Age				
65-79	**60 (13.2)**	Ref	-	-
≥80	**13 (20.6)**	1.63	0.89-2.97	0.11
ASA				
1-2	**10 (9.5)**	Ref	-	-
3-4	**63 (15.3)**	1.71	0.88-3.34	0.11
BMI				
≤25 kg/m²	**32 (14.2)**	Ref	-	-
25-30 kg/m²	**22 (11.9)**	0.80	0.46-1.38	0.42
>30 kg/m²	**13 (15.1)**	0.93	0.49-1.77	0.82
First Hb at admission				
>10g/dL	**67 (14.1)**	Ref	-	-
≤10g/dL	**6 (13.6)**	1.16	0.51-2.69	0.72
Procedure type				
Hepatectomy	**19 (20.2)**	Ref	-	-
Pancreatectomy	**54 (12.7)**	0.61	0.36-1.03	0.07

Table 3. Multivariable Cox proportional regression analysis

	TPA			TPV			HUAC			
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value	Score
Factors selected										
Sex										
Female	Ref	-	-	Ref	-	-	Ref	-	-	0
Male	1.38	0.81-2.35	0.23	1.42	0.84-2.38	0.19	1.42	0.84-2.41	0.19	3
CCI										
0-3	Ref	-	-	Ref	-	-	Ref	-	-	0
≥ 4	2.98	1.50-5.91	0.002	3.07	1.51-6.26	0.002	2.91	1.47-5.77	0.002	8
Diagnosis										
Benign	Ref	-	-	Ref	-	-	Ref	-	-	0
Malignant	3.85	1.13-13.06	0.03	3.52	1.04-11.96	0.04	3.94	1.17-13.30	0.03	10
Sarcopenia										
No	Ref	-	-	Ref	-	-	Ref	-	-	0
Sarcopenic	1.60	0.94-2.71	0.08	1.64	0.97-2.77	0.06	1.85	1.10-3.10	0.02	4

demonstrated an almost 3 times greater risk of mortality within 1 year following surgery (HR 2.91, CI 95% 1.45-5.77, p=0.002), while patients undergoing surgery for a malignant disease process demonstrated an almost 4 times greater risk of mortality following surgery (HR 3.94, CI 95% 1.17-13.30, p=0.03). Of note, patients presenting with sarcopenia as defined by HUAC demonstrated an 85% increased risk in mortality following surgery (HR 1.85, CI 95% 1.1-3.1, p=0.02). Areas under the receiver operating characteristic curve (AUROC) were used to quantify relative increments in the discriminatory ability of the final model with and without sarcopenia defined using HUAC (Figure 2). Of note, the inclusion of sarcopenia improved the discriminatory ability of the prediction model (p<0.001, Figure 2). Bootstrap validation of the model with 150 iterations demonstrated minimal evidence of model overfit.

Development of Risk-stratification Score

Point estimates obtained from the final multivariable model (including sarcopenia defined by HUAC) were used to generate a 25 point weighted risk-stratification score to predict preoperatively the risk of mortality among elderly patients undergoing HPB surgery.

Specifically, each parameter was assigned a weighted score (male sex; 3 points, CCI≥4; 8 points, malignant disease; 10 points, sarcopenia defined by HUAC; 4 points, Figure 3) and risk of mortality was categorized relative to the total score.

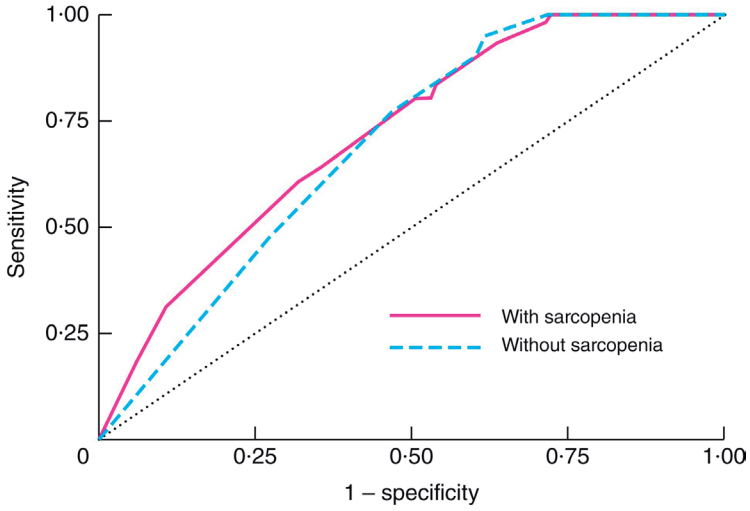


Figure 2. Area under the receiver operator curve characteristics demonstrating improved discrimination from 0.69 to 0.72 with inclusion of sarcopenia measured by HUAC.

One-year mortality was noted to be 2.2% among patients scoring 0-10 (low risk), 14.4% among patients scoring 11-20 (intermediate risk) and 23.3% among for patients scoring between 21 and 25 (high risk, p<0.001, Figure 3).

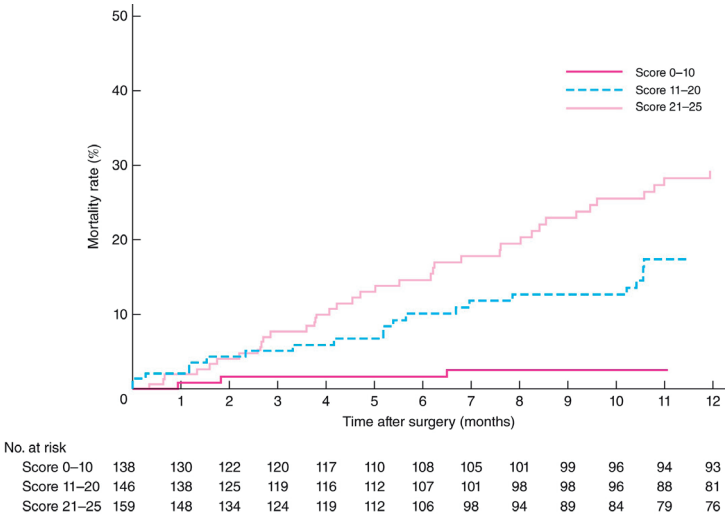


Figure 3. 1-year survival among patients undergoing HPB surgery stratified according to risk- stratification weighted score.

Discussion

Although mortality following HPB surgery has decreased dramatically over the past two decades, recent reports suggest that mortality among elderly patients undergoing HPB procedures still remains as high as 5 times greater than that for the overall population.[2,3,31] Given the heterogeneity in physiological reserve and therefore postoperative outcomes within the aging surgical population, appropriate risk stratification among the elderly is critical to help better predict and potentially avoid the high observed mortality.[11,12,21] Using a cohort of 518 patients aged ≥65 years, the present study identified preoperative morphometric and clinical parameters predictive of 1-year all-cause mortality following complex HPB surgery. Of note, among this elderly cohort of patients, despite most patients being preoperatively classified as high-risk according to their ASA score, there was significant heterogeneity in 1-year mortality risk. The current study was important because an accurate, risk-stratification tool with appropriate discrimination and calibration to identify patients at greatest risk for 1-year mortality using clinical and morphometric data was developed. In particular, with the inclusion of sarcopenia, a surrogate for patient frailty, we were able to identify those patients at highest risk for short-term mortality. Identification of such patients may assist in directing these individuals to interventions such as prehabilitation prior to surgery.[5]

While the use of frailty measures to appropriately risk-stratify patients has been widely recognized for medical conditions, the use of similar metrics for surgical patients has remained limited at best. A small number of studies have assessed the role of preoperative frailty among elderly patients undergoing surgery.[4,11,12,21] These studies have been limited, however, in their approach in that most included only limited clinical measurements, as well as subjective definitions of frailty.[4,10,13] In the current study, we used sarcopenia or muscle wasting as a metric to measure preoperative patient frailty / physiological reserve. Although not widely used, previous research has demonstrated sarcopenia to be an accurate, objective measure of frailty, with sarcopenic patients being at increased odds of postoperative complications and mortality.[15-18,20] The present study is unique in that it risk-stratifies patients undergoing HPB surgery using a clinical risk score that combined clinical and morphometric factors to assess patient frailty in an elderly population. In the past, the use of sarcopenia has been limited by disagreement in definitions regarding how to measure muscle mass / wasting.[15,20] For example, while previous research has suggested the use of total psoas area (TPA) as a means to quantify and measure patient frailty, more recent work has suggested that total psoas volume (TPV) and psoas density (HUAC) may be more accurate

means to measure sarcopenia and therefore frailty.[16,17,20,32] In the current study, it was noted that the use of psoas density was a more accurate measure of patient frailty compared with both TPV and TPA, and also independently predicted early mortality at 1- year. In a report by Joglekar et al. of patients undergoing pancreatic surgery, HUAC rather than other measures of sarcopenia was independently predictive of postoperative complications, longer length of stay and longer ICU stays.[20] A measure of radiation attenuation, HUAC can be readily calculated from preoperative cross-sectional imaging that is routinely performed prior to HPB surgery.[20] Additionally, while TPA and TPV can sometimes be difficult to measure in obese patients, HUAC is able to account for fat infiltration thereby facilitating assessment among obese patients.[33-35] Taken together, findings from the current study, as well as other published evidence, strongly suggest that preoperative radiological assessment of sarcopenia may help identify patients who are frail and therefore at high risk of mortality. In turn, such data may be used to facilitate health-care decision-making, and allow surgeons, patients, and caregivers to better manage perioperative expectations. For example, accurate preoperative identification of frail patients may allow identification of those individuals most at risk for postoperative complications and permit early intervention to improve short term outcomes following HPB surgery.[5]

The appropriate and accurate preoperative identification of frail patients is particularly important among elderly patients undergoing surgery.[10-12,21] Due to substantial heterogeneity in disease presentation and variable physiological effects of aging, standard indications and guidelines for treatment are often not generalizable to the elderly population.[4] Specifically, multiple chronic comorbidities, polypharmacy, dysregulation of physiological systems, altered hormonal function and decreased immune responses can all contribute to the variable presentation and therefore outcomes among older patients undergoing surgery.[36-40] Further, given that the proportion of elderly patients is expected to increase four-fold within the next ten years, preoperative identification and intervention for those elderly patients most at risk is critical.[41] Older, frail patients are at greater risk for developing postoperative complications that often result in significant functional disability requiring labour-intensive and costly support in the form of additional procedures, greater intensity of care and the need for nursing assistance at discharge.[41]

In the current study, a 25 point composite score using 4 easy and readily available parameters to appropriately identify patients at greatest risk for 1-year mortality after surgery is proposed. Of note, all cause 1-year mortality ranged widely from

2.2% to 23.3% among low and high-risk patients, respectively. While previous studies have proposed the assessment of frailty or physiologic reserve via subjective clinical assessments such as exhaustion and decreased activity, this study combines morphometric and clinical parameters to develop an objective risk- stratification tool to identify frail, elderly patients.[4,11,12,21] Specifically, sarcopenic patients (defined by HUAC), demonstrated an 85% greater risk of mortality, while the inclusion of sarcopenia measured by HUAC increasing the discriminative power of the model by about 3%. This incremental increase is consistent with previously studies that have assessed the effect of frailty specific parameters in predicting 1-year mortality.[42] For example, a recent systematic review of patients undergoing cardiac surgery noted that the addition of frailty specific parameters resulted in a mean incremental increase of 4% in the discriminative power of conventional risk scores.[42] These authors concluded that the use of composite frailty measures represents a more accurate method for identifying frail patients.[42]

The present study had several limitations. The current analyses were limited only to HPB procedures. As such, future work is necessary to assess the performance of the proposed score among patients undergoing a wider variety of surgical procedures. In addition, it is possible that due to the omission of disease-specific parameters as well as additional postoperative measures including functional status and quality of life, certain important factors predictive of mortality were unaccounted for. Finally, given that the current study was performed at a single center, the risk-stratification score requires further external validation in an independent dataset. Internal validation with bootstrapping techniques did, however, suggest a good model fit with minimal overfitting.

This study demonstrates that sarcopenia as measure by HUAC is an accurate measure of frailty among elderly patients undergoing complex HPB surgery and is an independent predictor of 1-year mortality. In addition, a 25 point risk-stratification score that incorporated clinical and morphometric parameters accurately identifies elderly patients at the highest risk for 1-year morality following surgery. As such, the proposed score represents a convenient manner for clinicians to help identify those elderly patients who are most likely to be frail and therefore at the highest risk of suffering an early death within 1 year of HPB surgery.

References

1 Berger NA, Savvides P, Koroukian SM, Kahana EF, Deimling GT, Rose JH, et al. Cancer in the elderly. Trans Am Clin Climatol Assoc 2006;117:147–55; discussion 155–6.

2 Spolverato G, Ejaz A, Hyder O, Kim Y, Pawlik TM. Failure to rescue as a source of variation in hospital mortality after hepatic surgery. Br J Surg 2014;101:836–46. doi:10.1002/bjs.9492.

3 Mayo SC, Pulitano C, Marques H, Lamelas J, Wolfgang CL, de Saussure W, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. J Am Coll Surg 2013;216:707–16; discussion 716–8. doi:10.1016/j.jamcollsurg.2012.12.029.

4 Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg 2010;210:901–8. doi:10.1016/j.jamcollsurg.2010.01.028.

5 Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 2014; 121:937–47. doi:10.1097/ALN.0000000000000393.

6 Rockwood K. Frailty and its definition: a worthy challenge. J Am Geriatr Soc 2005;53:1069–70. doi: 10.1111/j.1532-5415.2005.53312.x.

7 Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95. doi:10.1503/cmaj.050051.

8 Rose M, Pan H, Levinson MR, Staples M. Can frailty predict complicated care needs and length of stay? Intern Med J 2014;44:800–5. doi:10.1111/imj.12502.

9 Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora RC. Frailty and perioperative outcomes: a narrative review. Can J Anaesth 2014. doi:10.1007/s12630-014-0273-z.

10 Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26:1091–101. doi:10.1093/annonc/mdu540.

11 Melin AA, Schmid KK, Lynch TG, Pipinos II, Kappes S, Matthew Longo G, et al. Preoperative frailty Risk Analysis Index to stratify patients undergoing carotid endarterectomy. J Vasc Surg 2014. doi: 10.1016/j.jvs.2014.10.009.

12 McAdams-DeMarco MA, Law A, Salter ML, Chow E, Grams M, Walston J, et al. Frailty and early hospital readmission after kidney transplantation. Am J Transplant 2013;13:2091–5. doi:10.1111/ajt.12300.

13 Revenig LM, Canter DJ, Taylor MD, Tai C, Sweeney JF, Sarmiento JM, et al. Too frail for surgery? Initial results of a large multidisciplinary prospective study examining preoperative variables predictive of poor surgical outcomes. J Am Coll Surg 2013;217:665–70.e1. doi:10.1016/j.jamcollsurg.2013.06.012.

14 Reisinger KW, van Vugt JLA, Tegels JJW, Snijders C, Hulsewé KWE, Hoofwijk AGM, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015;261:345–52. doi:10.1097/SLA.0000000000000628.

15 Amini N, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, et al. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. J Gastrointest Surg 2015. doi:10.1007/s11605-015-2835-y.

16 Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB (Oxford) 2011;13:439–46. doi:10.1111/j.1477- 2574.2011.00301.x.

17 Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg 2012;16:1478–86. doi: 10.1007/s11605-012-1923-5.

18 Dodson RM, Firoozmand A, Hyder O, Tacher V, Cosgrove DP, Bhagat N, et al. Impact of sarcopenia on outcomes following intra-arterial therapy of hepatic malignancies. J Gastrointest Surg 2013;17: 2123–32. doi:10.1007/s11605-013-2348-5.

19 Valero V, Amini N, Spolverato G, Weiss MJ, Hirose K, Dagher NN, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. J Gastrointest Surg 2015;19:272–81. doi:10.1007/s11605-014-2680-4.

20 Joglekar S, Asghar A, Mott SL, Johnson BE, Button AM, Clark E, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol 2015;111: 771–5. doi:10.1002/jso.23862.

21 Kim S, Han H-S, Jung H, Kim K, Hwang DW, Kang S-B, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg 2014;149:633–40. doi:10.1001/jamasurg.2014.241.

22 Ejaz A, Spolverato G, Kim Y, Frank SM, Pawlik TM. Variation in triggers and use of perioperative blood transfusion in major gastrointestinal surgery. Br J Surg 2014;101:1424–33. doi:10.1002/bjs.9617.

23 Ejaz A, Frank SM, Spolverato G, Kim Y, Pawlik TM. Potential Economic Impact of Using a Restrictive Transfusion Trigger Among Patients Undergoing Major Abdominal Surgery. JAMA Surg 2015. doi: 10.1001/jamasurg.2015.81.

24 American Society of Anesthesiologists - American Society of Anesthesiologists n.d. http://www.asahq.org/ (accessed May 1, 2015).

25 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

26 WHO :: Global Database on Body Mass Index n.d. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed May 1, 2015).

27 Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–35. doi:10.1016/S1470-2045(08)70153-0.

28 Sober E. Instrumentalism, Parsimony, and the Akaike Framework. Philos Sci 2002;69:S112–23. doi: 10.1086/341839.

29 Steyerberg EW, Bleeker SE, Moll HA, Grobbee DE, Moons KG. Internal and external validation of predictive models: A simulation study of bias and precision in small samples. J Clin Epidemiol 2003;56: 441–7. doi:10.1016/S0895-4356(03)00047-7.

30 Steyerberg EW, Harrell FE, Borsboom GJJ., Eijkemans MJ., Vergouwe Y, Habbema JDF. Internal validation of predictive models. J Clin Epidemiol 2001;54:774–81. doi:10.1016/S0895-4356(01)00341-9.

31 Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in Hospital Volume and Failure to Rescue for Pancreatic Surgery. J Gastrointest Surg 2015. doi:10.1007/s11605-015-2800-9.

32 Dodson RM, He J, Pawlik TM. Resection and transplantation for hepatocellular carcinoma: factors influencing surgical options. Future Oncol 2014;10:587–607. doi:10.2217/fon.13.225.

33 Waters DL, Baumgartner RN. Sarcopenia and obesity. Clin Geriatr Med 2011;27:401–21. doi: 10.1016/j.cger.2011.03.007.

34 Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr 2014;68:1001–7. doi:10.1038/ejcn.2014.117.

35 Batsis JA, Barre LK, Mackenzie TA, Pratt SI, Lopez-Jimenez F, Bartels SJ. Variation in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with different research definitions: dual-energy X-ray absorptiometry data from the National Health and Nutrition Examination Survey 1999-2004. J Am Geriatr Soc 2013;61:974–80. doi:10.1111/jgs.12260.

36 Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333–41.

37 Cappola AR, Bandeen-Roche K, Wand GS, Volpato S, Fried LP. Association of IGF-I levels with muscle strength and mobility in older women. J Clin Endocrinol Metab 2001;86:4139–46. doi:10.1210/ jcem.86.9.7868.

38 Varadhan R, Walston J, Cappola AR, Carlson MC, Wand GS, Fried LP. Higher levels and blunted diurnal variation of cortisol in frail older women. J Gerontol A Biol Sci Med Sci 2008;63:190–5.

39 Leng SX, Cappola AR, Andersen RE, Blackman MR, Koenig K, Blair M, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA- S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging Clin Exp Res 2004;16:153–7.

40 Leng SX, Yang H, Walston JD. Decreased cell proliferation and altered cytokine production in frail older adults. Aging Clin Exp Res 2004;16:249–52.

41 Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005; 242:326–41; discussion 341–3.

42 Bagnall NM, Faiz O, Darzi A, Athanasiou T. What is the utility of preoperative frailty assessment for risk stratification in cardiac surgery? Interact Cardiovasc Thorac Surg 2013;17:398–402. doi:10.1093/icvts/ ivt197.

Supplementary Table: Comparison of variables included in the Cox regression model (Stepwise regression using AIC vs. Lasso) with their corresponding regression coefficients

Characteristic	Stepwise (AIC)	Lasso
	HR (95% CI)	HR (95% CI)
Age	Not selected	1.36 (0.70-2.63)
Sex	1.42 (0.84-2.41)	1.38 (0.81-2.35)
CCI	2.91 (1.47-5.77)	2.88 (1.45-5.71)
ASA	Not selected	Not selected
Malignancy	3.94 (1.17-13.30)	3.79 (1.12-12.80)
BMI	Not selected	Not selected
Preoperative Hemoglobin	Not selected	Not selected
Procedure type	Not selected	Not selected
Sarcopenia*	1.85 (1.10-3.10)	1.90 (1.14-3.15)

*defined using HUAC (Hounsfield Unit Average Calculation)

AIC: Akaike Information Criterion , CCI: Charlson comorbidity index, ASA: American Society of Anesthesiologists (ASA) physical classification grade, BMI: Body Mass Index

PART II Prognosis after Surgery

CHAPTER 6

Quality and Performance of Validated Prognostic Models for Survival after Resection of Hepatobiliary or Pancreatic Cancer: A Systematic Review

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Submitted

Abstract

Background Many prognostic models have been proposed to predict disease-free survival (DFS) or overall survival (OS) for patients after resection of hepatobiliary or pancreatic (HPB) cancer. The objective of this systematic review was to evaluate the performance of these prognostic models on external validation. The secondary objective was to assess methodological study quality regarding model derivation.

Methods The PRISMA guidelines were followed. All external validation studies of prognostic models for patients with resected primary or secondary malignant HPB tumors were identified. Model performance was assessed by model discrimination and calibration. Quality assessment of the model derivation involved cohort description, statistical analyses, reporting of results, and model performance.

Results In total, 49 external validation studies were identified, which overall validated 70 different prognostic models; 14 for Colorectal Liver Metastases, 29 for Hepatocellular Carcinoma, 10 for Pancreatic Carcinomas and 17 for Biliary Cancers. Since some models were validated multiple times for both OS and DFS; 181 validations were performed in total. In CRLM 1 model was identified with good performance (AUC/C-index >0.70). Only 14 (36.8%) models for hepatocellular carcinoma had good performance on validation. Other hepatobiliary malignancy models demonstrated moderate performance as well. Model calibration was rarely assessed; 42 validations (23.2%) performed no calibration at all, 120 validations (66.3%) only reported survival curves, and 19 validations (10.5%) detailed calibration curves. Methodological quality of derivation studies was poor; 19 (42%) of the derivation studies adequately reported the handling of missing data and only 7 (16%) studies used continuous prognostic factors in the model.

Discussion Most prognostic models in HPB surgery suffer from poor methodological quality and poor performance on external validation.

Introduction

Many prognostic models have been proposed to predict survival for individual patients after resection of hepatobiliary or pancreatic cancer.[1-9] More accurate prediction of outcomes may improve shared decision-making and personalized medicine.[1-9] For example, postoperative models can be used to guide adjuvant therapy and surveillance for recurrent disease. The performance of a prognostic model is determined by discrimination and calibration.[10] Discrimination is the ability of the model to determine which patient is high-risk and which patient is low-risk. Calibration is the agreement between the observed and predicted outcomes for individual patients.[10] Model performance should be judged at external validation prior to clinical use. Non-validated models are at a risk of overestimating predictive ability, a risk known as optimism.[10]

Developing a prognostic model (model derivation) is a complex process. A recent systematic review found that the majority of prognostic models in high-impact journals do not follow methodological recommendations limiting their applicability and reliability.[11] As such, we sought to perform a systematic review to identify studies that externally validated one or more prognostic models for survival among patients who underwent a resection for hepatobiliary or pancreatic cancer. We sought to assess model performance at external validation, as well as determine the methodological quality of the studies in which the prognostic models were developed.

Methods

The PRISMA Statement was followed for the reporting of this systematic review (www.prisma-statement.org). A comprehensive search of Embase, Medline, Web of Science, the Cochrane database, and Google Scholar was performed, using the search terms provided in supplemental document A. The last search was conducted on November 15th, 2017. Eligible studies performed an external validation of one or more prognostic models for disease-free survival (DFS) or overall survival (OS) among patients who underwent a resection of primary or secondary cancer of the liver, pancreas, or bile ducts. The tumor types included Colorectal Liver Metastases (CRLM), Hepatocellular Carcinoma (HCC), Pancreatic Duct Adenocarcinoma (PDAC), Pancreatic Neuro-Endocrine Tumor (PNET), Intrahepatic Cholangiocarcinoma (ICC), Perihilar Cholangiocarcinoma (PHC), and Distal Cholangiocarcinoma (DCC). All studies written in the English language and published after 1990 were considered. Non-original articles (i.e. reviews or expert opinions) were excluded. Studies with prognostic models containing prognostic factors that are

not used in clinical practice (e.g., RNA/DNA sequencing data or liquid biopsies) were also excluded. Studies were excluded if no model performance measures were reported.[12] Studies with patients treated with transplantation, ablation, or other techniques other than resection were also excluded. Finally, studies were excluded if they were applied to patients after recurrence of malignancy.

Validation studies

Two reviewers (SB and BGa) independently assessed the abstracts of all studies identified by the search. Eligibility was determined by reviewing the full manuscript of potentially relevant studies. Disagreement between the reviewers was resolved by discussion. Descriptive, methodological, and outcome data from each validation study were extracted using a standard form by two reviewers (SB and BGa) and independently validated by a third reviewer (JV). If a validation study validated more than one prognostic model, data was extracted for each validated model. Descriptive statistics included type of malignancy, publication date, method of treatment, number of prognostic factors, sample size, type of outcome, and performance (discrimination and/or calibration assessment).

Performance of the prognostic models at external validation was evaluated by discrimination and calibration. Discrimination was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC), Harrell's concordance index (c-index), the Brier score, or a similar measure.[10,13] Because the c-index was the most commonly reported discrimination measure, it was used as the principal measure of external validity. The c-index is the probability, that for two random patients, the patient with the worst *predicted* survival had the worst *observed* survival. A c-index of 0.5 indicates no predictive discrimination and a value of 1.0 indicates perfect separation of patients with different outcomes.[13] For binary outcomes, i.e. studies in which time to event is disregarded, the AUC equals the c-index.[13] An AUC/c-index of < 0.6 was considered poor quality, while a c-index between 0.6-0.7 was considered moderate quality, and a c-index above 0.7 was considered good quality. Calibration is the agreement between observed outcomes and predictions for individual patients. Calibration is assessed using the calibration plot, intercept and/or slope. Because a number of the proposed models do not provide an estimate of OS or DFS, assessment of the calibration of the models in validation studies was made difficult. For example, the AJCC staging systems imply a worse prognosis for higher stages, but do not accompany that prediction with a survival estimate. Survival curves can be used to grossly compare prognosis per risk group in the validation study with prognosis and model estimates in the derivation study.

Derivation studies

The included validation studies performed an external validation of one or more prognostic models. Using the reference lists of these studies, we identified the corresponding publications describing the development (i.e. derivation) of these models. To determine the methodological quality of these models, the following data was extracted: publication date, participant information, candidate prognostic factors information, outcome information, statistical power information, selection of prognostic factors, handling of missing values, presentation of results, and model performance and validation. No consensus guideline exists to determine the quality of model derivation studies. Therefore, a review by participants of the Cochrane Prognostic Studies group was used as a guideline.[11] Based on this review we systematically performed a quality assessment considering cohort description, statistical analyses, reporting of results, and model performance.

Results

Validation studies

Electronic searches identified 7,779 results (Figure 1). After removing duplicates, 5,147 studies remained, of which 181 full-text articles were screened. Of the full-text articles, 48 external validation studies met the inclusion criteria. These 48 studies performed 181 model validations; 134 for OS and 47 for DFS. The total number of patients in which a model was externally validated ranged from 42 to 21,512 patients. The median number of patients in which CRLM models were validated was 286 (range: 97-1151). The median number of patients in which a validation was performed was 774 (range: 42-3138) for HCC and 540 for hepatobiliary tumors (range: 75-21,512). All external validation studies are referenced in Table 1.

Derivation models

The validation studies validated 70 different prognostic models. Of the 70 included models, 27 (39%) were validated in only 1 study, whereas the rest was validated in 2 or more studies. These models were validated 35 times with DFS as the outcome and 61 times with OS as the outcome; 35 models were only validated for OS, 9 models only for DFS, and 26 models for both outcomes. The median number of prognostic factors in the models was 4 (range: 2-14). In 45 prognostic models (64%), statistical methods were used for model derivation; 25 models (36%) were consensus based. Of the statistically derived models, 14 were for predictions in CRLM, 19 for HCC, 3 for pancreatic carcinoma and 9 for cholangiocarcinoma.

Consensus based models included various editions of the American Joint Committee on Cancer (AJCC) TNM staging for HCC, ICC, PHC, DCC, and PDAC. Other well-known consensus based models for HCC included the Barcelona Clinic Liver Cancer (BCLC), the International Hepatopancreatobiliary Association (IHPBA) HCC staging, the Japan Integrated Score (JIS), and the Chinese HCC staging system. For pancreatic neuroendocrine tumors consensus based models included the ENETS pancreatic neuro-endocrine tumor classification and the WHO pancreatic neuro-endocrine tumor classification (both the 2004 and 2010 edition).

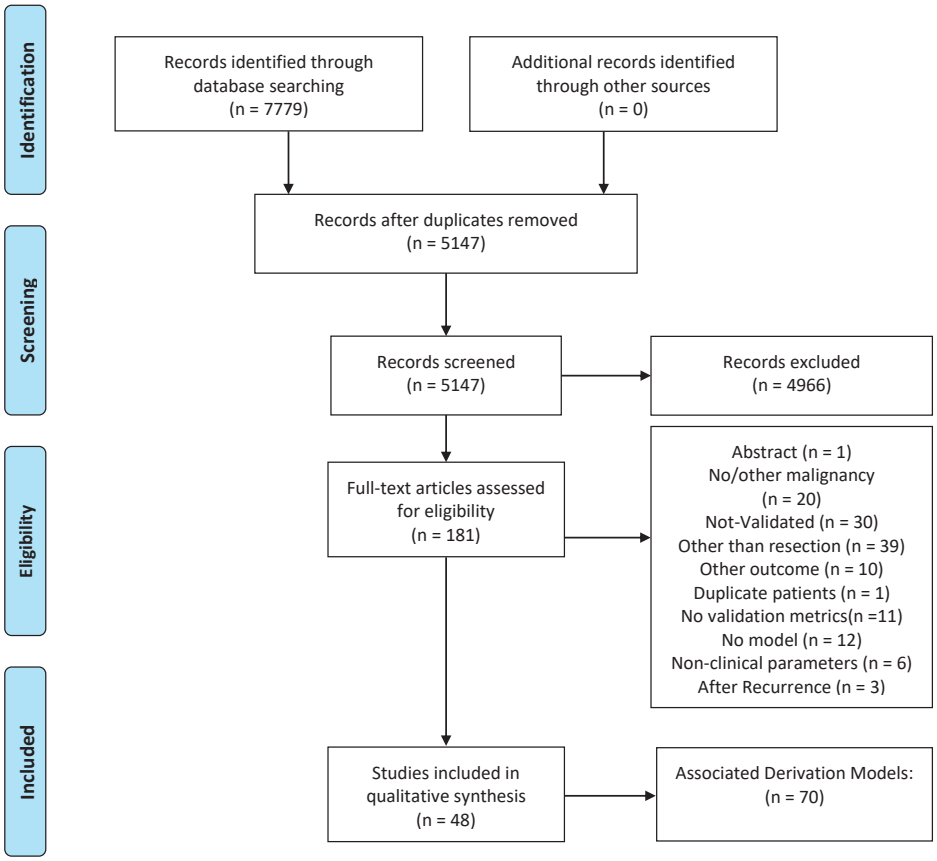

Figure 1. Prisma Flow Diagram, to find studies that validate prognostic models after resection of HPB cancer.

Performance of models at validation - discrimination

Table 1A-D present the performance of 70 derivation models that were validated in 48 external validation studies. Across all types of cancer and outcomes, 30 models (31%) performed poorly at external validation with an AUC or c-index below 0.60, 43 models (45%) had moderate performance with a c-index between 0.6 and 0.7, and 23 models (24%) had a good performance (green background in Table 1).

For CRLM, only 1 out of 14 (7%) models (Kanemitsu's preoperative prognostic model) reached an average c-index of 0.7 on external validation for OS (Table 1A).[14] However, this model was only validated in one study of 113 patients.[15] The Clinical Risk Score by Fong et al. was the only model validated in more than two different patient cohorts, but performed poorly with an average c-index of 0.57 for DFS and 0.54 for OS.[16]

For HCC, models were validated for 38 different outcomes (n=11 DFS; n=27 OS). In total 15 models (40%) showed good discriminative ability in repeated validation efforts (depicted in green in Table 1B). The model with the highest c-index was the LCSGJ staging (0.89 for OS), however it was only validated in 1 cohort of 42 patients. The highest c-index in models that were validated in multiple cohorts was JIS for OS (0.76), in a total number of 3115 patients over 5 studies.

Among patients with pancreatic cancer (Table 1C), the pancreatoduodenectomy prognostic index (PPI) was validated with a c-index of 0.74. Only one large validation study was identified (n = 21,512 patients). For pancreatic neuro-endocrine tumors, the WHO 2010 and the modified WHO 2010 achieved a c-index of 0.70 and 0.87 respectively, although in small cohorts (205 patients and 127 patients respectively). Four studies were validated twice (MSKCC Staging, AJCC 7th, ENETS and WHO 2010).

For biliary cancers 24 different models and outcomes were validated (Table 1D). Most AJCC staging systems performed sub-par, with a c-index <0.7. Only for distal cholangiocarcinoma (DCC), the 5th and 7th AJCC staging systems reached an average c-index of 0.7 or higher. For ICC and DCC, 2 statistics based models had good discrimination (c-index > 0.7) at validation (Wang's nomogram and Yeh's nomogram). However, the validation cohort for Yeh's model was small. Most of the available models were only validated once or twice, except the AJCC 6th and 7th edition, the LCSGJ staging, Okabayashi staging and Wang nomogram.

Table 1 Validation of prognostic models; (A) CRLM, (B) HCC and (C) Pancreatobiliary Tumors. Models validated with a median c-index of ≥ 0.70 are colored green, models validated with a median c-index of 0.60-0.70 are colored yellow, while those with a lower median c-index are colored red.

A Colorectal Liver Metastases

Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus or Statistics Based	Calibration Curve/ Kaplan Meier
DFS	Beppu et al.	6	[35]	234	0.59	S	CC
	Clinical Risk Score (Fong)	5	[36,37]	948	0.57 (0.55-0.58)	S	KM
	Iwatsuki et al.	5	[36,37]	948	0.58 (0.55-0.60)	S	KM
	Konopke et al.	3	[36]	286	0.61	S	KM
	Mayo Staging DFS	4	[36]	286	0.54	S	KM
	Nagashima	5	[36]	286	0.59	S	KM
	Nordlinger	7	[36,37]	948	0.58 (0.56-0.60)	S	KM
	Rees postoperative	7	[36]	286	0.64	S	KM
	Rees preoperative	7	[36]	286	0.59	S	KM
OS	Adam Nomogram	5	[38]	97	0.64	S	-
	Clinical Risk Score (Fong)	5	[36,37,39]	1151	0.54 (0.53-0.56)	S	KM
	Iwatsuki et al.	5	[36,37]	948	0.56 (0.53-0.59)	S	KM
	Kanemitsu postoperative	6	[15]	113	0.69	S	KM
	Kanemitsu preoperative	5	[15]	113	0.70	S	KM
	Konopke et al.	3	[36]	286	0.58	S	KM
	Mayo Staging DSS	4	[36]	286	0.55	S	KM
	MSKCC Staging	10	[15,39]	316	0.64 (0.60-0.68)	S	CC
	Nagashima	5	[36]	286	0.62	S	KM
	Nordlinger	7	[36,37]	948	0.60 (0.55-0.64)	S	KM
	Rees postoperative	7	[36]	286	0.63	S	KM
	Rees preoperative	7	[36]	286	0.59	S	KM

B Hepatocellular Carcinoma

Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus or Statistics Based	Calibration Curve/ Kaplan Meier
Pulmonary DFS	Li Nomogram	6	[40]	218	0.82	S	CC
DFS	AJCC 6th	3	[41]	1313	0.53	C	KM
	AJCC 7th	3	[41-44]	3138	0.63 (0.51-0.65)	C	KM
	BCLC	4	[42,44]	1139	0.59 (0.58-0.60)	C	-
	CLIP	4	[42,44]	1139	0.58 (0.58-0.58)	S	-
	CUPI	6	[42,43]	1091	0.53 (0.51-0.54)	S	-
	JIS	8	[43]	686	0.58	C	-
	MSKCC Staging	4	[42,44]	1139	0.60 (0.58-0.62)	S	-
	Okuda	4	[42,44]	1139	0.53 (0.53-0.54)	S	-
	Li DFS	8	[45]	474	0.73	S	CC
	SLICER	8	[44]	734	0.64	S	-
OS	AJCC 6th	3	[41,46-51]	3910	0.70 (0.50-0.86)	C	KM
	AJCC 7th	3	[41,43,44,52-55]	4815	0.66 (0.50-0.76)	C	KM
	Artificial Networking	N/A	[49]	104	0.83	N/A	-
	BCLC	4	[44,49-58]	5813	0.68 (0.58-0.83)	C	KM
	Chinese Staging	3	[50]	438	0.72	C	KM
	CLIP	4	[44,46-48,51,52,54-57]	4364	0.69 (0.54-0.96)	S	KM
	CUPI	6	[43,47,51,57]	2235	0.58 (0.52-0.60)	S	KM
	EASL/AASLD	7	[59]	917	0.58	C	-
	GETCH	5	[57]	357	0.56	S	KM
	GPS	2	[52,56]	499	0.68 (0.61-0.76)	S	KM
	Hangzhou	4	[53]	774	0.69	S	KM
	HKLC	4	[55]	618	0.69	S	KM
	IHPBA	5	[49]	543	0.71	C	-
	JIS	8	[43,46,48,51,52,54,57]	3115	0.76 (0.53-0.87)	C	KM

B Hepatocellular Carcinoma (*continued*)

Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus or Statistics Based	Calibration Curve/ Kaplan Meier
	LCSGJ	5	[48]	42	0.89	C	KM
	Li OS	8	[45]	474	0.77	S	CC
	Li Postoperative	6	[60]	90	0.77	S	CC
	Li Preoperative	5	[60]	90	0.67	S	CC
	mGPS	2	[52,56,61]	702	0.67 (0.61-0.70)	S	KM
	MSKCC Staging	4	[44]	734	0.71	S	-
	Okuda	4	[44,47,51]	1926	0.59 (0.53-0.54)	S	KM
	Yang Postop	10	[54]	180	0.78	S	CC
	Yang Preop	7	[54]	180	0.74	S	CC
	Prognostic Index	2	[56,61]	552	0.63 (0.60-0.66)	N/A	KM
	PNI	2	[56,62]	738	0.57 (0.53-0.60)	N/A	KM
	SLICER	8	[44]	734	0.72	S	-
	Tokyo Score	4	[57]	357	0.61	S	KM

C Pancreatic Cancer PDAC Pancreatic Duct Adenocarcinoma, PNET Pancreatic Neuro-Endocrine Tumors

	Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus or Statistics Based	Calibration Curve/ Kaplan Meier
PDAC	DFS	AJCC 6th	3	[63]	21,512	0.61	C	KM
		AJCC 7th	3	[64]	212	0.68	C	KM
	OS	MSKCC Staging	14	[65,66]	618	0.68 (0.62-0.74)	S	CC
		PPI	3	[67]	194	0.74	S	KM
PNET	DFS	AJCC 7th	3	[68]	75	0.65	C	KM
		ENETS	3	[68]	75	0.66	C	KM
		Hochwald	2	[68]	75	0.68	S	KM
		WHO 2004	6	[68]	75	0.63	C	KM
		WHO 2010	2	[68]	75	0.67	C	KM
	OS	AJCC 7th	3	[69,70]	404	0.63 (0.58-0.68)	C	KM
		ENETS	3	[69,70]	404	0.69 (0.68-0.69)	C	KM
		WHO 2010	2	[70,71]	205	0.70 (0.60-0.80)	C	KM
		mWHO 2010	2	[71]	127	0.87	C	KM

D Biliary Malignancies ICC Intrahepatic Cholangiocarcinoma, PHC Perihilar Cholangiocarcinoma, DCC Distal Cholangiocarcinoma

	Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus Statistics Based	Calibration Curve/ Kaplan Meier
ICC	DFS	AJCC 7th	3	[72,73]	1160	0.58 (0.57-0.58)	C	KM
		Hyder	6	[72]	1054	0.52	S	KM
		LCSGJ	3	[72]	1054	0.56	C	M
		Nathan	3	[72]	1054	0.58	S	KM
		Okabayashi	3	[72]	1054	0.56	S	KM
		Renji Nomogram	8	[73]	106	0.65	S	CC
		SHPBSJ	3	[72]	1054	0.56	S	KM
		Wang	7	[72]	1054	0.61	S	KM
	OS	AJCC 6th	3	[74,75]	311	0.64 (0.63-0.64)	C	KM
		AJCC 7th	3	[8,72,74-77]	2928	0.64 (0.62-0.68)	C	KM
		AJCC 8th	3	[77]	1008	0.67	C	KM
		Fudan	5	[76]	188	0.55	S	KM
		Hyder	6	[72,76]	1242	0.63 (0.60-0.66)	S	CC
		LCSGJ	3	[8,72,74]	1547	0.64 (0.63-0.65)	C	KM
		Nathan	3	[8,72]	1421	0.64 (0.64-0.64)	S	KM
		Okabayashi	3	[8,72,74]	1547	0.67 (0.61-0.67)	S	KM
		SHPBSJ	3	[72]	1054	0.61	S	KM
		Wang	7	[8,72,76]	1324	0.72 (0.69-0.75)	S	CC
		Yeh	10	[75]	105	0.72 (0.64-0.79)	S	CC
PHC	OS	AJCC 7th	3	[78,79]	580	0.62 (0.57-0.66)	C	KM
		MSKCC Staging	3	[78,79]	540	0.65 (0.59-0.72)	S	CC

D Biliary Malignancies ICC Intrahepatic Cholangiocarcinoma, PHC Perihilar Cholangiocarcinoma, DCC Distal Cholangiocarcinoma (*continued*)

	Outcome	Model	Number of Covariates	Validation studies	Total Patients	C-index (range)	Consensus Statistics Based	Calibration Curve/ Kaplan Meier
DCC	OS	AJCC 5th	3	[80]	516	0.70	C	KM
		AJCC 6th	3	[80]	516	0.67	C	KM
		AJCC 7th	3	[80]	516	0.82	C	KM

D Biliary Malignancies ICC Intrahepatic Cholangiocarcinoma, PHC Perihilar Cholangiocarcinoma, DCC Distal Cholangiocarcinoma

Performance of models at validation - calibration

Kaplan-Meier survival estimates of the different risk groups were reported in 137 out of the 181 validation settings. In contrast, calibration plots or tables, for comparing predicted with observed survival for individual patients were only reported in 19 validations (10.5%), for 14 models (20%). Finally, calibration was not reported at all in 42 validations (23.2).

Quality assessment of derivation studies

In the majority of the 39 derivation studies, detailing the derivation of 45 statistics-based models, the cohort was well described (Table 2A). All studies reported clear inclusion criteria (n=45; 100%) and defined an inclusion period (n=45; 100%). A detailed description of the derivation cohort (n=43; 96%) and its follow-up (n=35; 78%) were provided in most studies. Prospective studies were a minority, with 71% (n=32) of studies describing a retrospective cohort.

Reporting of methods and analyses of the derivation studies is shown in Table 2B. Although the main outcome was OS in the majority of derivation studies, the definition of survival (e.g., calculated from diagnosis or resection) was only provided in 28 (62%) studies. Most studies (n=38, 84%) dichotomized or categorized continuous prognostic factors resulting in loss of information. Moreover, interaction of prognostic factors was rarely evaluated (n=5; 11%). Particularly models pertaining to CRLM cancer surgery were conducted in large prospective cohorts, with more than 15 events per prognostic factor in the multivariable analysis in 79% (n=11) of the studies. This was the case in 60% (n=27) of all studies. Handling of missing data was not adequately reported in most studies (n=26; 58%).

In the majority of the assessed studies, selection of the prognostic factors for the final model was conducted based on statistical analysis (Table 2C). The statistical methods were accurately described with clear criteria for selecting prognostic factors in 80% of studies. Univariable correlations between risk factors and outcomes were described in two thirds of the studies (67%), whereas multivariable correlation of the prognostic factors included in the model was described in fewer studies (n=29; 64%).

Evaluation of model performance in the derivation studies differed in quality (Table 2D). While about half of the studies analyzed discrimination using c-indices or AUC (n=25; 56%), presentation of the calibration of the models was lacking in 56% (n=25) of derivation studies. The Brier score, a measure for overall model performance, was missing in all derivation studies. Validity assessment using

bootstrapping techniques or internal validation was performed in approximately half of the derivation studies (n=20; 44%). External validation in derivation studies was performed in 14 studies (31%). For all reported characteristics one point could be earned, except for statistical selection of prognostic factors, resulting in a maximum total of 17 points. The average number of points achieved was 10/17. The c-index at validation was weakly associated with the number of points at derivation of the models (Figure 2A and 2B).

Table 2 Reporting of cohort description (A), analyses (B), results (C), and performance (D) in the model derivation studies. The numbers in the table are percentages. Percentages 0-32 are colored red, 33-65 are colored yellow, and 66 and up colored in green

A

	Number of Studies	Prospective Cohort	Inclusion Criteria Clear	Baseline Characteristics	Recruitment Dates	Follow-Up Reported
Colorectal Liver Metastases	14	29	100	93	100	93
Hepatocellular Carcinoma	19	42	100	100	100	58
Pancreas Carcinoma	3	33	100	100	100	100
Biliary Malignancies	9	0	100	89	100	89
Overall	45	29	100	96	100	78

B

	Outcome Definition	Interaction Tested	Continuous Predictors Used	Sample Size >15 per Predictor	Missing Data Reported	Handling of Missing Data
Colorectal Liver Metastases	79	14	14	79	21	50
Hepatocellular Carcinoma	74	5	11	58	16	37
Pancreas Carcinoma	0	0	33	67	33	67
Biliary Malignancies	33	22	22	33	0	33
Overall	62	11	16	60	16	42

C

	Based on Statistical Analysis	Clear Method for Variable Selection	Univariable Results Presented	Multivariable Results Presented
Colorectal Liver Metastases	100	86	71	71
Hepatocellular Carcinoma	79	95	74	47
Pancreas Carcinoma	100	67	0	67
Biliary Malignancies	100	44	67	89
Overall	91	80	67	64

D

	Calibration Analyzed	Discrimination Analyzed	Validity Assessment	External Validity Assessment	**Total Score**
Colorectal Liver Metastases	36	50	36	7	10
Hepatocellular Carcinoma	47	53	79	42	10
Pancreas Carcinoma	33	67	33	33	9
Biliary Malignancies	56	67	67	44	9
Overall	44	56	60	31	10

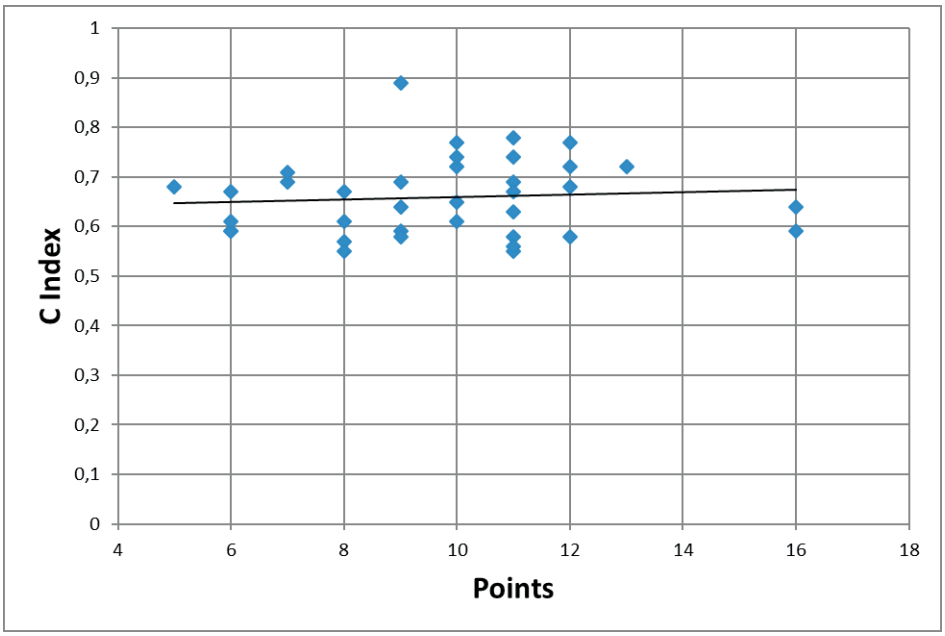

Figure 2A. C-index of OS as a function of derivation study quality

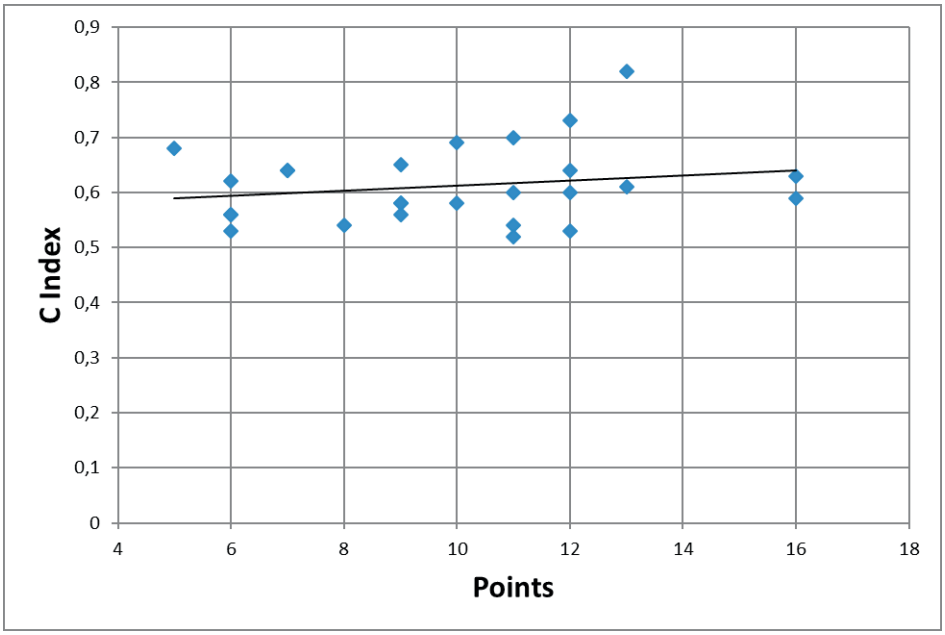

Figure 2B. C-index of DFS as a function of derivation study quality

Discussion

We identified 70 validated prognostic models for survival of patients after resection of CRLM, hepatobiliary or pancreatic cancers. Most prognostic models had poor performance (c-statistic <0.70) on external validation or were validated only in small cohorts (n<500). Exceptions include several HCC models (IHPBA, JIS, MSKCC, and SLICER), the Wang model for ICC, and the 7th edition of AJCC staging for DCC.[8,17-21] No prognostic model demonstrated a good performance at external validation in a large cohort for CRLM, PDAC, PNET, and PHC. Model quality was poor as reflected by inadequate handling of missing data and unnecessary dichotomization of continuous prognostic factors. Quality at validation was relatively poorer still in models for DFS, presumably because most studies were retrospective and follow-up was not protocolized.

For all hepatobiliary and pancreatic cancers, many models for the same outcome (OS, DFS) were available. The availability of multiple models for each type of cancer reflects the trend of making new models rather than validating existing models.[22-24] Small cohort size in derivation studies has contributed to poor model performance. Typically, performance may seem good in small derivation cohorts, but performance is often poor when applied to an external dataset for validation. This can partially be remedied by employing proper internal validation methods, most notably bootstrapping[12,25] and internal-external cross-validation (e.g., in multicenter studies each participating hospital's patients can be left out once).[25,26] Small cohort size is also a problem for external validation. For example, the average validation cohort of CRLM was only about 200 patients, while each year about 1 million people are diagnosed with colorectal cancer. A consequence of the small sample size of validation cohorts is the observed disagreement on model performance between external validations with small sample size.

The limited methodological quality of derivation studies also contributed to poor performance. Almost all derivation studies employed stepwise variable selection procedures. This method leads to spurious results in small studies, as the chance of biased cohort selection and lack of power increase.[10] Furthermore, information on missing data and the way it was handled was often lacking. Commonly, regression analysis has been performed using standard statistical software packages with complete cases only, whereas patients with any missing values are excluded, reducing statistical power.[10,27,28] Especially if systematic differences between complete and incomplete cases exists, analysis of complete cases only induces selection bias. If the missing data is related to patient characteristics, imputation of data is the most suitable way to minimize bias.[10,29] Appropriate handling of missing

data when developing a prognostic model, might help improve its performance in external patient cohorts. Furthermore, the exact approach of the multivariable model development was often not reported. Dichotomizing continuous prognostic factors at arbitrary cutoffs also contributed to bias and less power.[30] The majority of studies presented the final model in a simplified form, such as a risk score or a nomogram. Although this makes a model easy to interpret, precision is lost by rounding numbers in a risk score or imprecise and cumbersome measurement of outcomes using a nomogram.[30]

The goal of prognostic models is to improve shared decision-making and personalized medicine. For example, a patient with excellent predicted OS is unlikely to benefit from adjuvant systemic chemotherapy or intensive surveillance for recurrent disease. However, most prognostic models report individual outcomes based on patient and tumor characteristics, regardless of subsequent treatment. "Predictive" models are necessary to determine and compare individual outcomes of various treatment options.[31] Without such "predictive" models, the individual predicted survival advantage of adjuvant chemotherapy can only be inferred from OS and DFS reported by prognostic models.

Historically, models have been developed with the ease of clinical use in mind. Therefore, many prognostic models have been simplified into simple risk scores and nomograms; for example, the Clinical Risk Score and Milan criteria. These models are still in use, but meet very few of the current recommendations for deriving a prognostic model.[16,32] Such simplifications are no longer necessary; for example, web-based calculators can calculate the exact individual outcomes. Ideally, prognostic models are integrated in a patient information system that automatically assembles all relevant prognostic factors (e.g., age and tumor stage) into individual predicted outcomes.

Future research should focus first on validating existing models in large cohorts. If existing models have poor performance (discrimination or calibration) at external validation with large cohorts, new models should be developed using large (international) cohorts. Prognostic models with readily available patient and tumor characteristics (e.g., age and tumor stage) are also important as a benchmark for novel prognostic biomarkers.[33,34] An exquisite model based on the expression of 50 genes is only relevant for prognostication if it results in a clinically meaningful improvement of the best available model with readily available patient and tumor characteristics.

Our study has several limitations. First, we only assessed externally validated prognostic models. Consequently, we may have excluded recent promising prognostic models that have not yet been validated. Secondly, calibration of models is difficult to quantify and summarize; consequently, we only evaluated whether calibration was reported at all.

In conclusion, prognostic models for survival after resection of hepatobiliary and pancreatic cancer mostly have poor methodological quality and poor performance on external validation. Guidelines for reporting prognostic models (i.e. TRIPOD statement) should be followed. Guidelines for deriving and validating prognostic models are needed. Future research should focus on external validation of existing models in very large cohorts, rather than deriving new models in small cohorts.

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References

1. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *The lancet oncology* 2009; **10**(11): 1045-52.
2. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.
3. International Bladder Cancer Nomogram C, Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 2006; **24**(24): 3967-72.
4. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007; **25**(11): 1316-22.
5. Song C, Kim K, Chie EK, et al. Nomogram prediction of survival and recurrence in patients with extrahepatic bile duct cancer undergoing curative resection followed by adjuvant chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013; **87**(3): 499-504.
6. van der Gaag NA, Kloek JJ, de Bakker JK, et al. Survival analysis and prognostic nomogram for patients undergoing resection of extrahepatic cholangiocarcinoma. *Ann Oncol* 2012; **23**(10): 2642-9.
7. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* 2011; **29**(35): 4627-32.
8. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 2013; **31**(9): 1188-95.
9. Wierda WG, O'Brien S, Wang X, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. *Blood* 2007; **109**(11): 4679-85.
10. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York: Springer; 2009.
11. Bouwmeester W, Zuithoff NP, Mallett S, et al. Reporting and methods in clinical prediction research: a systematic review. *PLoS Med* 2012; **9**(5): 1-12.
12. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology (Cambridge, Mass)* 2010; **21**(1): 128-38.
13. Frank E H, Kerry L LEE, Daniel B M. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* 1996; **15**(4): 361-87.
14. Kanemitsu Y, Kato T. Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. *World J Surg* 2008; **32**(6): 1097-107.
15. Takakura Y, Okajima M, Kanemitsu Y, et al. External validation of two nomograms for predicting patient survival after hepatic resection for metastatic colorectal cancer. *World J Surg* 2011; **35**(10): 2275-82.

16. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**(3): 309-18; discussion 18-21.

17. Makuuchi M, Belghiti J, Belli G, et al. IHPBA concordant classification of primary liver cancer: working group report. *J Hepatobiliary Pancreat Surg* 2003; **10**(1): 26-30.

18. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J Gastroenterol* 2003; **38**(3): 207-15.

19. Cho CS, Gonen M, Shia J, et al. A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. *J Am Coll Surg* 2008; **206**(2): 281-91.

20. Ang SF, Ng ES, Li H, et al. The Singapore Liver Cancer Recurrence (SLICER) Score for relapse prediction in patients with surgically resected hepatocellular carcinoma. *PLoS One* 2015; **10**(4): e0118658.

21. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology* 2010; **17**(6): 1471-4.

22. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009; **338**: b605.

23. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009; **338**: b606.

24. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. *JAMA* 1997; **277**(6): 488-94.

25. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal–external, and external validation. *Journal of Clinical Epidemiology* 2016; **69**(Supplement C): 245-7.

26. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001; **54**(8): 774-81.

27. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *American journal of epidemiology* 1995; **142**(12): 1255-64.

28. Little RJA, Rubin DB. Statistical analysis with missing data: John Wiley & Sons; 2014.

29. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. A gentle introduction to imputation of missing values. *Journal of clinical epidemiology* 2006; **59**(10): 1087-91.

30. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006; **25**(1): 127-41.

31. Oldenhuis CNAM, Oosting SF, Gietema JA, de Vries EGE. Prognostic versus predictive value of biomarkers in oncology. *European Journal of Cancer*; **44**(7): 946-53.

32. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**(11): 693-9.

33. Margonis GA, Buettner S, Andreatos N, et al. Anatomical Resections Improve Disease-free Survival in Patients With KRAS-mutated Colorectal Liver Metastases. *Ann Surg* 2017; **266**(4): 641-9.

34. Brudvik KW, Jones RP, Giuliante F, et al. RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases. *Ann Surg* 2017.

35. Okuno M, Hatano E, Seo S, et al. Indication for neoadjuvant chemotherapy in patients with colorectal liver metastases based on a nomogram that predicts disease-free survival. *J Hepato-Biliary-Pancreatic Sci* 2014; **21**(12): 881-8.

36. Roberts KJ, White A, Cockbain A, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. *Br J Surg* 2014; **101**(7): 856-66.

37. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: Value for risk scoring systems? *Ann Surg* 2007; **246**(2): 183-91.

38. Mavros MN, Hyder O, Pulitano C, Aldrighetti L, Pawlik TM. Survival of patients operated for colorectal liver metastases and concomitant extra-hepatic disease: External validation of a prognostic model. *J Surg Oncol* 2013; **107**(5): 481-5.

39. Reddy SK, Kattan MW, Yu C, et al. Evaluation of peri-operative chemotherapy using a prognostic nomogram for survival after resection of colorectal liver metastases. *HPB* 2009; **11**(7): 592-9.

40. Li J, Liu Y, Yan Z, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy. *Br J Cancer* 2014; **110**(5): 1110-7.

41. Huang JT, Zhang YJ, Peng ZW, et al. A modified TNM-7 staging system to better predict the survival in patients with hepatocellular carcinoma after hepatectomy. *Journal of Cancer Research and Clinical Oncology* 2013; **139**(10): 1709-19.

42. Ang SF, Ng ESH, Li H, et al. The Singapore Liver Cancer Recurrence (SLICER) Score for relapse prediction in patients with surgically resected hepatocellular carcinoma. *PLoS ONE* 2015; **10**(4).

43. Feng LH, Dong H, Lau WY, et al. Novel microvascular invasion-based prognostic nomograms to predict survival outcomes in patients after R0 resection for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2017; **143**(2): 293-303.

44. Fu YP, Yi Y, Huang JL, et al. Prognostic nomograms stratify survival of patients with hepatocellular carcinomawithout portal vein tumor thrombosis after curative resection. *Oncologist* 2017; **22**(5): 561-9.

45. Li J, Zhou J, Yang PH, et al. Nomograms for survival prediction in patients undergoing liver resection for hepatitis B virus related early stage hepatocellular carcinoma. *Eur J Cancer* 2016; **62**((Li J.; Yang P.-H.; Xia Y.; Wu D.; Lv G.; Wang K.; Wan X.-Y.; Lau W.Y.; Wu M.-C.; Shen F., shenfengehbh@sina.com) Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China): 86-95.

46. Chen TW, Chu CM, Yu JC, et al. Comparison of clinical staging systems in predicting survival of hepatocellular carcinoma patients receiving major or minor hepatectomy. *Eur J Surg Oncol* 2007; **33**(4): 480-7.

47. Lu W, Dong J, Huang Z, Guo D, Liu Y, Shi S. Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP, TNM and CUPI. *J Gastroenterol Hepatol* 2008; **23**(12): 1874-8.

48. Noda T, Sasaki Y, Yamada T, et al. Usefulness of the CLIP scoring system for prediction of postoperative prognosis of patients with large hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2009; **16**(4): 538-45.

49. Qiao G, Li J, Huang A, Yan Z, Lau WY, Shen F. An artificial neural networking model for the prediction of post-hepatectomy survival of patients with early hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; **29**(12): 2014-20.

50. Xu LB, Wang J, Liu C, et al. Staging systems for predicting survival of patients with hepatocellular carcinoma after surgery. *World J Gastroenterol* 2010; **16**(41): 5257-62.

51. Yang T, Zhang J, Lu JH, et al. A new staging system for resectable hepatocellular carcinoma: Comparison with six existing staging systems in a large Chinese cohort. *J Cancer Res Clin Oncol* 2011; **137**(5): 739-50.

52. Kinoshita A, Onoda H, Imai N, et al. The Glasgow Prognostic Score, an inflammation based prognostic score, predicts survival in patients with hepatocellular carcinoma. *BMC Cancer* 2013; **13**.

53. Liu C, Duan LG, Lu WS, et al. Prognosis evaluation in patients with hepatocellular carcinoma after hepatectomy: Comparison of BCLC, TNM and Hangzhou criteria staging systems. *PLoS ONE* 2014; **9**(8).

54. Yang P, Qiu J, Li J, et al. Nomograms for Pre- and Postoperative Prediction of Long-term Survival for Patients Who Underwent Hepatectomy for Multiple Hepatocellular Carcinomas. *Ann Surg* 2015.

55. Shen J, He L, Li C, et al. Prognostic nomograms for patients with resectable hepatocelluar carcinoma incorporating systemic inflammation and tumor characteristics. *Oncotarget* 2016; **7**(49): 80783-93.

56. Huang J, Xu L, Luo Y, He F, Zhang Y, Chen M. The inflammation-based scores to predict prognosis of patients with hepatocellular carcinoma after hepatectomy. *Med Oncol* 2014; **31**(4).

57. Kim BK, Kim SU, Park JY, Kim DY, Ahn SH, Han KH. Applicability of bclc stage for prognostic stratification in comparison with other staging systems; single center experience from long-term outcomes of 1,717 treatment-naive patients with hepatocellular carcinoma. *J Hepatol* 2012; **56**: S285-S6.

58. Ruan DY, Lin ZX, Wang TT, et al. Nomogram for preoperative estimation of long-term survival of patients who underwent curative resection with hepatocellular carcinoma beyond Barcelona clinic liver cancer stage A1. *Oncotarget* 2016; **7**(38): 61378-89.

59. Sposito C, Di Sandro S, Brunero F, et al. Development of a prognostic scoring system for resectable hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**(36): 8194-202.

60. Li Y, Xia Y, Li J, et al. Prognostic Nomograms for Pre- and Postoperative Predictions of Long-Term Survival for Patients Who Underwent Liver Resection for Huge Hepatocellular Carcinoma. *J Am Coll Surg* 2015; **221**(5): 962-74.

61. Wang JQ, Cheng PG, Li MY, Ma LM. Comparison of the prognostic value of C-reactive protein-based prognostic scores in patients with hepatitis B virus-related hepatocellular carcinoma. *Int J Clin Exp Med* 2016; **9**(5): 8272-9.

62. Zhang X, Li C, Wen T, Peng W, Yan L, Yang J. Postoperative Prognostic Nutritional Index Predicts Survival of Patients with Hepatocellular Carcinoma within Milan Criteria and Hypersplenism. 2017.

63. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC pancreatic cancer staging system: Report from the National Cancer Database. *Cancer* 2007; **110**(4): 738-44.

64. Liu KH, Hsu CH, Hsu JT, et al. A nomogram for predicting the probability of recurrence in patients with carcinomas located in the ampulla of Vater. *J Cancer* 2017; **8**(3): 425-33.

65. De Castro SMM, Biere SSAY, Lagarde SM, Busch ORC, Van Gulik TM, Gouma DJ. Validation of a nomogram for predicting survival after resection for adenocarcinoma of the pancreas. *Br J Surg* 2009; **96**(4): 417-23.

66. Ferrone CR, Kattan MW, Tomlinson JS, Thayer SP, Brennan MF, Warshaw AL. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. *J Clin Oncol* 2005; **23**(30): 7529-35.

67. Dasari BV, Roberts KJ, Hodson J, et al. A model to predict survival following pancreaticoduodenectomy for malignancy based on tumour site, stage and lymph node ratio. *HPB* 2016; **18**(4): 332-8.

68. Liu TC, Hamilton N, Hawkins W, Gao F, Cao D. Comparison of WHO classifications (2004, 2010), the Hochwald grading system, and AJCC and ENETS staging systems in predicting prognosis in locoregional well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol* 2013; **37**(6): 853-9.

69. Ellison TA, Wolfgang CL, Shi C, et al. A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: A validation of current staging systems and a new prognostic nomogram. *Ann Surg* 2014; **259**(2): 204-12.

70. Ye L, Ye H, Zhou Q, et al. A retrospective cohort study of pancreatic neuroendocrine tumors at single institution over 15 years: New proposal for low- and high-grade groups, validation of a nomogram for prognosis, and novel follow-up strategy for liver metastases. *Int J Surg* 2016; **29**: 108-17.

71. Ricci C, Casadei R, Taffurelli G, et al. Validation of the 2010 WHO classification and a new prognostic proposal: A single centre retrospective study of well-differentiated pancreatic neuroendocrine tumours. *Pancreatology* 2016.

72. Buettner S, Galjart B, van Vugt JLA, et al. Performance of prognostic scores and staging systems in predicting long-term survival outcomes after surgery for intrahepatic cholangiocarcinoma. 2017.

73. Jeong S, Cheng Q, Huang L, et al. Risk stratification system to predict recurrence of intrahepatic cholangiocarcinoma after hepatic resection. *BMC Cancer* 2017; **17**(1).

74. Ali SM, Clark CJ, Mounajjed T, et al. Model to predict survival after surgical resection of intrahepatic cholangiocarcinoma: The Mayo Clinic experience. *HPB* 2015; **17**(3): 244-50.

75. Yeh CN, Wang SY, Chen YY, et al. A Prognostic Nomogram for Overall Survival of Patients After Hepatectomy for Intrahepatic Cholangiocarcinoma. *Anticancer Res* 2016; **36**(8): 4249-58.

76. Doussot A, Groot-Koerkamp B, Wiggers JK, et al. Outcomes after Resection of Intrahepatic Cholangiocarcinoma: External Validation and Comparison of Prognostic Models. *J Am Coll Surg* 2015; **221**(2): 452-61.

77. Kim Y, Moris DP, Zhang XF, et al. Evaluation of the 8th edition American Joint Commission on Cancer (AJCC) staging system for patients with intrahepatic cholangiocarcinoma: A surveillance, epidemiology, and end results (SEER) analysis. *J Surg Oncol* 2017.

78. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-Development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.

79. Buettner S, van Vugt JL, Gani F, et al. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. 2016.

80. Wiltberger G, Krenzien F, Benzing C, et al. Prognostic Accuracy of the Seventh Edition of the TNM Classification Compared with the Fifth and Sixth Edition for Distal Cholangiocarcinoma. *Ann Surg Oncol* 2015: 1-7.

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operative* OR operation* OR resect* OR hepatectom* OR pancreatectom* OR whipple OR pancreaticoduodenectom*).ab,ti.) NOT (exp animals/ NOT humans/)

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(((nomogram*):ab,ti) OR ((((predict* NEAR/6 (model* OR surviv* OR mortalit* OR recurren* OR algorithm*))):ab,ti) AND ((validat* OR validit* OR (discriminat* NEAR/3 (perform* OR power*)) OR roc OR rocs OR (receiver* NEAR/3 operat* NEAR/3 (characteristic* OR curve*)) OR (area* NEAR/3 curve*) OR auc OR aucs OR concordan* OR calibrat* OR reproducib*):ab,ti))) AND ((((‘digestive system’ OR hepat* OR intrahepat* OR gastrointestin* OR liver OR pancrea* OR hpb OR billiar*) NEAR/3 (tumor* OR tumour OR neoplas* OR cancer OR carcino* OR adenocarcino* OR resect*)) OR hepatectom* OR pancreatectom* OR whipple OR pancreaticoduodenectom* OR cholangiocarcinom*):ab,ti) AND ((surg* OR operative* OR operation* OR resect* OR hepatectom* OR pancreatectom* OR whipple OR pancreaticoduodenectom*):ab,ti)

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TS=((((nomogram*)) OR ((((predict* NEAR/5 (model* OR surviv* OR mortalit* OR recurren* OR algorithm*)))) AND ((validat* OR validit* OR (discriminat* NEAR/2 (perform* OR power*)) OR roc OR rocs OR (receiver* NEAR/2 operat* NEAR/2 (characteristic* OR curve*)) OR (area* NEAR/2 curve*) OR auc OR aucs OR concordan* OR calibrat* OR reproducib*)))) AND ((((“digestive system” OR hepat* OR intrahepat* OR gastrointestin* OR liver OR pancrea* OR hpb OR billiar*) NEAR/2 (tumor* OR tumour OR neoplas* OR cancer OR carcino* OR adenocarcino* OR resect*)) OR hepatectom* OR pancreatectom* OR whipple OR pancreaticoduodenectom* OR cholangiocarcinom*)) AND ((surg* OR operative* OR operation* OR resect* OR hepatectom* OR pancreatectom* OR whipple OR pancreaticoduodenectom*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine) NOT (human* OR patient*)))

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((“nomograms”[mh] OR (nomogram*[tiab])) OR ((((survival[mh] OR mortality[mh] OR mortality[sh] OR “recurrence”[mh] OR “Neoplasm Recurrence, Local”[mh] OR “prognosis”[mh]) AND (“Models, Theoretical”[mh] OR “Algorithms”[mh])) OR ((predict*[tiab] AND (model*[tiab] OR surviv*[tiab] OR mortalit*[tiab] OR recurren*[tiab] OR algorithm*[tiab])))) AND (“Reproducibility of Results”[mh] OR “Validation Studies”[mh] OR “Validation Studies as Topic”[mh] OR “ROC Curve”[mh] OR “Area Under Curve”[mh] OR

(validat*[tiab] OR validit*[tiab] OR (discriminat*[tiab] AND (perform*[tiab] OR power*[tiab])) OR roc OR rocs OR (receiver*[tiab] AND (operating[tiab]) AND (characteristic*[tiab] OR curve*[tiab])) OR (area*[tiab] AND curve*[tiab]) OR auc OR aucs OR concordan*[tiab] OR calibrat*[tiab]))))) AND ("Gastrointestinal Neoplasms"[mh] OR "Hepatectomy"[mh] OR "Pancreatectomy"[mh] OR ((("digestive system" OR hepatic*[tiab] OR hepato*[tiab] OR hepatob*[tiab] OR hepatoc*[tiab] OR intrahepat*[tiab] OR gastrointestin*[tiab] OR liver OR pancreas*[tiab] OR pancreat*[tiab] OR hpb OR billiar*[tiab]) AND (tumor*[tiab] OR tumour OR neoplas*[tiab] OR cancer OR carcino*[tiab] OR adenocarcino*[tiab] OR resect*[tiab])) OR hepatectom*[tiab] OR pancreatectom*[tiab] OR whipple OR pancreaticoduodenectom*[tiab] OR cholangiocarcinom*[tiab])) AND ("Surgical Procedures, Operative"[mh] OR "surgery"[sh] OR (surg*[tiab] OR operation*[tiab] OR operative*[tiab] OR resect*[tiab] OR hepatectom*[tiab] OR pancreatectom*[tiab] OR whipple OR pancreaticoduodenectom*[tiab])) NOT (animals[mh] NOT humans[mh]) AND publisher[sb]

Google scholar

nomogram|nomograms "liver|pancreas|pancreatic|hepatic|hpb surgery|resection" |hepatectomy|hepatectomies|pancreatectomy|pancreaticoduodenectomy|pancreatectomies|pancreaticoduodenectomies|whipple

Supplemental Document B. Included Models

Colorectal Liver Metastases

Based on Statistical Analysis

1. **Adam et al.** Adam R, de Haas RJ, Wicherts DA, et al. Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? Ann Surg 2011; 253(2): 349-59.
2. **Beppu et al.** Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2012; 19(1): 72-84.
3. **Fong Clinical Risk Score.** Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999; 230(3): 309-18; discussion 18-21.
4. **Iwatsuki et al.** Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 1999; 189(3): 291-9.
5. **Kanemitsu preoperative.** Kanemitsu Y, Kato T. Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. World J Surg 2008; 32(6): 1097-107.
6. **Kanemitsu postoperative.** Kanemitsu Y, Kato T. Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. World J Surg 2008; 32(6): 1097-107.
7. **Konopke et al.** Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int 2009; 29(1): 89-102.
8. **Mayo Staging disease specific survival.** Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? Ann Surg 2007; 246(2): 183-91.
9. **Mayo Staging disease free survival.** Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? Ann Surg 2007; 246(2): 183-91.
10. **MSKCC.** Kattan MW, Gonen M, Jarnagin WR, et al. A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. Ann Surg 2008; 247(2): 282-7.
11. **Nagashima et al.** Nagashima I, Takada T, Matsuda K, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. J Hepatobiliary Pancreat Surg 2004; 11(2): 79-83.
12. **Nordlinger et al.** Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 1996; 77(7): 1254-62.
13. **Rees preoperative.** Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008; 247(1): 125-35.

14. **Rees postoperative.** Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008; 247(1): 125-35.

Hepatocellular Carcinoma

Based on Statistical Analysis

15. **CLIP.** A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998; 28(3): 751-5.

16. **CUPI.** Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 2002; 94(6): 1760-9.

17. **GETCH.** Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 1999; 31(1): 133-41.

18. **Glasgow Prognostic Scale (GPS).** Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 2003; 89(6): 1028-30.

19. **Hangzhou.** Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008; 85(12): 1726-32.

20. **HKLC.** Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014; 146(7): 1691-700 e3.

21. **LCSGJ.** Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg 2007; 245(6): 909-22.

22. **Li Nomogram.** Li J, Liu Y, Yan Z, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy. Br J Cancer 2014; 110(5): 1110-7.

23. **Li Overall Survival.** Li J, Zhou J, Yang PH, et al. Nomograms for survival prediction in patients undergoing liver resection for hepatitis B virus related early stage hepatocellular carcinoma. *Eur J Cancer* 2016

24. **Li Disease Free Survival.** Li J, Zhou J, Yang PH, et al. Nomograms for survival prediction in patients undergoing liver resection for hepatitis B virus related early stage hepatocellular carcinoma. *Eur J Cancer* 2016

25. **Li preoperative.** Li Y, Xia Y, Li J, et al. Prognostic Nomograms for Pre- and Postoperative Predictions of Long-Term Survival for Patients Who Underwent Liver Resection for Huge Hepatocellular Carcinoma. J Am Coll Surg 2015; 221(5): 962-74 e4.

26. **Li postoperative.** Li Y, Xia Y, Li J, et al. Prognostic Nomograms for Pre- and Postoperative Predictions of Long-Term Survival for Patients Who Underwent Liver Resection for Huge Hepatocellular Carcinoma. J Am Coll Surg 2015; 221(5): 962-74 e4.

27. **mGPS.** McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis 2007; 22(8): 881-6.

28. **MSKCC.** Cho CS, Gonen M, Shia J, et al. A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. J Am Coll Surg 2008; 206(2): 281-91.

29. **Okuda.** Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985; 56(4): 918-28.

30. **SLICER.** Ang SF, Ng ESH, Li H, Ong YH, Choo SP, et al. (2015) The Singapore Liver Cancer Recurrence (SLICER) Score for Relapse Prediction in Patients with Surgically Resected Hepatocellular Carcinoma. PLOS ONE 10(4): e0118658.

31. **Tokyo.** Tateishi R, Yoshida H, Shiina S, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 2005; 54(3): 419-25.

32. **Yang preoperative.** Yang P, Qiu J, Li J, et al. Nomograms for Pre- and Postoperative Prediction of Long-term Survival for Patients Who Underwent Hepatectomy for Multiple Hepatocellular Carcinomas. Ann Surg 2016; 263(4): 778-86.

33. **Yang postoperative.** Yang P, Qiu J, Li J, et al. Nomograms for Pre- and Postoperative Prediction of Long-term Survival for Patients Who Underwent Hepatectomy for Multiple Hepatocellular Carcinomas. Ann Surg 2016; 263(4): 778-86.

Consensus Based Models

34. **AJCC 6th Edition.** Greene F, Page D, Fleming I, Balch C, Haller D, Morrow M. AJCC Cancer Staging Manual. 6th edition ed: Springer 2002.

35. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

36. **Artificial Neural Network.** Qiao G, Li J, Huang A, Yan Z, Lau WY, Shen F. An artificial neural networking model for the prediction of post-hepatectomy survival of patients with early hepatocellular carcinoma. J Gastroenterol Hepatol 2014; 29(12): 2014-20.

37. **BCLC.** Llovet JM, Fuster J, Bruix J. Prognosis of hepatocellular carcinoma. Hepato-gastroenterology 2002; 49(43): 7-11.

38. **Chinese Staging.** Yan P, Yan LN. Staging of hepatocellular carcinoma. Hepatobiliary & pancreatic diseases international : HBPD INT 2003; 2(4): 491-5.

39. **EASL/AASLD.** European Organisation For Research And Treatment Of Cancer. EASLEORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943

40. **IHPBA.** Makuuchi M, Belghiti J, Belli G, et al. IHPBA concordant classification of primary liver cancer: working group report. J Hepatobiliary Pancreat Surg 2003; 10(1): 26-30.

41. **JIS.** Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). Journal of Gastroenterology 2003; 38(3): 207-15.

42. **Prognostic Index (Validation Study).** Huang J, Xu L, Luo Y, He F, Zhang Y, Chen M. The inflammation-based scores to predict prognosis of patients with hepatocellular carcinoma after hepatectomy. Med Oncol 2014; 31(4).

43. **Prognostic Nutritional Index (PNI).** Nozoe T, Ninomiya M, Maeda T, Matsukuma A, Nakashima H, Ezaki T. Prognostic nutritional Index: A tool to predict the biological aggressiveness of gastric carcinoma. Surgery Today 2010; 40(5): 440-3.

Intrahepatic Cholangiocarcinoma

Based on Statistical Analysis

44. **Fudan.** Jiang W, Zeng ZC, Tang ZY, et al. A prognostic scoring system based on clinical features of intrahepatic cholangiocarcinoma: the Fudan score. Ann Oncol 2011; 22(7): 1644-52.

45. **Hyder et al.** Hyder O, Marques H, Pulitano C, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. JAMA Surg 2014; 149(5): 432-8.

46. **Nathan.** Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol 2009; 16(1): 14-22.

47. **Okabayashi.** Okabayashi T, Yamamoto J, Kosuge T, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer 2001; 92(9): 2374-83.

48. **Renji Nomogram.** Jeong S, Cheng Q, Huang L, et al. Risk stratification system to predict recurrence of intrahepatic cholangiocarcinoma after hepatic resection. *BMC Cancer* 2017; **17**(1).

49. **SHPBSJ.** Uenishi T, Ariizumi S, Aoki T, et al. Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2014; 21(7): 499-508.

50. **Wang.** Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013; 31(9): 1188-95.

51. **Yeh.** Yeh CN, Wang SY, Chen YY, et al. A Prognostic Nomogram for Overall Survival of Patients After Hepatectomy for Intrahepatic Cholangiocarcinoma. *Anticancer Res* 2016; **36**(8): 4249-58.

Consensus Based Models

52. **AJCC 6th Edition.** Greene F, Page D, Fleming I, Balch C, Haller D, Morrow M. AJCC Cancer Staging Manual. 6th edition ed: Springer 2002.

53. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

54. **AJCC 8th Edition.** Amin MB, Edge S, Greene F, et al. (eds.) AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017.

55. **LCSGJ.** The Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer, Second edn. Tokyo: Kanehara; 2003.

Perihilar Cholangiocarcinoma

Based on Statistical Analysis

56. **MSKCC.** Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. Ann Oncol 2015; 26(9): 1930-5.

Consensus Based Models

57. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

Distal Cholangiocarcinoma

Consensus Based Models

58. **AJCC 5th Edition.** Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP, O'Sullivan B, Sobin LH, Yarbro JW. AJCC Cancer Staging Manual. 5th edition ed: Lippincott – Raven. 1997.

59. **AJCC 6th Edition.** Greene F, Page D, Fleming I, Balch C, Haller D, Morrow M. AJCC Cancer Staging Manual. 6th edition ed: Springer 2002.

60. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

Pancreatic Neuro-Endocrine Tumor

Based on Statistical Analysis

61. **Hochwald.** Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol 2002; 20(11): 2633-42.

Consensus Based Models

62. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

63. **ENETS.** Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449(4): 395-401.

64. **Modified WHO 2010.** Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. 2010; 23(6): 824-33.

65. **WHO 2004.** DeLellis RA, Lloyd RV, Heitz PU, et al. Pathology and Genetics of Tumours of Endocrine Organs. IARC Press: Lyons, France, 2004.

66. **WHO 2010.** Bosman FT, Carneiro F, Hruban RH, et al., editors. WHO classification of tumours of the digestive system. International Agency for Research on Cancer; Lyon (France): 2010.

Pancreatic Adenocarcinoma

Based on Statistical Analysis

67. **MSKCC.** Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic Nomogram for Patients Undergoing Resection for Adenocarcinoma of the Pancreas. Annals of Surgery 2004; 240(2): 293-8.

68. **Pancreatoduodenectomy prognostic index (PPI).** Dasari BV, Roberts KJ, Hodson J, et al. A model to predict survival following pancreaticoduodenectomy for malignancy based on tumour site, stage and lymph node ratio. HPB (Oxford) 2016; 18(4): 332-8.

Consensus Based Models

69. **AJCC 6th Edition.** Greene F, Page D, Fleming I, Balch C, Haller D, Morrow M. AJCC Cancer Staging Manual. 6th edition ed: Springer 2002.

70. **AJCC 7th Edition.** Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging handbook: from the AJCC cancer staging manual 7th edition. New York: Springer; 2009.

CHAPTER 7

Performance of Prognostic Scores and Staging Systems in Predicting Long-Term Survival Outcomes after Surgery for Intrahepatic Cholangiocarcinoma

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Abstract

Introduction: We sought to validate the commonly used prognostic models and staging systems for intrahepatic cholangiocarcinoma (ICC) in a large multi-center patient cohort.

Methods: The overall (OS) and disease free survival (DFS) prognostic discriminatory ability of various commonly used models were assessed in a large retrospective cohort. Harrell's concordance index (c-index) was used to determine accuracy of model prediction.

Results: Among 1,054 ICC patients, median OS was 37.7 months and 1-, 3- and 5-year survival, were 78.8%, 51.5% and 39.3%, respectively. Recurrence of disease occurred in 454 (43.0%) patients with a median DFS of 29.6 months. One-, 3- and 5- year DFS were 64.6%, 46.5 % and 44.4%, respectively. The prognostic models associated with the best OS prediction were the Wang nomogram (c-index 0.668) and the Nathan staging system (c-index 0.639). No model was proficient in predicting DFS. Only the Wang nomogram exceeded a c-index of 0.6 for DFS (c-index 0.602). The c-index for the AJCC staging system was 0.637 for OS and 0.582 for DFS.

Conclusions: While the Wang nomogram had the best discriminatory ability relative to OS and DFS, no ICC staging system or nomogram demonstrated excellent prognostic discrimination. The AJCC staging for ICC performed reasonably, although its overall discrimination was only modest-to-good.

Introduction

Intrahepatic cholangiocarcinoma (ICC) occurs in approximately 1-2 per 100,000 persons, making it the second most common primary hepatic malignancy.[1-3] Although ICC mostly develops as a well-differentiated carcinoma, only a minority (15%) of patients presents with resectable disease at the time of diagnosis.[4] Complete surgical resection remains the only option for cure. The estimated median survival after resection of ICC ranges from 27 to 36 months.[5-9] Postoperative survival estimates for individual patients can have consequences with regards to surveillance strategies and decisions about adjuvant chemotherapy.[10]

The most common staging for ICC is the TNM system in the American Joint Committee on Cancer (AJCC) staging manual.[11] While the AJCC staging system is widely adopted, TNM categorization can be limited in providing individual patient-specific prognosis among patients with biliary cancers. As such, several groups have proposed new prognostic models and nomograms.[12-13] In addition, some groups including the Liver Cancer Study Group of Japan (LCSGJ)[14], the Society of Hepatobiliary Surgery Japan (SHPBSJ)[15], Okabayashi *et al.*,[16] and Nathan *et al.*[17] have offered a wide range of different staging systems that have been proposed to discriminate overall survival (OS) better. External validation of these proposed prognostic staging schemes has been largely lacking, however. When developing a prediction model, there is an inherent risk of overestimating both its accuracy and generalizability. External validation of any staging proposal is therefore necessary in large, multicenter cohorts of patients. Since only a few prognostic ICC models have been tested in such cohorts, further evaluation of these models is important. As such, the objective of the current study was to define the predictive ability of the available proposed prognostic models for patients with resected ICC in a large cohort of patients from multiple international high-volume centers.

Methods

All patients undergoing resection for ICC between January 1, 1990, and July 1, 2016 at one of 12 participating major hepatobiliary institutions in the United States, Asia, Oceania and Europe were identified (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia; Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Ottowa General Hospital,

Ottowa, Canada; Royal Prince Alfred Hospital, Sydney, Australia; San Raffaele Hospital, Milan, Italy; Erasmus University Medical Centre Rotterdam, Rotterdam, the Netherlands). Patient records in each participating center were assessed retrospectively and entered into a central standardized registry for each institution.

Sociodemographic and clinicopathologic data were collected and included age, sex and race, tumor size, histologic grade, presence of nodal metastases, final resection margin and the presence of vascular and/or perineural invasion. A minor hepatectomy was defined as a hepatic resection of less than 3 Couinaud segments. Margin status was categorized as R0 for tumor negative resection margins, R1 for microscopically positive margins and R2 for macroscopically positive margins. Only patients undergoing surgery for histologically confirmed ICC were included in the study population; patients who did not undergo resection were excluded. Patients who underwent transplantation were also excluded. The respective institutional review boards of each participating institution approved this study.

Included Models

Seven frequently used postoperative nomograms and staging systems for resected ICC patients were selected for this study. The prognostic models included those proposed by Wang *et al.*,[18] the AJCC TNM 7th edition,[11] Hyder *et al.*,[13] Liver Cancer Study Group of Japan (LCSGJ)[14], the Society of Hepatobiliary Surgery Japan (SHPBSJ)[15], Okabayashi *et al.*,[16] and Nathan *et al.*[17], which are summarized in Table 1.

Statistical analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. Percentages for each variable were calculated based on available data, excluding missing values. Univariable comparison of categorical variables was performed using the Pearson chi-square test. Univariable comparison of continuous variables was performed using the Mann-Whitney U-test. In order to ascertain the validity of our results we performed additional multiple imputations for the Wang (51.8% missing) and Hyder (23.9% missing) nomograms, the only models with larger numbers of missing patients. Since c-indices cannot be pooled using Rubin's rules, we provided the median and range.[19]

The primary outcome of the study was overall survival (OS). The secondary outcome was disease-free survival (DFS). OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up, while DFS

Table 1 Summary of the included prognostic scores and staging systems

Component	Wang Nomogram	AJCC 7th	LCSGJ Staging	Society of Hepatobiliary Surgery Japan	Okabayashi	Nathan Staging	Hyder Nomogram
CEA, preoperative	0-100 µg/L	-	-	-	-	-	-
CA 19-9, preoperative	0-1,000 U/mL	-	-	-	-	-	-
Vascular Invasion	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	No, Microscopic, Macroscopic
Lymph Node Metastases	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No, Insufficiently Harvested
Direct Invasion / Local Metastases	Yes / No	Yes / No	-	-		Yes / No	-
Number of lesions	1, 2-3, ≥4	Solitary, Multiple	Solitary, Multiple	Solitary, Multiple	Solitary, Multiple	Solitary, Multiple	Solitary, Multiple
Tumor diameter	0-22 cm	-	≤ 2cm, > 2 cm	≤ 2cm, > 2 cm		-	1-15 cm
Periductal / Serosal Invasion	-	Yes / No	Yes / No	-		Yes / No	-
Distant metastases	-	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	-
Age	-	-	-	-	-	-	25-85 years
Cirrhosis	-	-	-	-	-	-	Yes / No

was calculated from the date of surgery to the date of first-known radiographically or pathologically confirmed metastasis. Both survival estimates were determined using the Kaplan-Meier method. The log-rank test was used to compare the strata of the prognostic models. Cox regression was performed to evaluate the effect of well-known prognostic variables in this particular cohort of patients. Each of the variables included in the models Schoenfeld residuals were plotted, in order to evaluate if the proportional hazards assumption was not violated. A sub-analysis among the patients who had a mass-forming ICC was conducted for the SHPBSJ and Okabayashi staging systems, because these staging systems were originally developed in cohorts of patients with mass-forming ICC.[15,16]

Model performance was assessed using Harrell's concordance index (c-index). The c-index provides the probability that, in a randomly selected pair of patients, in which one patient dies before the other, the patient who died first had the worse predicted outcome from the nomogram. Analyses were performed using SPSS 22.0 (IBM, New York) and R version 3.03 (http://www.r-project.org) with the *rms* package. All tests were 2-sided and $p<0.05$ defined statistical significance.

Results

Cohort description

1,054 patients who underwent resection for ICC and met the inclusion criteria were identified (Table 2). Median patient age was 59 years (IQR 51, 68) and the majority of patients were male (n=568, 53.9%). Most patients had an ASA classification of II (n=486, 52.0%) or III (n=274, 29.3%). At the time of surgery, six out of ten patients underwent a major hepatectomy involving more than 3 Couinaud segments (n=60, 59.9%). Almost half of patients underwent a formal portal lymphadenectomy (n=463, 45.1%). On final pathology, the majority of patients had an R0 resection (n=882, 86.4%). Morphologically, most patients had a mass-forming ICC (n=892; 92.1%), while a minority had a papillary (n=31; 3.2%) or periductal infiltrating (n=45; 4.5%) growth pattern. Lymph node metastases were noted in 17.5% of patients (n=184).

For each prognostic model, patients were allocated into the different risk groups, based on disease characteristics (Tables 3 and 4). The number of missing values which resulted in patients excluded from analysis was small in most prognostic models. More specifically, 99 (9.4%) of patients were not included in the AJCC TNM staging, 33 (3.1%) in the LCSGJ staging, 42 (4.0%) in the SHPBS staging,

Table 2. Baseline characteristics of the validation cohort (n = 1,054)

Variable	n (%) / median (IQR)
Gender	
Male	568 (53.9)
Female	485 (46.1)
Age, years	59 (51-68)
Race	
Caucasian	626 (61.6)
African-American	39 (3.8)
Asian	329 (32.4)
Other	22 (2.2)
ASA	
I	104 (11.1)
II	486 (52.0)
III	274 (29.3)
IV	71 (7.6)
BMI	25.4 (22.6-28.2)
Period of Treatment	
1990-2000	35 (3.4)
2001-2005	115 (11.1)
2006-2010	422 (40.8)
2011-2016	463 (44.7)
Type of Resection	
Minor Hepatectomy (<3 segments)	419 (40.9)
Right Hepatectomy	167 (16.3)
Left Hepatectomy	193 (18.8)
Extended Right Hepatectomy	128 (12.5)
Extended Left Hepatectomy	96 (9.4)
Central Hepatectomy	21 (2.1)
Number of tumors	1 (1-1)
Morphologic Type	
Mass-forming	892 (92.1)
Papillary	31 (3.2)
Periductal Infiltrating	45 (4.6)
Tumor size (cm)	6.1 (4.3-9.0)
Major Vascular Invasion	100 (9.7)
Microvascular Invasion	257 (25.6)
Perineural Invasion	152 (16.4)
Invasion of Adjacent Organs	77 (7.5)
Satellite Lesions	233 (22.6)

Table 2. Baseline characteristics of the validation cohort (n = 1,054) (*continued*)

Variable	n (%) / median (IQR)
Intrahepatic Metastases	75 (7.3)
Lymphadenectomy	463 (45.1)
Lymph Nodes Harvested	2 (0-5)
Lymph Node Metastases	184 (17.5)
Extrahepatic Metastases	40 (3.8)
Margin Status	
R0	882 (86.4)
R1	134 (13.1)
R2	5 (0.5)

25 (2.4%) in the Okabayashi staging, and 91 (8.6%) in the Nathan staging system. The nomograms by Wang (51.8% missing) and Hyder (23.9% missing) had a considerably higher proportion of missing patients. In the Wang nomogram, the median points score was 40.1 (IQR 23.2, 63.6). One hundred twenty-seven patients (25.0%) were allocated in the group <23.4 points, 255 (50.1%) in the group 23.4-64.9, and 127 in the group >64.9. Of note, the main reason the Wang nomogram could not be determined for a subset of patients (n=548), were missing values for both CEA and CA19-9.

In the AJCC 7th staging schema, the majority of patients were allocated into stage I and II (n = 692, 72.2%). In the LCSGJ staging system, almost 6 out of every 10 patients were allocated in stage II (n = 607, 59.3%), which was identical to the allocation using the SHPBSJ staging system. In the Okabayashi staging system, 61.8% of the patients had stage I disease and 299 (29.0%) had stage III disease, while only 94 patients were allocated into the other stages. In the staging by Nathan, 398 (41.2%) patients had stage I disease, 360 (37.2%) had stage II disease and 209 (21.6%) had stage III or IV disease. Patients had an average score of 12.9 (IQR 10.9-15.9) when using Hyder's nomogram.

Overall survival and disease free survival

After a median follow-up of 27 months, nearly half of patients were deceased (n=521, 49.7%). Median OS was 37.7 months and 1-, 3- and 5-year survival, were 78.8%, 51.5% and 39.3%, respectively. Recurrence of disease occurred in 454 (43.1%) patients during follow-up. Median disease-free survival was 29.6 months and 1-, 3- and 5- year DFS were 64.6%, 46.5 % and 44.4%, respectively.

Table 3. Prognostic value of the individual components

Component	Overall Survival				Disease Free Survival			
	Hazard Ratio	95% CI	P - value	C-index	Hazard Ratio	95% CI	P - value	C-index
CEA, preoperative								
Continuous (µg/L)	1.00	1.00-1.00	0.003	0.570	1.00	1.00-1.00	0.001	0.514
CA 19-9, preoperative								
Continuous (U/mL)	1.00	1.00-1.00	<0.001	0.634	1.00	1.00-1.00	0.369	0.550
Vascular Invasion								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	1.57	1.19-2.06	0.001	0.519	1.59	1.19-2.13	0.002	0.522
Microscopic	1.28	1.02-1.59	0.031		0.91	0.72-1.16	0.451	
Macroscopic	1.64	1.24-2.17	<0.001	0.542	1.54	1.15-2.07	0.004	0.521
Lymph Node Metastases								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	2.48	2.02-3.05	<0.001	0.565	1.62	1.30-2.03	<0.001	0.539
Direct Invasion / Local Metastases								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	2.76	2.11-3.60	<0.001	0.544	1.80	1.27-2.56	<0.001	0.515
Number of lesions								
Single	Ref.	-	-	-	Ref.	-	-	-
Multiple	1.88	1.53-2.30	<0.001	0.551	1.58	1.26-1.97	<0.001	0.534
2-3	1.75	1.39-2.19	<0.001		1.46	1.14-1.89	0.003	
≥4	2.45	1.69-3.55	<0.001	0.552	2.13	1.38-3.27	<0.001	0.536

Table 3. Prognostic value of the individual components (*continued*)

Component	Overall Survival				Disease Free Survival			
	Hazard Ratio	95% CI	P - value	C-index	Hazard Ratio	95% CI	P - value	C-index
Tumor diameter								
Continuous (cm)	1.07	1.04-1.09	<0.001	0.577	1.06	1.03-1.09	<0.001	0.586
≤2 cm	Ref.	-	-	-	Ref.	-	-	-
>2 cm	2.17	1.22-3.85	0.008	0.513	2.10	1.12-3.92	0.021	0.512
Periductal / Serosal Invasion								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	2.42	2.01-2.91	<0.001	0.616	1.59	1.31-1.92	<0.001	0.566
Distant metastases								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	2.65	1.67-4.20	<0.001	0.514	1.48	0.81-2.69	0.200	0.505
Age								
Continuous (years)	1.00	1.00-1.01	0.384	0.519	0.98	0.97-0.99	<0.001	0.582
Cirrhosis								
No	Ref.	-	-	-	Ref.	-	-	-
Yes	1.01	0.76-1.35	0.939	0.506	1.35	1.02-1.80	0.037	0.522

Components of the prognostic models of interest were evaluated separately for prognostic ability with regards to OS and DFS (Table 3). Except for age and cirrhosis, all variables were associated with OS. Of note, direct invasion of adjacent organs (HR: 2.76, 95%CI 2.11-3.60, $p < 0.001$) and distant metastases (HR: 2.64, 95%CI 1.67-4.19, $p < 0.001$) were the factors most strongly associated with OS. The continuous variable CA19-9 had the best c-index of 0.634. With regards to DFS, tumor diameter >2 cm was strongly associated with risk of disease recurrence (HR: 2.10, 95%CI 1.12-3.92). Plotted Schoenfeld residuals demonstrated that the proportional hazards assumption was not violated for any of the variables.

Comparison of scoring systems

Data on the performance of the models regarding the OS prediction are presented in Table 4 and Figure 1; the ability of the models to predict DFS is presented in Table 5 and Figure 2. Although there was a decline in OS and DFS with each progressive stage in most models, the highest stage was not always associated with the worst survival. For example, in the higher stages of several models, no differences in OS and DFS were observed (Figures 1 and 2). The Wang nomogram was the only prognostic model in which incremental, clear differences among the survival curves in the bottom quartile, interquartile range and the upper quartile were identified for both OS and DFS.

The prognostic models providing the best prediction of OS at all time points were the Wang nomogram and the Nathan staging system. These prediction methods also yielded the highest c-statistics (0.668 and 0.639). No model exceeded a c-index of 0.7 for OS. The ability of the models to predict DFS is presented in Table 5 and Figure 2. No model was proficient in predicting DFS. The only model to exceed a c-index of 0.6 for DFS, which indicates fair discrimination, was the nomogram by Wang and colleagues. For both OS and DFS, the Hyder nomogram had the lowest predictive capacity. Both the SHPBSJ (OS c-index: 0.606, DFS c-index: 0.558) and the Okabayashi staging systems (OS c-index: 0.600, DFS c-index: 0.558) did not perform better within the mass-forming ICC sub-cohort. The imputed datasets for the Wang and Hyder nomograms did not show large differences, compared to the complete case analysis. The Wang nomogram had a c-index of 0.674 (0.670-0.680) for OS and 0.601 (0.597-0.604) for DFS, which seemed to be similar to the estimate in the complete-case analysis. For the Hyder nomogram, the c-index for OS was 0.614 (0.613-0.616) and the c-index for DFS was 0.542 (0.541-0.548).

Table 4. Prediction of overall survival by the included prognostic scores and staging systems

Staging / Nomogram	# At Risk Start Study (%)	Hazard Ratio	95% CI	1-Year		3-Year		5-Year		C-statistic (SE)
				# At risk	OS Rate	# At risk	OS Rate	# At risk	OS Rate	
Wang Nomogram										0.668 (0.021)*
Cont.		1.01	1.01-1.01							
<23.4	129 (25.3)	Ref.	-	112	91.2	56	78.8	22	66.9	
23.4-64.9	260 (51.1)	2.23	1.51-3.29	197	82.9	72	53.6	25	40.8	
>64.9	120 (23.6)	4.87	3.22-7.36	68	67.0	13	28.8	3	13.1	
AJCC 7th										0.637 (0.021)
I	399 (41.6)	Ref.	-	328	87.6	165	67.2	76	56.4	
II	293 (30.6)	2.10	1.69-2.62	193	78.1	71	42.7	27	27.5	
III	63 (6.6)	2.50	1.72-3.63	29	62.3	13	44.1	3	18.5	
IV A	161 (16.8)	3.24	2.53-4.15	81	63.4	20	23.9	10	15.4	
IV B	42 (4.4)	3.65	2.40-5.54	17	63.3	6	24.1	1	0.1	
LCSGJ										0.631 (0.012)
I	29 (2.8)	Ref.	-	26	96.4	18	88.1	8	78.0	
II	607 (59.3)	1.95	1.00-3.78	453	84.0	208	59.7	98	47.9	
III	172 (16.8)	3.31	1.68-6.56	107	73.4	46	43.5	18	29.9	
IV A	7 (0.7)	5.34	1.78-16.00	5	85.7	0	0.0	0	0.0	
IV B	209 (20.4)	5.41	2.75-10.67	90	63.2	20	35.7	6	10.0	
Society of Hepatobiliary Surgery Japan										0.611 (0.012)
I	29 (2.9)	Ref.	-	27	96.4	18	88.1	8	78.0	
II	607 (59.8)	1.94	1.00-3.78	453	84.0	208	59.7	98	47.9	
III	172 (16.9)	3.31	1.67-6.55	107	73.4	46	43.5	18	29.9	
IV A	155 (15.3)	5.28	2.66-10.48	73	65.0	14	24.3	3	8.1	
IV B	52 (5.1)	5.59	2.65-11.80	19	62.1	5	17.3	3	13.8	

Table 4. Prediction of overall survival by the included prognostic scores and staging systems (*continued*)

Staging / Nomogram	# At Risk Start Study (%)	Hazard Ratio	95% CI	1-Year		3-Year		5-Year		C-statistic (SE)
Okabayashi										0.607 (0.012)
I	638 (61.8)	Ref.	-	480	84.5	228	61.4	108	49.5	
II	55 (5.3)	1.54	1.03-2.30	32	71.3	15	51.7	4	34.4	
III A	130 (12.6)	1.85	1.45-2.37	83	75.0	33	38.5	14	26.8	
III B	169 (16.4)	2.77	2.21-3.47	79	64.3	17	24.0	5	9.8	
IV	40 (3.9)	3.58	2.24-5.72	11	56.3	3	17.0	1	11.4	
Nathan Staging										0.639 (0.013)
I	398 (41.2)	Ref.	-	327	88.0	165	67.9	76	57.0	
II	360 (37.2)	2.20	1.79-2.72	225	75.3	85	42.4	31	26.3	
III	167 (17.3)	3.42	2.69-4.36	85	63.4	21	22.8	8	11.1	
IV	42 (4.3)	4.64	2.90-7.43	11	53.6	3	16.2	1	10.8	
Hyder Nomogram										0.599 (0.017)*
Cont.		1.09	1.06-1.12							
<10.9	191 (23.8)	Ref.	-	156	86.4	72	68.0	29	59.8	
10.9-15.9	423 (52.6)	1.30	0.99-1.71	290	82.7	117	55.9	48	44.2	
>15.9	190 (23.6)	2.41	1.79-3.25	100	68.5	33	36.8	10	24.5	

Table 5. Prediction of disease free survival by the included prognostic scores and staging systems

Staging / Nomogram	# At Risk Start Study (%)	Hazard Ratio	95% CI	1-Year		3-Year		5-Year		C-statistic (SE)
				# At risk	DFS Rate	# At risk	DFS Rate	# At risk	DFS Rate	
Wang Nomogram										0.607 (0.020)*
Cont.		1.01	1.01-1.01							
<23.4	129 (25.3)	Ref.	-	45	64.0	15	39.1	7	36.5	
23.4-64.9	260 (51.1)	1.71	1.22-3.40	59	38.3	17	15.9	8	14.7	
>64.9	120 (23.6)	2.59	1.77-3.80	23	31.4	5	10.0	4	10.0	
AJCC 7th										0.582 (0.014)
I	399 (41.6)	Ref.	-	225	69.3	97	51.0	52	48.4	
II	293 (30.6)	1.50	1.20-1.88	122	58.8	49	38.6	22	33.8	
III	63 (6.6)	1.18	0.73-1.89	20	66.5	9	49.4	6	42.3	
IV A	161 (16.8)	1.83	1.42-2.37	54	50.2	21	28.6	15	28.6	
IV B	42 (4.4)	2.88	1.83-4.54	9	48.2	1	6.4	1	6.4	
LCSGJ										0.562 (0.012)
I	29 (2.8)	Ref.	-	20	91.3	10	70.3	6	70.3	
II	607 (59.3)	1.55	0.80-3.02	323	67.4	153	50.3	98	48.2	
III	172 (16.8)	2.06	1.03-4.12	68	60.7	33	41.9	17	36.8	
IV A	7 (0.7)	3.65	1.22-10.90	2	33.3	1	33.3	1	33.3	
IV B	209 (20.4)	2.56	1.29-5.06	69	53.6	31	31.9	22	31.9	
Society of Hepatobiliary Surgery Japan										0.563 (0.012)
I	29 (2.9)	Ref.	-	20	91.3	10	70.3	6	70.3	

Table 5. Prediction of disease free survival by the included prognostic scores and staging systems (*continued*)

Staging / Nomogram	# At Risk Start Study (%)	Hazard Ratio	95% CI	1-Year		3-Year		5-Year		C-statistic (SE)
				# At risk	DFS Rate	# At risk	DFS Rate	# At risk	DFS Rate	
II	607 (59.8)	1.55	0.80-3.02	323	67.4	155	50.6	98	48.2	
III	172 (16.9)	2.06	1.03-4.12	68	60.7	33	41.9	17	36.8	
IV A	155 (15.3)	2.51	1.26-5.00	58	54.4	25	32.9	17	32.9	
IV B	52 (5.1)	3.19	1.47-6.92							
Okabayashi										0.557 (0.012)
I	638 (61.8)	Ref.	-	343	68.4	166	51.4	106	49.2	
II	55 (5.3)	1.35	0.87-2.11	20	60.0	9	46.2	3	38.5	
III A	130 (12.6)	1.34	1.02-1.78	54	60.9	27	40.7	15	36.7	
III B	169 (16.4)	1.68	1.32-2.13	62	54.1	26	31.3	18	31.3	
IV	40 (3.9)	1.70	0.93-3.11	7	50.3	5	35.9	4	35.9	
Nathan Staging										0.581 (0.013)
I	398 (41.2)	Ref.	-	224	69.5	97	51.3	52	48.7	
II	360 (37.2)	1.48	1.19-1.83	145	60.1	59	39.3	29	34.5	
III	167 (17.3)	2.06	1.60-2.65	54	49.0	18	24.7	13	24.7	
IV	42 (4.3)	1.47	0.80-2.70	9	56.0	6	42.7	5	42.7	
Hyder Nomogram										0.521 (0.016)*
Cont.		1.03	1.00-1.06							
<10.9	191 (23.8)	Ref.	-	105	65.8	41	53.9	20	50.4	
10.9-15.9	423 (52.6)	1.10	0.84-1.43	201	64.8	93	48.6	56	47.4	
>15.9	190 (23.6)	1.25	0.92-1.69	84	61.7	46	42.5	31	42.5	

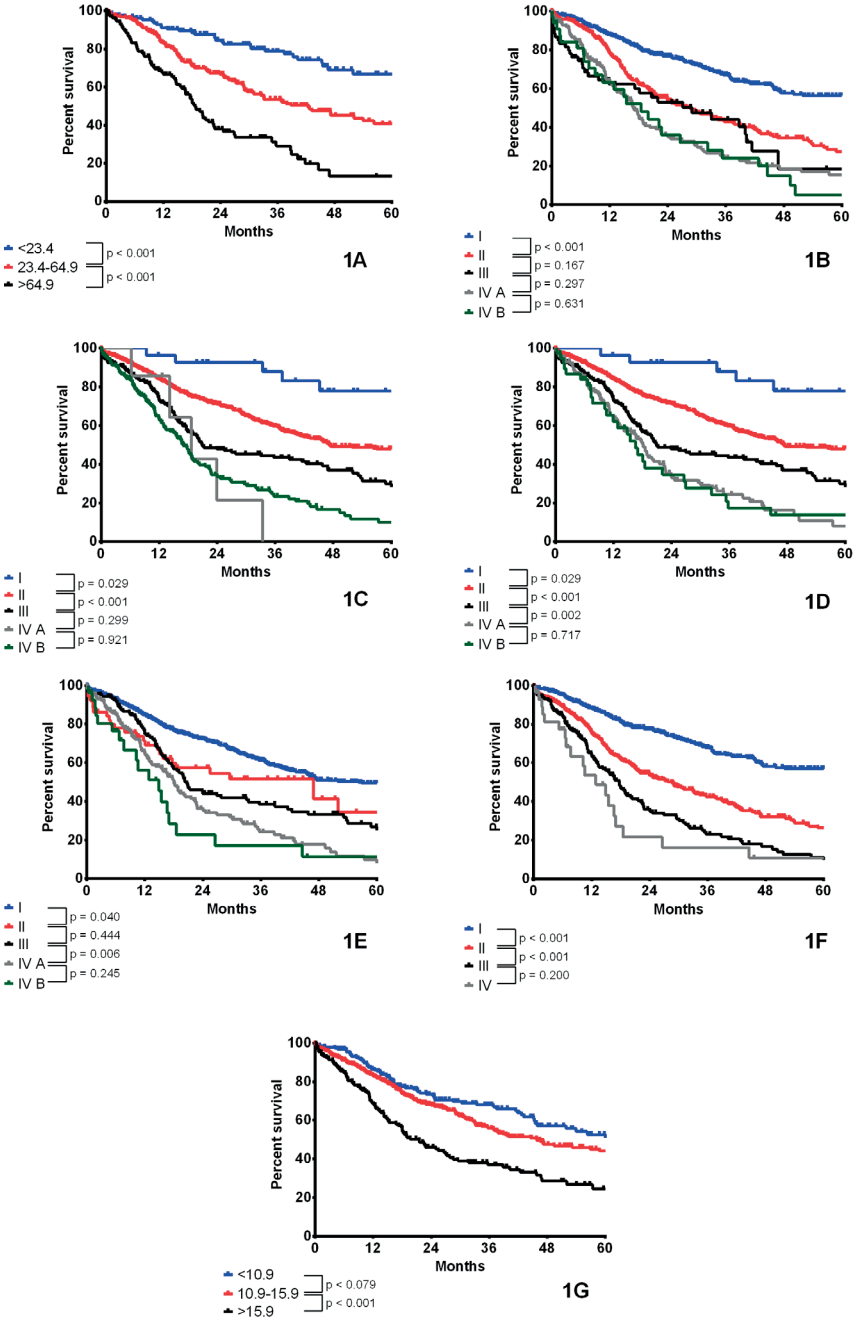

Figure 1. Overall survival stratified by the different prognostic models. A) Wang Nomogram Score, B) AJCC 7th edition stage, C) LCSGJ stage, D) SHPBS stage, E) Okabayashi stage, F) Nathan stage, G) Hyder nomogram score

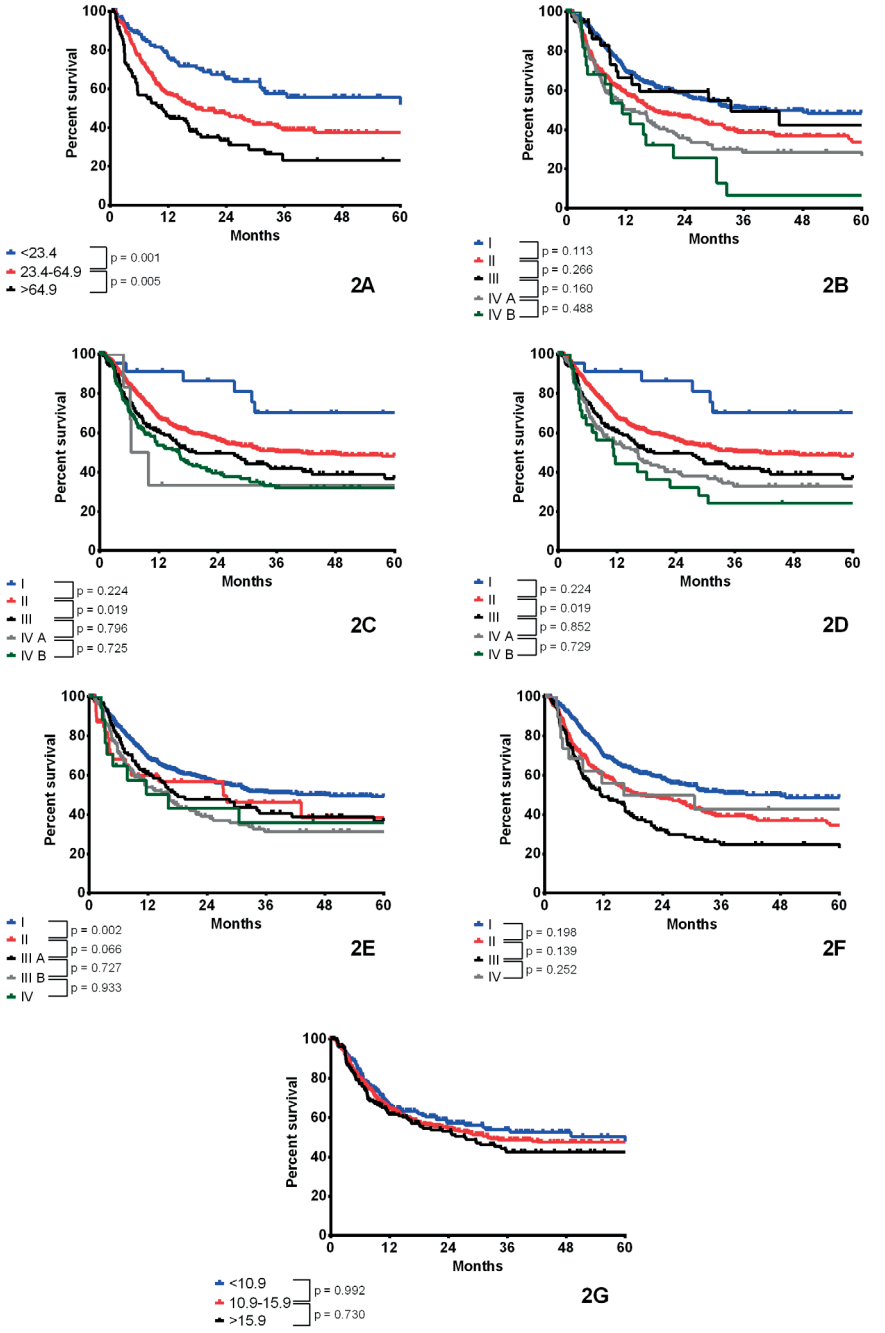

Figure 2. Disease free survival stratified by the different prognostic models. A) Wang Nomogram Score, B) AJCC 7th edition stage, C) LCSGJ stage, D) SHPBS stage, E) Okabayashi stage, F) Nathan stage, G) Hyder nomogram score

Discussion

Prognostic models are frequently used in order to determine prognosis and predict adverse outcomes in malignant HPB surgery.[18,20-27] Because of the vast difference in characteristics among individual patients diagnosed with ICC, different approaches in adjuvant therapy, follow-up, and further surgical treatment can be tailored to individual patients with the help of these models.[12,28-30] In this study, we examined the ability of established nomograms and staging systems to predict OS and DFS in one of the largest Western cohorts of ICC to date. We quantified the predictive ability of each nomogram using Harrell's concordance index. Although the included prognostic models varied considerably, some variables were included in multiple models. Notably, vascular invasion, lymph node metastases, and number of lesions were included in all prognostic models. These risk factors had significant prognostic value in our cohort as well. After evaluating model performance, we noted that no single model reached the threshold for good discrimination (i.e. a c-index of 0.7) for both OS and DFS. The most often used AJCC TNM staging system performed reasonable compare with the other prognostic models (OS c-index: 0.637, DFS c-index: 0.582). In line with previous studies,[10,18] the nomogram by Wang and colleagues performed the best in predicting OS (c-index 0.668) and DFS (c-index 0.607).

ICC prognostic models have been developed in different populations for different purposes. While the AJCC staging includes all ICC patients, other models pertain only to patients who have undergone surgical resection. For example, the nomogram by Wang *et al.* was designed to predict individual OS after resection of ICC.[18] Prognostic factors in this model included CEA, CA19-9, vascular invasion, presence of lymph node metastases, direct invasion and local metastases, number of tumors, and tumor diameter. A similar nomogram was developed by Hyder *et al.* Risk factors for survival after resection in this model included age, number of tumors, tumor diameter, cirrhosis, lymph node metastases, and macrovascular invasion.[13] A notable feature of the Hyder nomogram was that it categorized patients who did not undergo a lymphadenectomy as Nx, instead of N0 like the other prognostic models. Other staging systems, such as those examined in the current study, were proposed as an alternative to the AJCC and included the Liver Cancer Study Group of Japan (LCSGJ)[14], the Society of Hepatobiliary Surgery Japan (SHPBSJ)[15], Okabayashi *et al.*,[16] and Nathan *et al.* staging systems.[17] Similar to nomograms, these staging systems sought to better differentiate prognosis among patients and more individualized prognostication. One difference in the SHPBSJ and the Okabayashi staging systems versus the other staging systems was the inclusion of only patients with mass-forming ICC, the most common

ICC morphology.[15,16] Although the prognostic models differed considerably and used different cut-offs and units for the variables, the included factors included in the models had marked overlap. Vascular invasion, lymph node metastases and number of lesions were included in all prognostic models. These risk factors have been associated with worse prognosis in many previous studies.[10] On the other hand, age and cirrhosis were included only in the nomogram by Hyder *et al.* Interestingly, tumor size was been removed from the T-stage in the 7th edition of the AJCC staging system, but was included in 4 out of the 7 prognostic models, indicating its importance in prognostication. To this point, tumor size has been re-introduced into the new, recently published 8th edition AJCC ICC staging system.

Due to the low incidence of ICC compared with other HPB malignancies, derivation studies for prognostic models often have lacked statistical power. Underpowered studies are at a risk of over-fitting the model to the data, causing decreased reproducibility. The current study is important because it externally evaluated current ICC models in a large and multicenter cohort. In particular, the data suggested that most prognostic models lacked the ability to identify patients with higher risk of recurrence or mortality, as demonstrated by the relatively low c-statistic associated with the different models. In previous studies by Doussot *et al.* and Nathan *et al.* similar poor results were demonstrated, although the sample size of the study cohorts were smaller than the current study.[10,17] Although multiple well-known prognostic factors are used in the prognostic models, accurate estimation of their impact on survival remains elusive. The most commonly used prognostic factors were patient- and tumor-specific factors, with a limited number of factors such as number of tumors and vascular invasion. In addition, these factors were often analyzed in a binary fashion in many models, further limiting their predictive ability. It stands to reason that the potential prognostication of ICC, a complex biological process, based on a small number of binary predictors whose impact has only been measured in small cohorts, is limited.

In order to improve the predictive ability of current and new prognostic models, new determinants of biological processes in the form of biomarkers will be needed. Biomakers such as CEA and CA19-9 have previously been correlated with tumor processes and clinical outcomes.[31,32] Only the Wang nomogram, however, utilized these biomarkers in a prognostic model. The superior discriminating ability of the Wang nomogram may relate to the importance of these biomarkers in prognostic models. In addition, a recent meta-analysis identified several other immunohistochemistry biomarkers associated with ICC.[33] To this end, some

investigators have proposed that a composite biomarker profile that combines clinical factors (CEA and CA19-9) with pathological biomarkers may improve the accuracy of prognostic models and guide treatment in patients with resected ICC.[34] The potential of this approach has been proven with the recent successes of biomarker based prediction in breast cancer and colorectal cancer.[35,36]

Results of the current study should be interpreted in the context of several limitations. The inclusion of multiple centers did not allow for the standardization of operative approach or treatment-based protocols. The multi-center nature of the study does add to the generalizability, allowing the findings to be applied across a wide range of patient populations. Another limitation was the unavailability of preoperative values of CEA and CA19-9 in a number of patients. The lack of CEA and CA19-9 data was likely related to the varied clinical practice across centers, as well as the relatively recent identification of CEA and CA19-9 as important prognostic factors. We believe these missing values did not influence our results, as analysis after multiple imputations led to the same results. Additionally, due to the small number of patients with a tumor morphology, other than mass-forming ICC, we were unable to assess prognostic models for each morphology separately. Finally, not all patients underwent lymphadenectomy and therefore the "true" nodal status of these patients could not be determined. It is likely that a subset of these patients did indeed harbor occult nodal metastasis.

In conclusion, while the Wang nomogram had the best discriminatory ability relative to OS and DFS, no staging system or nomogram demonstrated excellent prognostic discrimination. The most widely adopted AJCC staging for ICC performed reasonably compared with other prognostic models, although its overall discrimination was only modest-to-good. Further research into the optimization of ICC prognostic models, possibly with inclusion of specific biomarkers, is warranted.

References

1. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma--focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010; **11**(5): 1159-66.
2. Singal AK, Vauthey JN, Grady JJ, Stroehlein JR. Intra-hepatic cholangiocarcinoma--frequency and demographic patterns: thirty-year data from the M.D. Anderson Cancer Center. *J Cancer Res Clin Oncol* 2011; **137**(7): 1071-8.
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009; **136**(4): 1134-44.
4. Buettner S, van Vugt JL, Ijzermans JN, Groot Koerkamp B. Intrahepatic Cholangiocarcinoma: current perspectives. *Onco Targets Ther* 2017; **2017:10**: 1131-42.
5. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery* 2002; **132**(4): 555-63; discission 63-4.
6. Konstantinidis IT, Koerkamp BG, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2015.
7. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 2008; **248**(1): 84-96.
8. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011; **29**(23): 3140-5.
9. Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol* 2014; **110**(2): 163-70.
10. Doussot A, Groot-Koerkamp B, Wiggers JK, et al. Outcomes after Resection of Intrahepatic Cholangiocarcinoma: External Validation and Comparison of Prognostic Models. *J Am Coll Surg* 2015; **221**(2): 452-61.
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. Chicago, IL: Springer; 2009.
12. Buettner S, van Vugt JL, Gani F, et al. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. *J Gastrointest Surg* 2016; **20**(10): 1716-24.
13. Hyder O, Marques H, Pulitano C, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014; **149**(5): 432-8.
14. Sakamoto Y, Kokudo N, Matsuyama Y, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: Analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer* 2016; **122**(1): 61-70.
15. Uenishi T, Ariizumi S, Aoki T, et al. Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2014; **21**(7): 499-508.

16. Okabayashi T, Yamamoto J, Kosuge T, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. *Cancer* 2001; **92**(9): 2374-83.

17. Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2009; **16**(1): 14-22.

18. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 2013; **31**(9): 1188-95.

19. Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *J Clin Epidemiol* 2003; **56**(1): 28-37.

20. Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol* 2009; **10**(11): 1045-52.

21. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.

22. International Bladder Cancer Nomogram C, Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 2006; **24**(24): 3967-72.

23. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007; **25**(11): 1316-22.

24. Song C, Kim K, Chie EK, et al. Nomogram prediction of survival and recurrence in patients with extrahepatic bile duct cancer undergoing curative resection followed by adjuvant chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013; **87**(3): 499-504.

25. van der Gaag NA, Kloek JJ, de Bakker JK, et al. Survival analysis and prognostic nomogram for patients undergoing resection of extrahepatic cholangiocarcinoma. *Ann Oncol* 2012; **23**(10): 2642-9.

26. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* 2011; **29**(35): 4627-32.

27. Wierda WG, O'Brien S, Wang X, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. *Blood* 2007; **109**(11): 4679-85.

28. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**(12): 2893-917.

29. Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 2002; **94**(6): 1760-9.

30. Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5. *Eur J Cancer* 2015.

31. Grobmyer SR, Wang L, Gonen M, et al. Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. *Ann Surg* 2006; **244**(2): 260-4.

32. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol* 2009; **16**(11): 3048-56.

33. Ruys AT, Groot Koerkamp B, Wiggers JK, Klumpen HJ, ten Kate FJ, van Gulik TM. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21**(2): 487-500.

34. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; **60**(6): 1268-89.

35. Lech G, Slotwinski R, Slodkowski M, Krasnodebski IW. Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances. *World J Gastroenterol* 2016; **22**(5): 1745-55.

36. Le Du F, Ueno NT, Gonzalez-Angulo AM. Breast Cancer Biomarkers: Utility in Clinical Practice. *Curr Breast Cancer Rep* 2013; **5**(4).

CHAPTER 8

Conditional Probability of Long-Term Survival after Resection of Hilar Cholangiocarcinoma

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Abstract

Background: While traditional survival analyses focus on factors determined at the time of surgery, conditional survival (CS) estimates prognosis relative to time following treatment. We sought to compare actuarial and CS among patients undergoing curative intent surgery for hilar cholangiocarcinoma.

Methods: 242 patients undergoing surgery between 2000 and 2014 were identified using a multi-institutional database. CS was calculated as the probability of surviving an additional 3 years, given that the patient had already survived "x" years from surgery.

Results: Median patient age was 67 years (IQR: 57-73) and most patients were male (n=140, 57.9%). Lymph node metastases were noted in 79 (32.6%) patients while an R0 margin was obtained in 66.1% (n=160). Median OS was 22.3 months. Actuarial survival decreased over time from 46.3% at 2 years following surgery to 18.2% at 5 years; in contrast, the 3-year CS (CS_3) increased with time (CS_3 at 2 years was 39.3% versus 54.4% at 5 years). CS_3 exceeded actuarial survival for high-risk patients with patients with perineural invasion demonstrating an actuarial survival of 15.4% at 5 years versus CS_3 of 37.6% at 2 years following surgery (Δ=22.2%).

Conclusions: CS provides a more accurate, dynamic estimate for survival, especially among high-risk patients.

Introduction

Hilar cholangiocarcinoma (HC) is the most common malignancy arising from the biliary tract accounting for 50-67% of all cases of cholangiocarcinoma.[1,2] Despite only 25% of patients presenting with resectable disease at the time of diagnosis, complete surgical resection remains the only option for cure with an estimated 5-year survival ranging from 11-42%.[3,4] Given the poor prognosis associated with HC, appropriate risk-stratification of patients is important to inform decisions pertaining to cure, surveillance and palliation. Currently, there exist two commonly used prognostic classification tools for patients with HC: the Bismuth-Corlette Classification and the American Joint Committee on Cancer (AJCC) Classification System.[5,6] While these prognostic classification schemes have identified important risk factors for HC including nodal disease and margin status, their ability to predict long-term survival remains limited. Specifically, constructed using traditional survival estimates, these prognostic classification systems are unable to account for changes in survival probability relative to the time elapsed from diagnosis.[7] Under such circumstances, conditional survival (CS), which accounts for the changing probability of survival over time, has been identified as a more clinically relevant measure to predict long-term survival.[8,9]

CS is based on the underlying premise that as a patient survives past a given time point, the survival probability changes compared to the time of initial diagnosis.[10] As such, CS has been proposed as a more clinically useful measure to predict long-term survival compared with traditional survival estimates. Furthermore, the use of CS estimates to predict long-term survival may help facilitate appropriate risk-stratification of patients, as well as determine more accurate end-points for future randomized, controlled trials. In prospective studies, CS estimates can be taken into account in order to approximate the impact of elapsed time on the study population, because the group after extended follow up may differ significantly from the group that was originally randomized. To this point, previous reports on patients undergoing surgery for lung, pancreatic and breast cancer have demonstrated more accurate estimates for disease-free and overall survival using CS.[8,9,11,12] However, to our knowledge, no previous research has assessed CS among patients undergoing surgery for HC. Given this, the aim of the current study was to define conditional survival among patients undergoing curative intent surgery for HC. Additionally, we sought to assess the prognostic ability of previously established risk factors relative to the time elapsed after surgery.

Methods

Data Sources and Patient Population

Patients undergoing surgery for hilar cholangiocarcinoma between January 1, 2000 and December 31, 2014 at one of ten institutions participating in the Extrahepatic Biliary Malignancy Consortium were identified (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina). Only patients with histologically confirmed hilar cholangiocarcinoma and patients who underwent curative intent surgery for their primary tumor were included. Patients who died within 30 days of surgery were excluded.

Standard demographic and clinicopathologic data were collected for each patient including age, sex, race, primary tumor size, AJCC 7th Edition stage and T-stage, histologic grade, presence of nodal disease, final resection margin, and the presence of vascular and / or perineural invasion. Tumor size was defined as the largest diameter of the tumor in the resected specimen. If multiple tumors were resected, the largest diameter was used to define tumor size. Histologic grade was defined as either well, moderate, or poorly differentiated with the highest histologic grade used to define tumor grade among patients with multiple resected specimens. Margin and nodal status were determined using the final postoperative pathologic report. Margin status was considered to be R1 when microscopic tumor remnants were present in the resection margin, and R0 when this was not the case. Lymph node metastases were scored as either present or absent. Additionally, treatment specific information including the extent of surgery, receipt of lymphadenectomy, as well as the receipt of pre- or postoperative chemo- or radiotherapy were also collected for each patient. A major liver resection was defined as the removal of three or more Couinaud segments. Postoperative complications were scored according to the Clavien-Dindo classification. The institutional review board of each participating institutional approved this study.

Statistical analysis

Summary statistics were provided as whole numbers and percentages for categorical variables and medians with interquartile range (IQR) for continuous variables. The primary outcome of interest was OS, defined as the time interval between the

date of surgery and the date of death or last available follow-up, as appropriate. Estimates for OS were calculated using the Kaplan-Meier method. Differences in survival between patient groups were assessed using the Mantel-Haenszel test. A Cox proportional hazards model was built to identify potential risk factors for overall survival. Specifically, patient and disease factors evaluated included age, sex, primary tumor size, T-stage, histologic grade, lymph node metastases, margin status, and tumor invasion (vascular and / or perineural). Results from the Cox models were subsequently reported as hazard ratios (HR) and corresponding 95% confidence intervals (CI).

Conditional survival was defined as the probability of surviving an additional number of "y" years given that a patient had already survived for "x" years and was calculated as $CS_{(y|x)}=S_{(x+y)}/S_{(x)}$, with $S_{(x)}$ representing the OS at x years estimated using the Kaplan-Meier method. For example, the CS for surviving another year among patients who had already survived 4 years, $CS_{(1|4)}$, was calculated by dividing the 5-year Kaplan-Meier survival estimate $S_{(5)}$ by the 4-year Kaplan-Meier survival estimate $S_{(4)}$. In some cases we were unable to give an estimate of 3-year conditional survival, because no events occurred within the 3-year interval. In these cases we did not give an estimation.[8,9,13,14] Differences in CS were assessed using linear regression and standardized differences. Standardized differences (d) can be used as the index to contrast 2 rates such that $d < 0.1$ represents very small differences; $0.1 \leq d < 0.3$, small differences; $0.3 \leq d < 0.5$, moderate differences, and $d \geq 0.5$, considerable differences. All analyses were performed using SPSS 22.0 (IBM, New York). All tests were 2-sided and $p<0.05$ defined statistical significance.

Results

Demographic and Clinicopathologic Characteristics

A total of 242 patients who underwent curative intent surgery for HC and met inclusion criteria were identified (table 1). The median patient age was 67 years (IQR 57-73) with a majority of patients being male (n=140, 57.9%) and Caucasian (n=184, 78.3%). Neoadjuvant chemotherapy was administered to 4.1% (n=10) of patients, whereas only 2.5% (n=6) of patients received neoadjuvant radiotherapy. At the time of surgery, the majority (n=179, 74.9%) of patients underwent a major hepatic resection; 239 (98.8%) patients underwent an open resection, whereas 1 patient underwent a laparoscopic resection and 2 patients underwent a laparoscopic resection that was converted to an open procedure. A

Table 1. Demographic and Clinicopathologic Characteristics

Variable	N, (%) / Median (IQR)
Age, y	67 (57-73)
< 65	110 (45.5)
≥ 65	132 (54.5)
Sex	
Male	140 (57.9)
Female	102 (42.1)
Race	
Caucasian	184 (78.3)
African American	17 (7.2)
Other	34 (14.5)
BMI	25.1 (22.2-28.6)
Functionally Independent	217 (98.2)
Comorbidities	
Hypertension	99 (43.2)
History of Cardiac Disease	26 (11.4)
Diabetes	36 (15.7)
Preoperative Jaundice	190 (79.2)
Type of Resection	
Minor Resection (< 3 Couinaud Segments)	60 (25.1)
Major Resection (≥ 3 Couinaud Segments)	179 (74.9)
Margin Status	
R0	160 (66.1)
R1	82 (33.9)
Tumor Size	2.5 (1.8-3.9)
≤ 2.5 cm	116 (51.1)
> 2.5 cm	111 (48.9)
Grade	
Well Differentiated	43 (19.1)
Moderately/poorly differentiated	182 (80.9)
Bismuth-Corlette Class	
I	28 (12.6)
II	37 (16.6)
IIIa	58 (26.0)
IIIb	47 (21.1)
IV	53 (23.8)
AJCC 7th Edition Stage	
Stage I & II	114 (58.2)
Stage III & IV	82 (41.8)
AJCC T-stage	
T1-T2	157 (80.1)
T3-T4	39 (19.9)

Table 1. Demographic and Clinicopathologic Characteristics (*continued*)

Variable	N, (%) / Median (IQR)
Lymph Node Metastases	
No	163 (67.4)
Yes	79 (32.6)
Lymphovascular Invasion	
No	118 (60.8)
Yes	76 (39.2)
Perineural Invasion	
No	47 (22.7)
Yes	160 (77.3)

portal vein resection was performed in 19 (7.9%) patients; 4 patients had a formal segmental portal vein resection and reconstruction. On final histopathology, 82 (33.9%) patients had a positive (R1) surgical margin. The median tumor size was 2.5 cm (1.8-3.9) and the majority of tumors were classified as moderately differentiated (n=131, 58.2%). Nodal disease was observed in 79 (32.6%) patients while 160 (77.3%) patients had tumors with perineural invasion.

Following surgery, 150 (64.4%) patients developed a postoperative complication, 83 (56.4%) of which were classified as grade III or higher. The most common complications were intra-abdominal abscesses and fluid collections requiring percutaneous drainage, which were observed in 18.6% (n=43) and 21.8% (n=51) of patients, respectively.

Factors Associated with Overall Survival

The median actuarial OS among all patients was 22.3 months with an estimated 1-, 3- and 5-year OS of 75.6% (95%CI 69.9-81.2), 46.3% (95%CI 39.3-53.0) and 18.2% (95%CI 12.6-24.6), respectively (Figure 1). On Cox regression analyses, several patient and disease specific characteristics were associated with a worse OS. Specifically, age at diagnosis >65 years (HR 1.36, 95%CI 1.01-1.85, p=0.04), a greater T-stage (AJCC 7th T-Stage III or IV; HR 1.73; 95% CI 1.14-2.61; p=0.009), presence of nodal metastasis (HR, 1.71; 95% CI, 1.24-2.36, p=0.001), and overall advanced disease stage (AJCC Stage III-IV; HR 1.81; 95% CI 1.27-2.58, p=0.001) were each associated with worse OS.

Comparison of Overall and Conditional Survival

In contrast to actuarial OS, which was observed to decrease from the time of surgery, estimates for CS increased over time as surviving patients accrued more survival time (Figure 2). For example, while actuarial OS decreased from 26.6% at

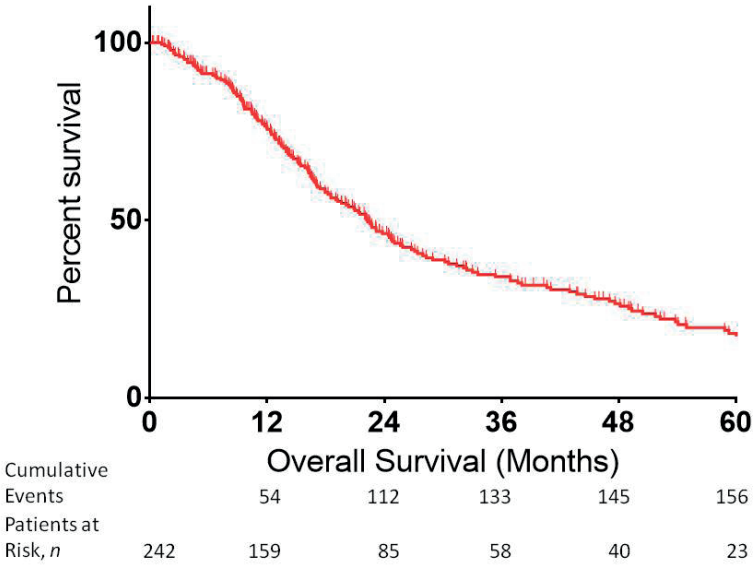

Figure 1. Overall survival among all patients undergoing curative intent surgery for hilar cholangiocarcinoma.

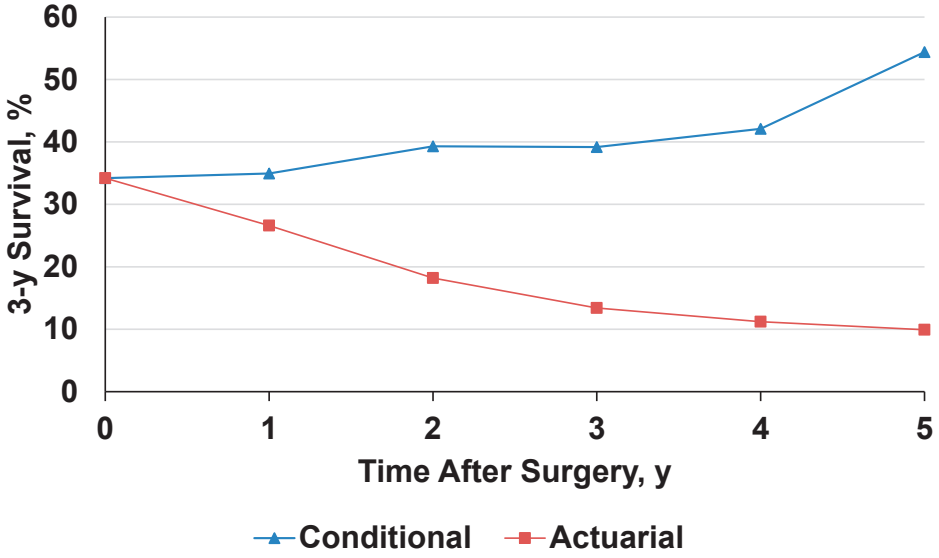

Figure 2. A comparison of 3-year actuarial survival and 3-year conditional survival among all patients undergoing a curative intent surgery for hilar cholangiocarcinoma.

4 years to 9.9% at 8 years following surgery, 3-year conditional survival (CS_3) was noted to increase from 35.0% at 1-year versus 54.4% at 5-years following surgery. Of note, the 3-year CS estimates given the patient had already survived for 1-, 2-, and 5-years were 35.0%, 39.3%, and 54.4%, respectively (Table 2).

Table 2. Conditional Survival

Total Survival Time, y	If the Patient Has Survived. %						
	1 y	2 y	3 y	4 y	5 y	6 y	7 y
1							
2	60.8						
3	44.9	73.9					
4	35.0	57.5	77.8				
5	23.9	39.3	53.2	68.4			
6	17.6	28.9	39.2	50.4	73.6		
7	14.7	24.2	32.7	42.1	61.5	83.6	
8	13.0	21.4	28.9	37.2	54.4	73.9	88.4

Patients who reach a certain survival point after resection of intrahepatic cholangiocarcinoma given that they have already survived a certain amount of time (%). For example, if a patient has survived to 3 years, the survival probability of reaching 5 years of total survival is 53.2%.

To further compare differences in actuarial OS versus CS, additional analyses were performed stratified by clinicopathologic characteristics such as age, nodal status, depth of invasion, as well as margin status and tumor stage. As expected, older patient age, the presence of nodal metastasis, perineural invasion, T3/T4 disease, as well as advanced overall AJCC stage were all associated with decreased actuarial OS (all $p<0.05$, Table 3). For example, patients with nodal metastases had a substantially worse 5-year actuarial OS (8.7%) versus patients without nodal disease (22.7%) ($p=0.001$). Similarly, the 5-year actuarial OS for patients with stage I/II disease was 27.7% compared with 5.8% for patients with stage III/IV disease ($p=0.001$). Interestingly, CS_3 estimates exceeded actuarial OS for patients in high-risk subgroups (Figures 3a-e). For example, among patients who had an R1 margin at the time of surgery, the "all comer" observed 5-year actuarial OS was 8.4%; however, among patients who had an R1 margin but survived to year 2 following surgery, the chances of being alive an additional 3 years (i.e. CS_3, based on being alive for 2 years a cumulative total of 5 years from surgery) was 22.8% (Δ=14.4%)(Table 4). Differences in actuarial versus CS were also noted among patients with tumors characterized by adverse biologic features. For example, among patients with perineural invasion the calculated actuarial 5-year OS was

Table 3. Overall Survival Stratified by Risk Factors

Variable	Patient Survival, %				p Value*
	1 y	3 y	5 y	8 y	
All Patients	75.6 (159)	34.2 (58)	18.2 (23)	9.9 (9)	
Age, y					
< 65	81.2 (78)	36.8 (29)	20.7 (12)	11.4 (4)	0.048
≥ 65	70.7 (80)	31.9 (28)	15.9 (10)	8.7 (4)	
Sex					
Male	80.8 (96)	31.8 (32)	17.8 (12)	8.3 (4)	0.687
Female	68.8 (62)	37.0 (25)	18.6 (10)	12.2 (5)	
Margin Status					
R0	77.7 (109)	37.5 (39)	23.6 (19)	11.9 (7)	0.056
R1	71.4 (49)	27.7 (18)	8.4 (3)	- (1)	
Tumor Size					
≤ 2.5 cm	73.2 (77)	35.4 (30)	21.3 (13)	5.0 (2)	0.744
> 2.5 cm	79.3 (74)	35.3 (26)	17.3 (10)	15.4 (8)	
Grade					
Well Differentiated	77.6 (31)	42.6 (15)	17.8 (4)	0.0 (0)	0.562
Moderately/poorly differentiated	73.7 (114)	30.3 (36)	17.8 (15)	12.7 (7)	
AJCC Stage					
Stage I & II	79.3 (75)	45.6 (32)	27.7 (15)	18.2 (7)	0.001
Stage III & IV	68.5 (48)	21.1 (11)	5.8 (2)	0.0 (0)	
AJCC T-stage					
T1-T2	74.6 (98)	40.1 (39)	24.3 (16)	14.3 (6)	0.008
T3-T4	75.0 (25)	15.3 (4)	0.0 (0)	0.0 (0)	
Lymph Node Metastases					
No	80.3 (112)	40.1 (45)	22.7 (19)	13.2 (9)	0.001
Yes	66.2 (46)	22.3 (12)	8.7 (3)	0.0 (0)	
Lymphovascular Invasion					
No	82.9 (80)	41.7 (32)	24.2 (14)	6.1 (2)	0.067
Yes	67.1 (45)	26.1 (12)	15.2 (5)	- (3)	
Perineural Invasion					
No	85.9 (34)	47.8 (15)	34.5 (10)	21.6 (3)	0.040
Yes	72.3 (102)	29.8 (33)	15.4 (14)	5.9 (3)	

Overall survival Kaplan-Meier estimates, the numbers provided are percentages of patients alive. Number of patients at risk is depicted between the parentheses. *P-value is determined using the Mantel-Haenszel test.

only 15.4% versus an estimated CS_3 at 2 years of 37.6% (Δ=22.2%). Similarly, patients with nodal disease had an estimated 5-year actuarial OS of 8.7% based on actuarial data calculated from the time of their operation. In contrast, among patients with nodal metastasis who had survived 2 years, the estimate that these patients would still be alive in another 3 years was much higher, with an estimated CS_3 of 29.7% (Δ=21.0%).

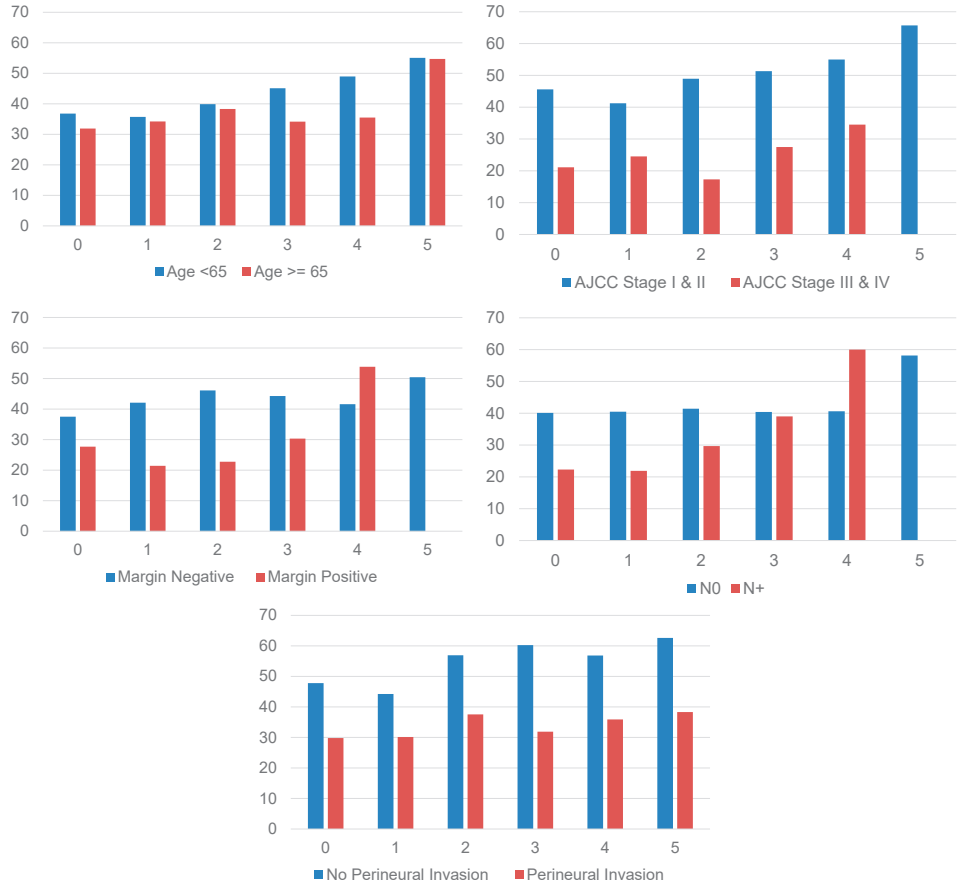

Figure 3. A comparison of 3-year conditional survival by (a) age (b) margin status (c) AJCC 7th edition tumors stage (d) presence of lymph node metastases (e) presence of perineural invasion

Table 4. 3 Year Conditional Survival Stratified by Risk Factor

Variables	Time Elapsed Since Operative Resection					
	0 y	1 y	2 y	3 y	4 y	5 y
All Patients	34.2	35.0	39.3	39.2	42.1	54.4
Age, y						
< 65	36.8	35.7	39.9	45.1	49.0	55.1
>= 65	31.9	34.2	38.3	34.2	35.5	54.7
d	0.10	0.03	0.03	0.23	0.27	0.01
Margin Status						
R0	37.5	42.1	46.1	44.3	41.6	50.4
R1	27.7	21.4	22.8	30.3	53.8	-
d	0.21	0.46	0.51	0.29	-0.25	-
AJCC Stage						
I & II	45.6	41.2	48.9	51.3	55.0	65.7
III & IV	21.1	24.5	17.3	27.5	34.5	-
d	0.54	0.36	0.71	0.50	0.42	-
AJCC T-stage						
T1-T2	40.1	39.7	48.7	52.1	62.9	58.8
T3-T4	15.3	15.3	-	-	-	-
d	0.58	0.57	-	-	-	-
Lymph Node Metastases						
No	40.1	40.5	41.4	40.4	40.6	58.7
Yes	22.3	21.9	29.7	39.0	60.0	-
d	0.39	0.41	0.25	0.03	-0.40	-
Perineural Invasion						
No	47.8	44.2	56.9	60.3	56.8	62.6
Yes	29.8	30.1	37.6	31.9	35.9	38.3
d	0.38	0.29	0.40	0.59	0.43	0.50

Discussion

HC is the most common malignancy of the biliary tract, accounting for up to two-thirds of all cases of cholangiocarcinoma.[1,2] HC has traditionally been associated with a poor prognosis with 5-year survival ranging from 11-42% among patients following curative surgical resection. Given this, identifying high-risk patients is important to guide decisions pertaining to treatment, surveillance and / or palliation. Although prognostic classification systems have been proposed for HC, these schemes are limited because data are only derived from the time of surgery.[15] As such, these traditional survival estimates do not account for changes

in survival probability over time accrued from the initial diagnosis.[8,9] In contrast, CS estimates account for changes in survival probabilities over time and therefore may be more accurate in predicting long-term survival.[8,9] Although previously reported for patients with bladder, gastric and colon cancer, to the best of our knowledge no previous report has assessed conditional survival among patients with HC. The current study is important because we were able to define CS estimates for patients undergoing curative intent surgery for HC using a large, multi-centric cohort of patients. Of note, CS estimates increased over time and were consistently higher than traditional OS estimates. To further explore differences in conditional and actuarial survival estimates, additional stratified analyses were performed using certain demographic and clinicopathologic characteristics. Interestingly, CS estimates were consistently higher among all patient strata with the magnitude of differences between CS and actuarial OS estimates highest among patients with high-risk factors traditionally associated with a worse OS such as perineural invasion and nodal metastasis.

In describing prognosis following surgery, most studies report survival based on a Kaplan Meier survival curve determined from factors derived at the time of surgery. While traditionally used to estimate survival, such curves have been criticized as being inaccurate due to their "static" nature.[7] Rather than being fixed, in reality, the odds that a patient survives for an additional future period of time changes as the patients accrues survival time.[8,9] As such, in order to be more clinically meaningful to patients and providers, survival data should chart the way the odds of survival change over time. Unlike traditional survival estimates, CS estimates a patient's survival odds given the pre-condition of having already survived a certain length of time. In fact, for a wide range of advanced cancers, including cancers with a particularly poor prognosis, there is evidence that the odds actually do improve with time.[9,13,14,16,17] Our group has previously demonstrated that CS estimates may provide critical quantitative information about the changing probability of survival over time among patients with gastric cancer, gastrointestinal stromal tumors, pancreatic cancer, as well as intrahepatic cholangiocarcinoma.[9,14,16,17] For example, among patients with intrahepatic cholangiocarcinoma, we previously noted that, while actuarial OS decreased over time from 39% at 3 years to 16% at 8 years, the 3-year CS increased over time among those patients who survived.[14] Specifically, the CS_3 at 5 years (i.e. the probability of surviving to postoperative year 8 after having already survived to postoperative year 5) was 65% compared with a predicted 8-year actuarial OS of 16%. Of course, time since diagnosis is not the only factor that can affect prognosis, as clinical and tumor specific factors can also be drivers of long-term outcome.

In the current analysis of 242 patients, the median actuarial overall survival was 22.3 months. Consistent with previous reports, the current study identified patient age, T-stage, nodal status, presence of perineural invasion, margin status, as well as overall AJCC stage as important adverse prognostic factors.[18-20] Perhaps of greater interest, data from the current study demonstrated that these clinical and tumor characteristics were not "universally" associated with a prohibitively poor prognosis. In fact, while a lower actuarial survival was noted among patients demonstrating these adverse prognostic factors, the greatest improvement in CS was also noted among these subgroups of patients. For example, patients with nodal disease demonstrated an increase in CS of over 20% compared with patients who did not have nodal metastases. The reasons for differences in actuarial versus CS survival estimates is likely related to the fact that traditional actuarial estimates of survival are disproportionately influenced by high-risk patients many of whom may die within the first few years of surgery. However, those patients with high risk features who do live longer have in a sense "out-lived" some of the prognostic impact of these initial adverse factors.[14] In turn, the prognosis of patients who initially had the worse prognostic factors, but who are still alive after a period of time, are the most likely to have their future long-term prognosis inaccurately predicted using traditional actuarial survival estimates. As such, the use of CS to provide information on long-term prognosis is likely to be valuable in estimating long-term survival for patients with diseases that traditionally have a poor prognosis, such as HC.

Several limitations should be considered when interpreting results from the current study. Inherent to all retrospective analyses, there may have been a selection bias regarding the diagnosis and treatment of patients. In addition, the use of data from a multi-institutional cohort did not allow for the standardization of operative and / or perioperative approach among centers. However, given the rarity of HC, the use of data from multiple centers ensured a uniquely large sample size while also making our results more generalizable.

In conclusion, using a large, multi-institutional cohort of patients, we observed that overall survival following curative intent surgery for HC varied as a function of the survival time accrued since surgical resection. The relative improvement in CS estimates was greatest among that subgroup of patients with high risk factors. CS estimates can be used to provide important quantitative information regarding the changing probability of survival over time among patients with HC. In turn, CS may facilitate more accurate prognostication while also aiding in clinical decision making.

References

1. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**(5): 755-62.
2. Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; **228**(3): 385-94.
3. Zhang W, Yan LN. Perihilar cholangiocarcinoma: Current therapy. *World J Gastrointest Pathophysiol* 2014; **5**(3): 344-54.
4. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery* 2002; **132**(4): 555-63; discission 63-4.
5. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975; **140**(2): 170-8.
6. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; **234**(4): 507-17; discussion 17-9.
7. Mertens AC, Yong J, Dietz AC, et al. Conditional survival in pediatric malignancies: analysis of data from the Childhood Cancer Survivor Study and the Surveillance, Epidemiology, and End Results Program. *Cancer* 2015; **121**(7): 1108-17.
8. Nathan H, de Jong MC, Pulitano C, et al. Conditional Survival after Surgical Resection of Colorectal Liver Metastasis: An International Multi-Institutional Analysis of 949 Patients. *J Am Coll Surg* 2010; **210**(5): 755-64.
9. Mayo SC, Nathan H, Cameron JL, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. *Cancer* 2012; **118**(10): 2674-81.
10. Kurta ML, Edwards RP, Moysich KB, et al. Prognosis and conditional disease-free survival among patients with ovarian cancer. *J Clin Oncol* 2014; **32**(36): 4102-12.
11. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. *J Clin Oncol* 2003; **21**(16): 3035-40.
12. Ploussard G, Shariat SF, Dragomir A, et al. Conditional survival after radical cystectomy for bladder cancer: evidence for a patient changing risk profile over time. *Eur Urol* 2014; **66**(2): 361-70.
13. Cucchetti A, Piscaglia F, Cescon M, et al. Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. *Clin Cancer Res* 2012; **18**(16): 4397-405.
14. Spolverato G, Kim Y, Ejaz A, et al. Conditional probability of long-term survival after liver resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 535 patients. *JAMA Surg* 2015; **150**(6): 538-45.
15. Chaiteerakij R, Harmsen WS, Marrero CR, et al. A new clinically based staging system for perihilar cholangiocarcinoma. *Am J Gastroenterol* 2014; **109**(12): 1881-90.
16. Bischof DA, Kim Y, Dodson R, et al. Conditional disease-free survival after surgical resection of gastrointestinal stromal tumors: a multi-institutional analysis of 502 patients. *JAMA Surg* 2015; **150**(4): 299-306.

17. Kim Y, Ejaz A, Spolverato G, et al. Conditional survival after surgical resection of gastric cancer: a multi-institutional analysis of the us gastric cancer collaborative. *Ann Surg Oncol* 2015; **22**(2): 557-64.

18. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.

19. Valero V, 3rd, Cosgrove D, Herman JM, Pawlik TM. Management of perihilar cholangiocarcinoma in the era of multimodal therapy. *Expert Rev Gastroenterol Hepatol* 2012; **6**(4): 481-95.

20. Mao K, Liu J, Sun J, et al. Patterns and prognostic value of lymph node dissection for resected perihilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2015.

CHAPTER 9

Changing Odds of Survival over Time among Patients Undergoing Surgical Resection of Gallbladder Carcinoma

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Abstract

Background: While survival after malignancies is traditionally reported as actuarial survival, conditional survival (CS) may be more clinically relevant by accounting for "accrued" survival time as time progresses. We sought to compare actuarial and CS among patients with gallbladder carcinoma (GBC).

Methods: 312 patients who underwent curative intent surgery for GBC between 2000 and 2014 were identified using a multi-institutional database. Overall survival (OS) was estimated using the Kaplan-Meier method. CS was calculated as the probability of surviving an additional 3 years at year "x" after surgery using the formula $CS_3=S_{(x+3)}/S_x$.

Results: Among all patients, the median actuarial OS was 24.8 months (IQR 13.3-88.9). While actuarial survival decreased over time, 3-year CS (CS_3) increased, with CS_3 at 2 years after surgery noted to be 61.8% compared with the 5-year actuarial OS of 31.6%. Factors associated with reduced actuarial OS were positive margin status (HR=3.61, 95%CI=2.47-5.26), increasing tumor size (HR=1.02, 95%CI=1.01-1.02), higher tumor grade (HR=2.98, 95%CI=1.47-6.04), residual disease at re-resection (HR=2.78, 95%CI=1.49-3.49, p<0.001), and lymph node metastasis (HR=1.95, 95%CI=1.39-2.75, all p<0.001). The calculated CS_3 exceeded the actuarial survival within each high-risk patient subgroup. For example, patients with residual disease at re-resection had an actuarial survival 23.1% at 5 years versus a CS_3 of 56.3% in patients alive at 2 years (Δ=33.2%).

Conclusion: CS provides a more accurate, dynamic estimate for survival, especially among high-risk patients. CS estimates can be used to accurately predict survival and guide clinical decision-making.

Introduction

With an annual incidence of 2.2 per 100,000, gallbladder cancer (GBC) represents the most common cancer of the biliary tract and the sixth most common malignancy of the gastrointestinal tract.[1-4] However, there are marked variations in incidence and risk factors for GBC by gender, ethnicity and geographical region.[1-5] For example, while one of the most common causes of cancer mortality in India and Chile, GBC is less frequently encountered in the United States and Europe.[1-4] The relative rarity of GBC in these regions has therefore limited large, randomized clinical trials to guide management, with most previous reports being single-institutional, retrospective series.[5-8] Furthermore, previous reports have often categorized GBC with other biliary tract cancers, making the applicability of the existing literature questionable.[9]

Although less than 10% of all patients are amenable to surgery, complete surgical resection remains the only option for cure, with a 5-year survival ranging from 5-26%.[8,10-14] Despite the adoption of a radical surgical approach, a majority of patients who undergo a potentially curative surgical resection eventually develop recurrent metastatic disease.[8,10,11] Given this, reliable prognostic tools are required to aid patients and surgeons in decisions pertaining to surgery, adjuvant therapy, surveillance and palliation. Currently three prognostic classification schemes are commonly used to predict survival among patients with GBC; the Nevin staging system, the Japanese Society of Biliary Surgery (JSBS) staging system and the American Joint Committee on Cancer (AJCC) prognostic schema.[15-17] While these classification tools offer an important overall prognostic assessment, each is limited in the ability to predict long-term survival accurately. Specifically, constructed using data collected at the time of surgery / diagnosis, these prognostic schemes are unable to account for the varied prognosis among patients who have already survived for a period of time after surgery.[18] To this point, previous research from our own group as well as others has demonstrated that traditional estimates for overall survival (OS) rely too heavily on static risk factors determined at the time of surgery and are therefore disproportionately influenced by patients who die shortly following surgery.[18-25] Given this, conditional survival (CS), which accounts for the time a patient has already survived following surgery / diagnosis, has been proposed as a more accurate estimate of long-term survival.[21-23]

While the use of CS in predicting long-term survival has been assessed among patients with colorectal, bladder and pancreatic cancer, to the best of our knowledge, no previous research has reported on the use of CS among patients with GBC.[18-2523,26] Therefore, the aim of the current study was to define conditional

survival among patients with GBC using a large, multi-institutional cohort of patients. In particular, we sought to assess the impact of relevant patient and disease-specific characteristics on CS among patients undergoing surgery for GBC.

Methods

Data Sources and Patient Population

Sociodemographic and clinicopathologic data was collected for all patients undergoing surgery for GBC between January 1, 2000, and December 31, 2014 at ten academic institutions in the US (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina). Specifically, sociodemographic data collected included age, sex and race while clinicopathologic characteristics recorded included tumor size, AJCC-T-stage, histologic grade, presence of nodal disease, final resection margin and the presence of vascular and / or perineural invasion. Tumor size was defined using the diameter of the largest tumor within the resected specimen as per the 7th edition of the AJCC staging system. Histologic grade was defined as either well, moderate, or poorly differentiated. Using the final pathologic report, the presence of disease at the resection margin (R0: no disease at resected margin, R1: presence of disease at the resected surgical margin) and the presence of lymph node metastases was determined.

Only patients undergoing a curative intent surgery for histologically confirmed GBC were included in the final study population. To minimize potential confounding, patients who died within 30 days of their surgery were excluded from further analysis. This study was approved by the institutional review board of each participating institution.

Statistical analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up and estimated using the Kaplan-Meier method.

The Mantel-Haenszel test was used to compare differences in OS between patient groups. Associations between OS and potential risk factors (size of primary tumor, AJCC T-stage, histologic grade, lymph node metastases, margin status, and tumor invasion and the presence of residual disease requiring re-resection) were evaluated using Cox proportional hazards regression analyses and reported as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). Conditional survival was calculated as the probability of surviving an additional number of "y" years given that a patient has already survived for "x" years using the formula $CS_{(y|x)}=S_{(x+y)}/S_{(x)}$, with $S_{(x)}$ representing OS at x years.[18] Differences in CS were compared using linear regression analyses and standardized differences (*d*).[27,28] All analyses were performed using SPSS 22.0 (IBM, New York). A $p<0.05$ was used to define statistical significance.

Results

Demographic and Clinicopathologic Characteristics

A total of 312 patients were identified who met inclusion criteria. Among the entire cohort, the median age was 66 years (IQR 56-73) with two-thirds of patients being female (n=208, 66.7%; Supplemental Table 1). The most common race / ethnicity was Caucasian (n=208, 71.7%) followed by African-American (n=39, 13.4%) and Asian (n=20, 6.9%). Although 93.6% (n=250) of patients were classified as functionally independent at the time of surgery, comorbidities were commonly noted among the study cohort. Specifically, hypertension (n=157, 58.8%), diabetes mellitus (n=66, 24.7%), and a history of heart disease (n=32, 11.9%) were the most commonly noted comorbidities with 52 (19.5%) patients being either active smokers or having quit smoking in the 6 months prior to surgery.

The most commonly performed surgery was a radical cholecystectomy (n=240, 77.2%) with a majority of patients undergoing an open surgery (n=285, 91.9%). A negative microscopic margin (R0) was obtained in 85.4% of patients (n=264). The median tumor size was 3.0 cm (2.0-5.0) and a majority of tumors were classified as either T1 (n=24, 8.2%) or T2 (n=126, 43.2%) based on the 7th edition AJCC staging system. Similarly, most tumors were graded as either moderately- (n=141; 53.8%) or poorly- (n=91; 34.7%) differentiated. Lymph node metastases were noted in 122 (45.7%) patients and lymphovascular or perineural invasion noted in 49.4% (n=89) and 52.8% (n=94) of patients, respectively.

Actuarial Overall Survival and Risk Factors for Overall Survival

The median actuarial OS among all patients was 24.8 months (IQR 13.3-88.9) with 1-, 3-, and 5-year survival being 76.9%, 40.7%, 31.6%, respectively. OS was noted to decrease from 76.9% (95%CI 71.2-81.6) 1 year following surgery to 31.6% (95%CI 24.9-38.6) at postoperative year 5. At 10 years following surgery, survival was only 18.4% (95%CI 10.9-27.4, Figure 1a). On Cox proportional hazards analyses, a microscopically positive surgical margin (HR 3.61, 95%CI 2.47-5.26, p<0.001), increasing tumor size (HR 1.02; 95%CI 1.01-1.02, p<0.001), worse tumor grade (HR 2.98, 95%CI 1.47-6.04, p=0.002), the presence of residual disease requiring re-resection (HR 2.78, 95%CI 1.49-3.49, p<0.001), and lymph node metastases (HR 1.95, 95%CI 1.39-2.75, p<0.001) were all associated with a worse OS.

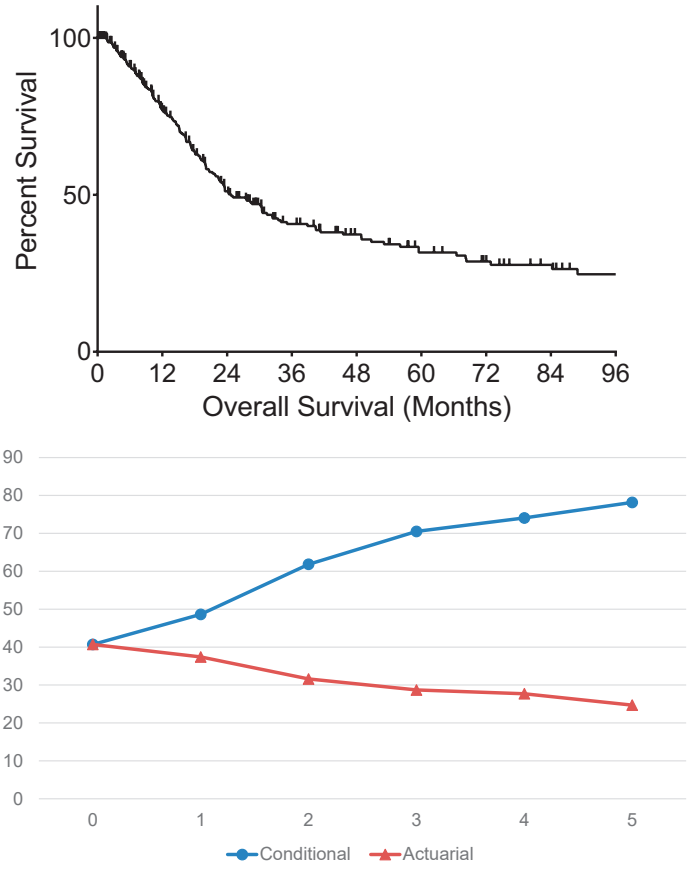

Figure 1. (a) Actuarial overall survival for the entire study cohort (b) Comparison of 3-year actuarial overall survival and 3-year conditional survival.

Comparison of Actuarial and Conditional Survival

While the actuarial OS was noted to decrease with time, CS increased with time from the date of surgery. Specifically, the 3-year conditional survival (CS_3), defined as the probability of surviving an additional 3 years, increased from 48.6% among patients who were still alive at 1 year following surgery to 61.8% among patients who were alive 2 years following surgery. In fact, among patients who had survived to 5 years following surgery the chance of survival to year 8 (i.e. CS_3 based on 5-year survival) was 78.2% (Figure 1b, Table 1).

Table 1. Conditional Survival Entire Cohort

Total Survival Time,	If the Patient Has Survived. %						
y	1 y	2 y	3 y	4 y	5 y	6 y	7 y
1							
2	66.4						
3	52.9	79.6					
4	48.6	73.2	91.9				
5	41.1	61.8	77.6	84.5			
6	37.3	56.2	70.5	76.7	90.8		
7	36.0	54.2	68.1	74.1	87.7	96.5	
8	32.1	48.3	60.7	66.0	78.2	86.1	89.2

The effect of patient and disease-specific characteristics on CS versus OS was then assessed via subgroup analyses of patients according to prognostic factors associated with survival on Cox regression analysis (Figure 2a-h). Factors including positive margin status, increasing tumor size, worse histological grade, a higher tumor T stage, lymph node metastases and lymphovascular or perineural invasion, as well as the presence of residual disease at re-resection were all associated with a worse OS. For example, 5-year actuarial survival was 38.0% (95%CI 10.9-27.4) among patients with a microscopically negative margin compared with 3.5% (95%CI 0.3-14.7) among patients with a positive surgical margin. Similarly, among patients without residual disease, 5-year actuarial survival was 46.7% (95%CI 32.9-59.4) compared with 23.1% (95%CI 12.4-35.8) among patients with residual disease (Table 2). In contrast, CS_3 estimates were noted to increase with time from surgery among each patient subgroup and exceeded the OS within each strata. For example, patients with T3/T4 tumors demonstrated an actuarial survival of 9.7% at 8 years compared with a CS_3 at 5 years of 75.2% (Δ=65.5%, Table 3). Similarly, patients with residual disease at re-resection demonstrated an 8-year actuarial OS of 15.0% compared with a CS_3 at 5 years of 64.9% (Δ=49.9%). Patients with lymph node metastases demonstrated an 8-year actuarial OS of 14.4% versus a CS_3 at 5 years of 65.8% (Δ=51.4%). Of note, differences in CS_3 and OS were less pronounced among patients within lower risk strata.

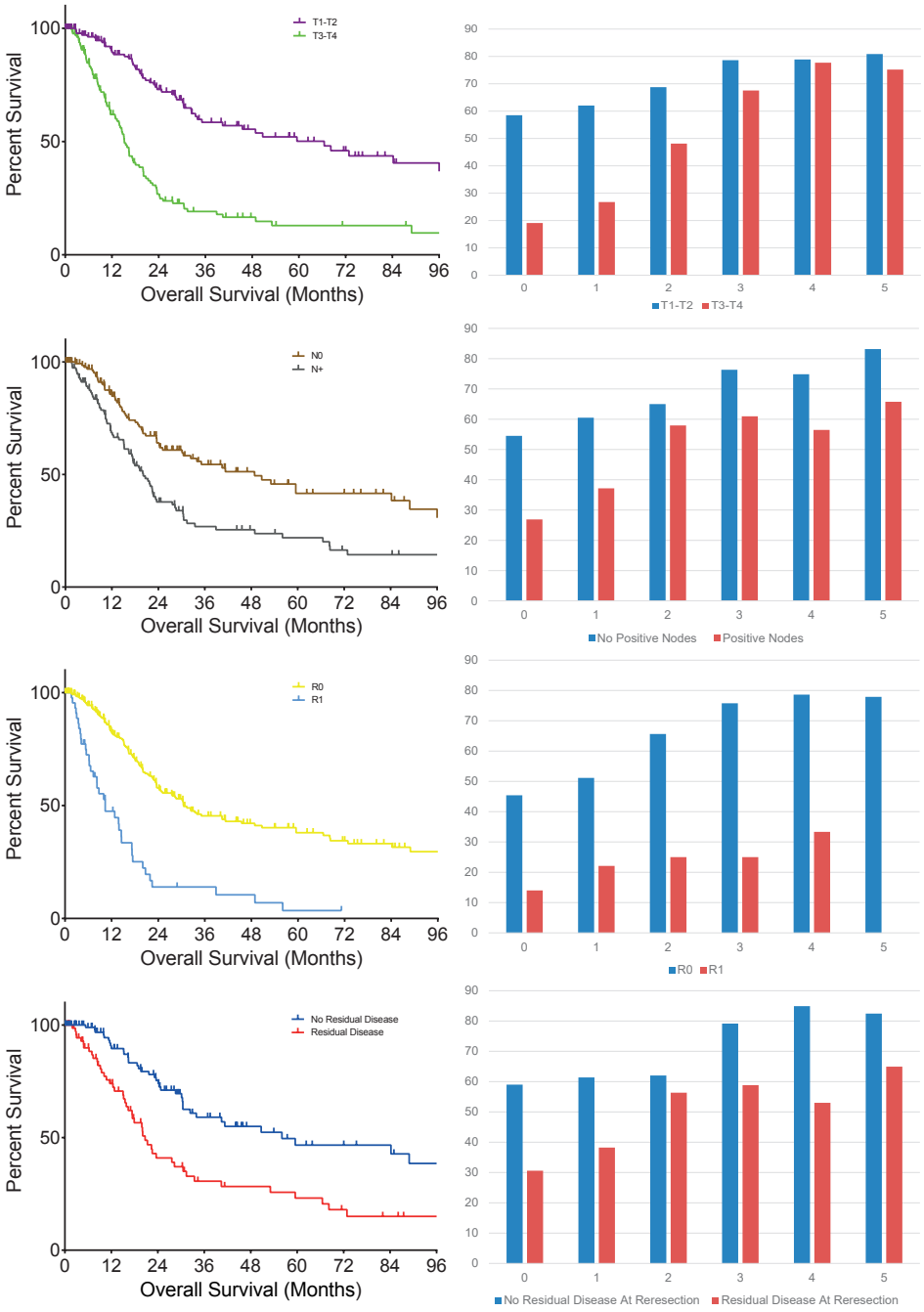

Figure 2. A comparison of actuarial overall survival and 3-year conditional survival stratified by risk factor

Table 2. Overall Survival Stratified by Risk Factor

	Patient Survival, %			
Variable	2 y	5 y	8 y	P Value
All Patients	51.1	31.6	24.7	
Age, y				
< 65	53.6	37.5	27.0	
>= 65	49.0	26.4	22.7	0.427
Sex				
Female	49.2	30.5	21.9	
Male	54.8	34.0	31.4	0.642
Type of Resection				
Minor	55.1	34.2	26.4	
Major	22.6	0.0	0.0	0.002
Margin Status				
R0	57.9	38.0	29.6	
R1	14.0	3.5	-	<0.001
Tumor Size				
<= 2.5 cm	59.1	41.8	38.0	
> 2.5 cm	38.4	21.0	21.0	0.007
Grade				
Well Differentiated	83.3	53.2	53.2	
Moderately differentiated	49.0	31.0	21.3	
Poorly differentiated	34.4	22.4	17.9	0.002
AJCC T-stage				
T1-T2	73.0	50.2	40.6	
T3-T4	26.8	12.9	9.7	<0.001
Lymph Node Metastases				
No	64.0	41.6	34.6	
Yes	37.8	21.9	14.4	<0.001
Lymphovascular Invasion				
No	67.6	34.0	30.2	
Yes	29.5	15.9	12.7	<0.001
Perineural Invasion				
No	68.2	41.4	37.6	
Yes	35.8	15.3	11.5	<0.001
Incidentally Discovered				
No	31.0	23.5	20.9	
Yes	61.3	35.3	26.2	0.001
Residual Disease Re-resection				
No	75.3	46.7	38.5	
Yes	41.0	23.1	15.0	<0.001

Table 3. 3-year Conditional Survival Stratified by Risk Factor

	Time Elapsed Since Operative Resection					
Variables	0 y	1 y	2 y	3 y	4 y	5 y
All Patients	40.7	48.6	61.8	70.5	74.1	78.2
Type of Resection						
Minor	43.9	52.4	62.1	70.6	73.0	77.2
Major	18.1	18.9	59.7	74.6	-	-
D	0.58	0.75	0.05	-0.09	-	-
Margin Status						
R0	45.4	51.2	65.6	75.8	78.6	77.9
R1	14.0	22.1	25.0	25.0	33.3	-
D	0.73	0.63	0.89	1.18	1.03	-
Tumor Size						
<= 2.5 cm	51.1	58.7	70.7	74.4	78.0	90.9
> 2.5 cm	32.1	37.7	54.7	65.4	79.8	-
D	0.39	0.43	0.34	0.20	-0.04	-
Grade						
Well Differentiated	62.0	70.3	63.9	85.8	-	-
Moderately/Poorly differentiated	35.8	43.3	63.9	65.6	68.2	73.4
D	0.54	0.57	0.00	0.48	-	-
AJCC T-stage						
T1-T2	58.5	62.0	68.8	78.6	78.9	80.9
T3-T4	19.1	26.8	48.1	67.5	77.7	75.2
D	0.88	0.76	0.43	0.25	0.03	0.14
Lymph Node Metastases						
No	54.5	60.5	65.0	76.3	74.9	83.2
Yes	26.9	37.2	57.9	61.0	56.5	65.8
D	0.59	0.48	0.15	0.34	0.39	0.41
Lymphovascular Invasion						
No	52.0	47.1	50.3	58.1	73.8	88.8
Yes	22.7	37.9	53.9	55.9	55.9	79.9
D	0.64	0.19	-0.07	0.04	0.38	0.25
Perineural Invasion						
No	57.3	61.6	60.3	65.6	72.9	90.8
Yes	26.2	31.9	42.7	43.9	54.8	75.2
D	0.66	0.62	0.36	0.45	0.38	0.43

Table 3. 3-year Conditional Survival Stratified by Risk Factor (*continued*)

	Time Elapsed Since Operative Resection					
Variables	0 y	1 y	2 y	3 y	4 y	5 y
Incidentally Discovered						
No	29.6	42.4	75.8	70.6	75.5	88.9
Yes	46.0	50.5	57.6	70.0	73.0	74.2
D	-0.34	-0.16	0.39	0.01	0.06	0.39
Residual Disease Re-resection						
No	59.0	61.4	62.0	79.2	84.9	82.4
Yes	30.6	38.2	56.3	58.8	53.0	64.9
D	0.60	0.48	0.12	0.45	0.73	0.41

Discussion

Although less than 10% of patients are amenable to surgery, complete surgical resection remains the only option for cure for patients with GBC with less than a third of patients surviving to 5 years.[1-4] Given the relative rarity of GBC in the United States and Europe, there are relatively few data reporting on long-term survival following surgery for GBC. In addition, most reports on GBC utilize data from single-institutional, retrospective series that often categorize GBC with other biliary tract cancers, thereby limiting the applicability of the data.[5-7] The current study is important in that it reports on long-term survival among a large cohort of patients undergoing surgery for GBC at 10 academic centers in the US. Using Cox proportional hazards regression analysis we were able to identify risk factors associated with a worse OS including advanced T-stage, the presence of nodal disease and a microscopically positive surgical margin. Perhaps of greater importance, we assessed the use of conditional survival to estimate long-term survival among a cohort of 312 patients who underwent resection and noted that survival increased among the subset of patients who survived varied periods of time from surgery. Furthermore, marked differences in conditional and actuarial survival were also observed when patients were categorized based on the observed risk factors. Interestingly, while conditional survival was consistently higher than actuarial survival among all patient subgroups, the effect was most pronounced among patients in those subgroups characterized by high risk factors.

For patients undergoing curative intent resection of GBC, the median actuarial survival was only 24.8 months. In addition, several patient and disease characteristics were strongly associated with worse long-term prognosis. Specifically, microscopically positive margins, increasing tumor size, a worse tumor grade, the

presence of residual disease, as well as the presence of lymph node metastases were all associated with a worse OS. Similar to data in the current study, Duffy and colleagues reported a median actuarial survival of 30.3 months in a single-institutional review of patients with GBC.[7] Factors associated with a decreased survival also included microscopically positive margins on final histopathology, as well as residual disease at the time of re-resection.[7] Similarly, de Aretxabela et al. also noted a worse actuarial survival among patients undergoing surgical resection for tumors classified as AJCC 7th Edition T3/T4 disease.[5,29] Collectively, results from the current study and previous reports highlight the ability of using certain risk factors to classify patients into different prognostic subgroups thereby aiding in patient and provider decision making.

Currently, these risk factors have been incorporated into three existing prognostic schemes to risk-stratify patients undergoing surgery for GBC: the Nevin staging system, the Japanese Society of Biliary Surgery prognostic scheme and the AJCC staging system.[15-17] These staging systems, however, may be limited because each one relies exclusively on data collected at the time of surgery and therefore cannot account for survival time accrued after surgery. In contrast, estimates for CS define survival probability, given the pre-condition of having already survived a certain length of time. To this point, in the current study, we sought to investigate the use of CS in predicting long-term survival following surgery for GBC. In contrast to actuarial survival, which was noted to decrease with time, estimates for CS improved as the life-time accrued from the date of surgery increased. In fact, upon stratified analyses, the difference between predicted actuarial survival and CS was greater among that strata of patients who had tumors characterized by traditionally poor risk factors. For example, among patients with T3/T4 tumors, 8-year actuarial survival was only 9.7% compared with a CS_3 at 5 years of 75.2%. Similarly, patients with nodal metastasis demonstrated an 8-year actuarial survival of 14.4% versus a CS_3 at 5 years of 65.8%. In effect, these data suggest that among patients who had T3/T4 or nodal disease who survived to 5 years, that these patients had a markedly better chance of living an additional 3 years than what would have been predicted at the time of surgery (Δ65.5% and Δ51.4%, respectively). These results are consistent with previous reports from our own group, as well as others, highlighting the potential for inaccurately estimating prognosis among patients who have survived a period of time following surgery.[21-26] In fact, the greatest increase in CS – and therefore difference from actuarial survival – was among patients who had the highest initial risk of death suggesting that as the time from surgery increases, the prognostic impact / importance of certain risk factors collected at the time of surgery decreases.[19] Under these circumstances, the

use of CS which accounts for life years accrued can serve as a more valuable tool in predicting long-term survival.

Results of the current study should be interpreted with the following limitations. First, while the use of a large multi-institutional database allowed for a large sample size and therefore an adequately powered analysis, we were unable to control for differences in clinical and operative practices between the 10 centers. As such, this may have resulted in some residual confounding of our results. Second, given the retrospective nature of the analysis, we were unable to exclude any selection bias that may have occurred regarding the treatment of patients. However, to minimize this, we included only patients undergoing curative intent surgery as well as those who did not die within the immediate postoperative time period (30 days). Furthermore, multiple sub-analyses were performed by prognostic factors to minimize the potential effect of differences in patient characteristics.

In conclusion, estimates for overall survival were observed to be dynamic and increased with time from surgery. Patients presenting with factors associated with a poor prognosis demonstrated the most appreciable increase in conditional versus actuarial survival. Conditional survival can therefore be used to provide a more accurate estimate for long-term prognosis among patients who have already survived over time and may serve as an important tool to inform patients and providers regarding adjuvant therapy, surveillance and palliation.

References:

1 Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 51:349–64.

2 Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. Cancer 2007;110:572–80. doi:10.1002/cncr.22815.

3 Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989-1995. Cancer 1998;83:2618–28.

4 Müller BG, De Aretxabala X, González Domingo M. A review of recent data in the treatment of gallbladder cancer: what we know, what we do, and what should be done. Am Soc Clin Oncol Educ Book 2014:e165–70. doi:10.14694/EdBook_AM.2014.34.e165.

5 De Aretxabala X, Roa I, Burgos L, Losada H, Roa JC, Mora J, et al. Gallbladder cancer: an analysis of a series of 139 patients with invasion restricted to the subserosal layer. J Gastrointest Surg 2006;10: 186–92. doi:10.1016/j.gassur.2005.11.003.

6 Foster JM, Hoshi H, Gibbs JF, Iyer R, Javle M, Chu Q, et al. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol 2007;14:833–40. doi: 10.1245/s10434-006-9097-6.

7 Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008;98: 485–9. doi:10.1002/jso.21141.

8 Wakabayashi H, Ishimura K, Hashimoto N, Otani T, Kondo A, Maeta H. Analysis of prognostic factors after surgery for stage III and IV gallbladder cancer. Eur J Surg Oncol 2004;30:842–6. doi:10.1016/j.ejso.2004.06.001.

9 Lepage C, Capocaccia R, Hackl M, Lemmens V, Molina E, Pierannunzio D, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5. Eur J Cancer 2015. doi:10.1016/j.ejca.2015.07.034.

10 Ishihara S, Miyakawa S, Takada T, Takasaki K, Nimura Y, Tanaka M, et al. Status of surgical treatment of biliary tract cancer. Dig Surg 2007;24:131–6. doi:10.1159/000101901.

11 Shimizu H, Kimura F, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, et al. Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. J Hepatobiliary Pancreat Surg 2007;14:358–65. doi:10.1007/s00534-006-1188-z.

12 Kai M, Chijiiwa K, Ohuchida J, Nagano M, Hiyoshi M, Kondo K. A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma. J Gastrointest Surg 2007;11:1025–32. doi:10.1007/s11605-007-0181-4.

13 Choi SB, Han HJ, Kim CY, Kim WB, Song T-J, Suh SO, et al. Surgical outcomes and prognostic factors for T2 gallbladder cancer following surgical resection. J Gastrointest Surg 2010;14:668–78. doi: 10.1007/s11605-009-1132-z.

14 Chijiiwa K, Nakano K, Ueda J, Noshiro H, Nagai E, Yamaguchi K, et al. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. J Am Coll Surg 2001;192:600–7.

15 Ishihara S, Horiguchi A, Miyakawa S, Endo I, Miyazaki M, Takada T. Biliary tract cancer registry in Japan from 2008 to 2013. J Hepatobiliary Pancreat Sci 2015. doi:10.1002/jhbp.314.

16 Nevin JE, Moran TJ, Kay S, King R. Carcinoma of the gallbladder: staging, treatment, and prognosis. Cancer 1976;37:141–8.

17 Oh TG, Chung MJ, Bang S, Park SW, Chung JB, Song SY, et al. Comparison of the sixth and seventh editions of the AJCC TNM classification for gallbladder cancer. J Gastrointest Surg 2013;17:925–30. doi:10.1007/s11605-012-2134-9.

18 Zabor EC, Gonen M, Chapman PB, Panageas KS. Dynamic prognostication using conditional survival estimates. Cancer 2013;119:3589–92. doi:10.1002/cncr.28273.

19 Spolverato G, Kim Y, Ejaz A, Alexandrescu S, Marques H, Aldrighetti L, et al. Conditional Probability of Long-term Survival After Liver Resection for Intrahepatic Cholangiocarcinoma. JAMA Surg 2015. doi:10.1001/jamasurg.2015.0219.

20 Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Terzi E, Bolondi L, et al. Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. Clin Cancer Res 2012;18:4397–405. doi:10.1158/1078-0432.CCR-11-2663.

21 Kim Y, Margonis GA, Prescott JD, Tran TB, Postlewait LM, Maithel SK, et al. Curative Surgical Resection of Adrenocortical Carcinoma: Determining Long-term Outcome Based on Conditional Disease-free Probability. Ann Surg 2015. doi:10.1097/SLA.0000000000001527.

22 Nathan H, de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, et al. Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. J Am Coll Surg 2010;210:755–64, 764–6. doi:10.1016/j.jamcollsurg.2009.12.041.

23 Mayo SC, Nathan H, Cameron JL, Olino K, Edil BH, Herman JM, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. Cancer 2012;118:2674–81. doi:10.1002/cncr.26553.

24 Kim Y, Ejaz A, Spolverato G, Squires MH, Poultsides G, Fields RC, et al. Conditional survival after surgical resection of gastric cancer: a multi-institutional analysis of the us gastric cancer collaborative. Ann Surg Oncol 2015;22:557–64. doi:10.1245/s10434-014-4116-5.

25 Bischof DA, Kim Y, Dodson R, Jimenez MC, Behman R, Cocieru A, et al. Conditional disease-free survival after surgical resection of gastrointestinal stromal tumors: a multi-institutional analysis of 502 patients. JAMA Surg 2015;150:299–306. doi:10.1001/jamasurg.2014.2881.

26 Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. J Clin Oncol 2003;21:3035–40. doi:10.1200/JCO.2003.04.521.

27 Crespi CM, Smith SK, Petersen L, Zimmerman S, Ganz PA. Measuring the impact of cancer: a comparison of non-Hodgkin lymphoma and breast cancer survivors. J Cancer Surviv 2010;4:45–58. doi:10.1007/s11764-009-0106-1.

28 Burnand B, Kernan WN, Feinstein AR. Indexes and boundaries for "quantitative significance" in statistical decisions. J Clin Epidemiol 1990;43:1273–84.

29 De Aretxabala X, Roa I, Hepp J, Maluenda F, Mordojovich G, Leon J, et al. Early gallbladder cancer: is further treatment necessary? J Surg Oncol 2009;100:589–93. doi:10.1002/jso.21389.

Supplemental Table 1

Variable	N, (%) / Median (IQR)
Age, y	66.2 (55.9-73.0)
< 65	147 (47.1)
≥ 65	165 (52.9)
Sex	
Male	208 (66.7)
Female	104 (33.3)
Race	
Caucasian	208 (71.7)
African American	39 (13.4)
Other	44 (14.9)
BMI	27.5 (23.2-31.7)
Functionally Independent	250 (93.6)
Comorbidities	
Hypertension	157 (58.8)
History of Cardiac Disease	32 (11.9)
Diabetes	66 (24.7)
Preoperative Jaundice	40 (14.4)
Type of Resection	
Minor Resection (< 3 Couinaud Segments)	280 (90.0)
Major Resection (≥ 3 Couinaud Segments)	31 (10.0)
Margin Status	
R0	264 (85.4)
R1	45 (14.6)
Tumor Size	
≤ 2.5 cm	84 (42.4)
> 2.5 cm	114 (57.6)
Grade	
Well Differentiated	30 (11.5)
Moderately/poorly differentiated	232 (88.5)
AJCC T-stage	
T1-T2	158 (54.1)
T3-T4	134 (45.9)
Lymph Node Metastases	
No	145 (54.3)
Yes	122 (45.7)

Supplemental Table 1 (*continued*)

Variable	N, (%) / Median (IQR)
Lymphovascular Invasion	
No	91 (50.6)
Yes	89 (49.4)
Perineural Invasion	
No	84 (47.2)
Yes	94 (52.8)

CHAPTER 10

Assessing the Impact of Common Bile Duct Resection in the Surgical Management of Gallbladder Cancer

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Abstract

Background

Although radical re-resection for gallbladder cancer (GBC) has been advocated, the optimal extent of re-resection remains unknown. The current study aimed to assess the impact of common bile duct (CBD) resection on survival among patients undergoing surgery for GBC.

Methods

Patients undergoing curative-intent surgery for GBC were identified using a multi-institutional cohort of patients. Multivariable Cox-proportional hazards regression was performed to identify risk factors for a poor overall survival (OS).

Results

Among the 449 patients identified, 26.9% underwent a concomitant CBD resection. The median number of lymph nodes harvested did not differ based on CBD resection (CBD, 4 [IQR: 2–9] vs. no CBD, 3 [IQR: 1–7], *P* =0.108). While patients who underwent a CBD resection had a worse OS, after adjusting for potential confounders, CBD resection did not impact OS (HR =1.40, 95%CI 0.87–2.27, *P* =0.170). Rather, the presence of advanced disease (T3: HR =3.11, 95%CI 1.22–7.96, *P* =0.018; T4: HR =7.24, 95%CI 1.70–30.85, *P* =0.007) and the presence of disease at the surgical margin (HR =2.58, 95%CI 1.26–5.31, *P*=0.010) were predictive of a worse OS.

Conclusions

CBD resection did not yield a higher lymph node count and was not associated with an improved survival. Routine CBD excision in the re-resection of GBC is unwarranted and should only be performed selectively.

Introduction

Each year, it is estimated that 2.2 per 100,000 patients are diagnosed with gallbladder cancer (GBC) making it the sixth most common cancer of the gastrointestinal tract and the most common malignancy of the biliary tract in the United States [1,2]. Patients may be diagnosed incidentally following a routine cholecystectomy or may present late after symptoms develop [3,4]. Regardless of presentation, the best option for potential cure among patients with GBC is complete surgical resection. Prognosis following surgical resection remains poor, however, with 5-year survival ranging from 10% to 90% depending on disease factors such as tumor grade, stage of disease, and the presence of lymph node metastasis [5-7].

Surgery for GBC typically involves a partial hepatectomy that can range from resection of the gallbladder fossa to a more formal anatomic resection of segments 4b and 5 to an extended right hepatectomy [8,9]. Furthermore, any oncologic-directed operation for GBC should include a regional lymphadenectomy to assess for nodal disease to establish prognosis and the potential need for adjuvant therapy [1,10]. The role for excision of the common bile duct (CBD) is, however, more controversial [11-13]. Due to a limited body of research as well as the variation in clinical practices among Eastern and Western centers, information on the role and potential benefit of CBD resection for GBC remains limited [3,11-18]. For example, data from several previous reports have suggested that routine CBD resection be performed at the time of surgery, while other studies argue for a more selective approach [3,4,8-10,19]. Accurate data on outcomes relative to the extent of resection, including the CBD, as well as data evaluating the impact of factors on clinical outcomes may help guide decisions. Therefore, the objective of the current study was to evaluate factors associated with resection of CBD resection, as well as assess the impact of CBD on peri-operative and long-term outcomes among patients undergoing curative-intent surgical resection of GBC using a large, multi-center database.

Methods

Data Sources and Study Population

Patients diagnosed with gallbladder cancer between January 1, 2000 and December 31, 2014 were identified using data collected from the Extra-hepatic Biliary Consortium. The Extra-hepatic Biliary Consortium represents a collaborative effort among 10 high-volume, academic medical centers across the United States (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta,

Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina). Sociodemographic and clinicopathologic data were collected on all patients diagnosed with a malignancy of the biliary tract. Specifically, sociodemographic data included age, sex, and race, while clinicopathologic data included American Society of Anesthesiologists (ASA) physical performance score, preoperative functional status, tumor size, American Joint Commission on Cancer (AJCC) T-Stage, histological grade, presence of lymph node metastasis, presence of vascular and/or perineural invasion as well as the presence of disease at the final surgical resection margin (R0: no disease at resected margin, R1: presence of disease at the resected surgical margin) [20]. Tumor size, tumor grade, the presence of lymph node metastasis, and disease at the resection margin were determined using the final histopathology report. Additionally, operative details pertaining to the type and extent of surgical resection were also recorded for each patient.

Only patients undergoing a curative intent surgical resection for histologically confirmed GBC were included within the study cohort. Patients who had macroscopic disease at the resection margin (R2 disease), presence of disease within N2 nodes and patients with metastatic disease were excluded from the final analysis assessing the survival benefit of CBD resection. Incidental disease was defined as the identification of GBC following a routine cholecystectomy while non-incidental disease was defined by the suspicion of gallbladder carcinoma prior to surgery. Overall survival (OS) was calculated from the date of initial surgery to the date of death or last follow-up, as appropriate. Death was confirmed for each patient using patient records as well as social security numbers/records. This study was approved by the Johns Hopkins Institutional Review Board as well as the institutional review boards of each institution participating in the Extra-hepatic Biliary Consortium.

Statistical Analysis

Categorical variables were presented as whole numbers and percentages, and compared using Pearson's chi-squared test. Continuous variables were described as medians with interquartile (IQR) range and compared using the Kruskal–Wallis test. OS was estimated using the Kaplan–Meier method and compared between patient groups using the log–rank test. Factors associated with OS were examined using multivariable Cox proportional hazards regression analysis. Results from

the multivariable analysis were presented as hazard ratios (HR) with corresponding 95% confidence intervals (95%CI). A *P*-value <0.05 was used to determine statistical significance. All analyses were performed using STATA version 14.0 (StataCorp, College Station, TX).

Results

Baseline Demographic and Disease Characteristics

A total of 449 patients were identified who underwent surgical resection for GBC (Table I). The median age of all patients was 66.3 years (IQR: 57.1–73.1), while over two-thirds of patients were female (n =292, 65.0%) and white (n =305, 67.9%). Although most patients were functionally independent at the time of surgery (n =363, 80.9%), comorbidity was common among the study cohort as 63.3% (n =191) of patients were classified as either ASA physical classification grade III or IV. At the time of diagnosis, the median CA-19-9 was 26.8 units/ml (IQR: 14.5–172.6) while the median preoperative serum albumin and bilirubin were 3.7 g/dl (IQR: 3.2–4.1) and 0.7 mg/dl (IQR: 0.5–1.6), respectively. Among all patients, a radical cholecystectomy (n =343, 76.4%) was the most commonly performed operation followed by a simple cholecystectomy (n =46, 10.4%), and a more formal hepatectomy (n =46, 10.4%).

Comparison of Patient Characteristics by Common Bile Duct Resection

Among patients who were included in the final analysis, a CBD resection was performed in 109 patients (34.2%). While patient demographics were comparable among patients who did and did not undergo a CBD resection, there were several differences in disease characteristics between the two patient groups (Table II). For example, patients who underwent a CBD resection were more likely to present with an advanced AJCC T-stage (AJCC T3 or T4: CBD, 57.0% vs. no CBD, 40.8%, *P* =0.002). Patients who underwent a CBD resection were more likely to undergo a concomitant lymphadenectomy; specifically, while 94.5% of patients who underwent a CBD resection had a least one lymph node sampled, only 81.5% of patients who did not undergo a CBD resection had a lymphadenectomy (*P*<0.001). Of note, the median number of lymph nodes harvested was comparable among patients who did and did not under go a CBD resection (median lymph nodes harvested: CBD, 4 [IQR: 2–9] vs. no CBD, 3 [1-7], *P* =0.108). Patients who underwent CBD resection were, however, more likely to have lymph node metastasis. Specifically, among patients who underwent CBD resection, over

one-half of patients (n =57, 52.3%) had lymph node metastasis versus only a third of patients (n =68, 32.4%) who did not undergo a CBD resection (*P* <0.001).

Table 1 Baseline Characteristics by Common Bile Duct Resection

	No CBD resection		**CBD resection**			**Total**	
Characteristic	**328**	**73.10%**	**121**	**26.90%**	***P*-value**	**449**	**100.00%**
Age, years, median (IQR)	66.6	(56.8–73.29)	67.1	(58.9–72.9)	0.883	66.3	(57.1–73.1)
Sex					0.064		
Male	123	37.5	34	28.1		157	35
Female	205	62.5	87	71.9		292	65
Race					0.08		
White	213	64.9	92	76		305	67.9
Black	43	13.1	10	8.3		53	11.8
Other	72	22	19	15.7		91	20.3
BMI, median (IQR)	28.1	(24.3–32.7)	25.9	(22.5–29.2)		27.5	(23.7–31.4)
ASA					0.159		
I/II	76	34.4	35	43.2		111	36.8
III/IV	145	65.6	46	56.8		191	63.3
Functional status					0.392		
Independent	262	79.8	101	83.5		363	80.9
Dependent	18	5.5	3	2.5		21	4.7
CA-19-9, median (IQR)	24	(15–157)	30	(11–281)	0.863	26.8	(14.5–172.6)
Albumin, median (IQR)	3.7	(3.1–4.1)	3.8	(3.3–4.2)	0.239	3.7	(3.2–4.1)
Peak bilirubin, median (IQR)	0.7	(0.5–1.3)	0.8	(0.4–4.45)	0.472	0.7	(0.5–1.6)
Operation type					<0.001		
Radical cholecystectomy	170	51.8	9	7.4		98	21.8
Cholecystectomy only	60	18.3	6	5		66	14.7
Bile duct resection only	2	0.6	8	6.6		10	2.2
Hepatectomy +bile duct resection	7	2.1	17	14.1		24	5.4
Other	89	27.1	9	7.4		98	21.8

Table 2 Tumor and Disease-Specific Characteristics by Common Bile Duct Resection

	No CBD resection		CBD resection			Total	
Characteristic	**210**	**65.80%**	**109**	**34.20%**	***P*-value**	**319**	**100.00%**
Tumor size, mm, median (IQR)	28	(18–47)	28	(18–47)	0.662	28	(18–47)
AJCC stage					0.002		
T1	30	14.9	3	3.1		33	11
T2	89	44.3	39	39.8		128	42.8
T3	72	35.8	47	48		119	39.8
T4	10	5	9	9.2		19	6.4
Lymph node metastasis					<0.001		
Nx	39	18.6	6	5.5		45	14.1
N0	103	49.1	46	42.2		149	46.7
N1	68	32.4	57	52.3		125	39.2
Margin status					0.201		
R0	181	87	89	81.7		270	85.2
R1	27	13	20	18.4		47	14.8

At the time of CBD resection, residual disease in the duct was found in 17 out of 121 (14.0%) patients. On final pathology, microscopic involvement of the bile duct (R1) margin was similar among patients who did (n =4) and did not (n =2) undergo CBD resection (P =0.442). Post-operatively, the incidence of complications was higher among patients undergoing a CBD (n =55, 48.3%) versus no CBD (n =109, 37.9%) resection (P =0.020).

Comparison of Risk Factors for Overall Survival

The median follow-up for the study cohort was 37.6 months (IQR: 12.3–82.1). Among all patients, median OS was 23.6 months (IQR: 12.0–88.9), while 1-, 2-, and 5-year OS were 74.9% (95%CI 69.2–79.6), 49.1% (IQR: 42.6–55.3), and 31.2% (95%CI 24.6–38.0), respectively. Several patient and disease-specific risk factors were associated with a worse OS. Specifically, on univariable analysis, the presence of lymph node metastasis, presence of disease at the time of re-resection, a greater AJCC T-stage, presence of disease at the surgical margin, advanced tumor grade, and the presence of lymphovascular or perineural invasion was associated with worse OS. Similarly, patients who underwent a CBD resection had a worse median OS (19.2 months, IQR: 9.2–33.9) compared with patients who did not undergo a CBD resection (32.4 months, IQR: 15.2–110.3, Fig. 1). However, on stratified analyses that took into account CBD resection and lymph node status,

only the presence of lymph node metastasis was associated with a worse OS (Fig. 2a and b). To further investigate whether CBD resection was independently associated with OS, multivariable analyses were performed that accounted for competing clinicopathologic risk factors. After adjusting for potential confounders, an advanced AJCC T-stage (T3 vs. T1: HR =3.11, 95%CI 1.22–7.96, *P* =0.018; T4 vs. T1: HR =7.24, 95%CI 1.70–30.85, *P* =0.007) and the presence of disease at the surgical margin (HR =2.58, 95%CI 1.26–5.31, *P* =0.010) were associated with an increased risk of death following surgical resection (Table III). Of note, resection of the CBD did not impact OS (HR =1.40, 95%CI 0.87–2.27, *P*=0.170).

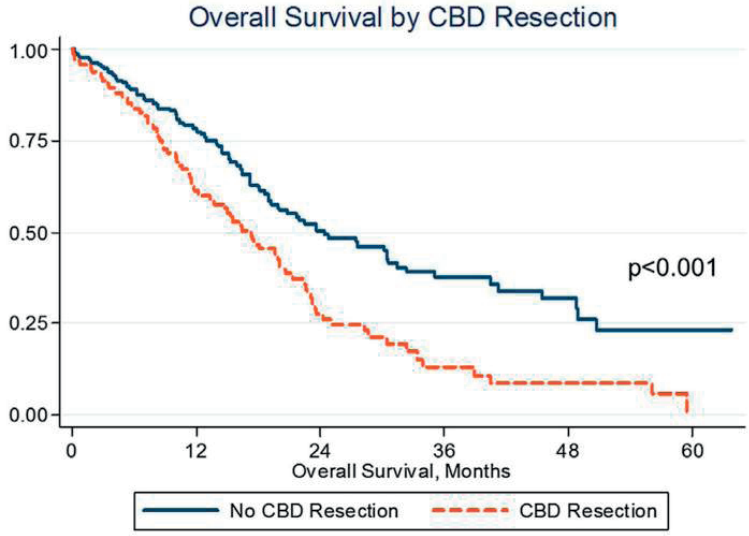

Figure 1 Comparison of overall survival by common bile duct resection.

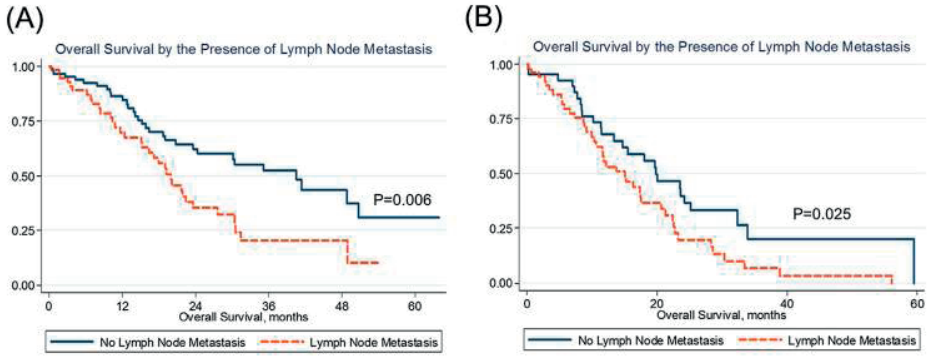

Figure 2 Comparison of overall survival by the presence of lymph node metastasis among patients who (a) underwent a common bile duct resection, (b) did not undergo a common bile duct resection.

Table 3. Multivariable Analysis of Factors Associated With Overall Survival

Characteristic	HR	95%CI		*P*-value
Age	1.01	0.99	1.03	0.171
Sex				
Male	Reference			
Female	1	0.64	1.58	0.994
Residual disease at Re-resection	1.47	0.93	2.33	0.102
AJCC T-stage				
T1	Reference			
T2	1.49	0.6	3.7	0.384
T3	3.11	1.22	7.96	0.018
T4	7.24	1.7	30.85	0.007
Lymph node metastasis				
N0	Reference			
Nx	2.71	1.44	5.08	0.002
N1	1.5	0.93	2.43	0.098
Margin status				
R0	Reference			
R1	2.58	1.26	5.31	0.01
CBD resection				
No CBD resection	Reference			
CBD resection	1.4	0.87	2.27	0.17

Discussion

Prognosis following GBC remains poor with 5-year survival ranging from 10% to 90% depending on disease stage [21]. While surgery remains the best chance at long-term survival, the extent of surgery, as well as the accurate identification of patients who would benefit most from surgical resection remains controversial [1,8,9,22]. In particular, whether the CBD should be routinely excised for GBC is unclear. While some surgeons routinely recommend the resection of the extrahepatic bile duct for GBC, other surgeons have advocated for a more selective approach given the possibility of post-CBD resection complications [15,23,24]. Most studies to date have included, however, only small single center series, with most data coming exclusively from East Asian hospitals [9,11,12,14,23,25]. The current study is important because it utilized the combined experience of 10 major hepatobiliary centers throughout the United States. In doing this, we were able to analyze a large cohort of patients with GBC to examine how often CBD resection was performed in these large tertiary centers, as well as define which factors were

associated with CBD resection. Among all patients who underwent surgery, nearly one in four patients (26.9%) had a concomitant CBD resection. Interesting, while CBD resection was not associated with a higher lymph node yield, it was associated with more aggressive underlying disease such as advanced tumor stage and lymph node metastasis. In turn, although patients who underwent CBD resection had a worse OS, the effect was attributable to a greater burden of disease/more aggressive disease among patients who underwent a concomitant CBD resection. To this end, after adjusting for all other potential risk factors, CBD resection was not associated with an increased risk of death. Rather, tumor specific factors—not surgical approach—were the drivers of long-term outcome.

Several centers in Asia have advocated for routine resection of the CBD [9,11,12]. For example, Shimizu et al. proposed routine resection of the extrahepatic bile duct [9]. The authors argued that gallbladder carcinoma may often extend into the subserosa or beyond and can invade the hepatoduodenal ligament. As such, Shumizu and coworkers advocated for routine CBD to facilitate lymphadenectomy, avoid bile duct ischemia, and increase the number of lymph nodes harvested [9]. Other studies have not, however, demonstrated similar potential benefits regarding CBD resection [13,16-18]. In a study from the Memorial Sloan Kettering Cancer center, D'Angelica and coworkers reported no difference in the number of lymph nodes harvested among patients who did and those who did not undergo a CBD resection [13]. Similarly, in the current study, we failed to find any difference in the median number of lymph nodes harvested or the median number of lymph node metastasis relative to CBD resection. In aggregate, the data suggest that resection of the CBD did not facilitate a more "thorough" lymphadenectomy, as reflected in the comparable lymph node counts among patients who did and did not undergo CBD resection.

Another theoretical benefit of CBD resection relates to survival. Several groups have proposed that radical resections that include the excision of the extra-hepatic biliary tree were associated with a survival advantage [11,14,25,26]. These surgeons point to the removal of potential occult cancer cells in the connective tissue, as well as the ability of CBD resection to address the issue of perineural invasion [11,12]. However, other investigators, including Makuuchi's group from Japan, have questioned the survival benefit of CBD resection [23]. Citing data showing no improvement in long-term survival, and the possible increased risk of complications after a bilioenteric anastomosis, the Makuuchi group recommended preservation of the extrahepatic bile duct in radical surgery for gallbladder cancer [23]. In the current study, resection of the CBD common bile duct resection was not associated

with an improvement in survival (Fig. 2). Rather patients who underwent CBD resection were more likely to have a more aggressive tumor biology (e.g., lymph node metastasis and advanced tumor stage) and, in fact, had a worse OS. Of note, after controlling for tumor-level factors, CBD was not associated with OS indicating that biological factors—not surgical approach—dictated long-term outcomes.

While not associated with increased lymph node yield or OS, CBD resection may result in an increased risk for postoperative morbidity associated with a bilioenteric anastomosis. To this point, using a multi-centric database of French patients, Fuks et al. reported no difference in recurrence-free and OS relative to CBD resection, but did demonstrate that CBD resection was associated with postoperative morbidity [15]. We similarly noted an increase in the incidence of peri-operative complications among patients who underwent CBD resection. As such, the use of CBD resection should likely be reserved for that subgroup of patients who require CBD resection to extirpate all disease in the biliary tree.

The current study should be interpreted with several limitations. As with all retrospective reports, the current study likely suffered from some selection bias that remained unaccounted even on multivariable analyses. In addition, while the use of multi-institutional data allowed for a greater sample size and more generalizable results, potential differences in clinical practices among centers could not be accounted for. However, given that each of the 10 centers were large, academic, referral centers, this variation in practices was likely negligible given the standardized practices at each center.

In conclusion, the current study demonstrates that underlying tumor biology and not the extent of surgical resection was the most important risk factor for long-term outcomes among patients with GBC. The aim for curative surgical resection should be to resect regional lymph nodes and to obtain negative surgical margins. Given that CBD resection did not yield a higher lymph node count, nor was it associated with improved long-term outcomes, a selective approach to the CBD should be employed.

References

1. Müller BG, De Aretxabala X, González Domingo M. A review of recent data in the treatment of gallbladder cancer: What we know, what we do, and what should be done. Am Soc Clin Oncol Educ Book. 2014:e165–e170.
2. Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin. 2016;51:349–364.
3. Hueman MT, Vollmer CM, Pawlik TM. Evolving treatment strategies for gallbladder cancer. Ann Surg Oncol. 2009;16:2101–2115.
4. Cavallaro A, Piccolo G, Di Vita M, et al. Managing the incidentally detected gallbladder cancer: Algorithms and controversies. Int J Surg. 2014;12:S108–S119.
5. De Aretxabala X, Roa I, Burgos L, et al. Gallbladder cancer: An analysis of a series of 139 patients with invasion restricted to the subserosal layer. J Gastrointest Surg. 2006;10:186–192.
6. Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989–1995. Cancer. 1998;83:2618–2628.
7. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC) J Surg Oncol. 2008;98:485–489.
8. Singh SK, Talwar R, Kannan N, et al. Aggressive Surgical Approach for Gallbladder Cancer: A single-center experience from northern India. J Gastrointest Cancer. 2015;46:399–407.
9. Shimizu H, Kimura F, Yoshidome H, et al. Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. J Hepatobiliary Pancreat Surg. 2007; 14:358–365.
10. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol. 2007;14:833–840.
11. Sakamoto Y, Kosuge T, Shimada K, et al. Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. J Surg Oncol. 2006;94:298–306.
12. Shimizu Y, Ohtsuka M, Ito H, et al. Should the extrahepatic bile duct be resected for locally advanced gallbladder cancer? Surgery. 2004;136:1012–1017. discussion 1018.
13. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol. 2009;16:806–816.
14. Nakamura S, Sakaguchi S, Suzuki S, et al. Aggressive surgery for carcinoma of the gallbladder. Surgery. 1989;106:467–473.
15. Fuks D, Regimbeau JM, Le Treut Y-P, et al. Incidental gallbladder cancer by the AFC-GBC-2009 study group. World J Surg. 2011;35:1887–1897.
16. Higuchi R, Ota T, Araida T, et al. Prognostic relevance of ductal margins in operative resection of bile duct cancer. Surgery. 2010;148:7–14.

17. Araida T, Higuchi R, Hamano M, et al. Should the extrahepatic bile duct be resected or preserved in R0 radical surgery for advanced gallbladder carcinoma? Results of a Japanese Society of Biliary Surgery Survey: A multicenter study. Surg Today. 2009;39:770–779.

18. Pawlik TM, Gleisner AL, Vigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: Implications for re-resection. J Gastrointest Surg. 2007;11:1478–1486. discussion 1486–1487.

19. De Aretxabala X, Roa I, Hepp J, et al. Early gallbladder cancer: Is further treatment necessary? J Surg Oncol. 2009;100:589–593.

20. Oh TG, Chung MJ, Bang S, et al. Comparison of the sixth and seventh editions of the AJCC TNM classification for gallbladder cancer. J Gastrointest Surg. 2013;17:925–930.

21. Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer, and pancreatic cancer in Europe Results of EUROCARE-5. Eur J Cancer. 2015;51:1999–2007.

22. Ercan M, Bostanci EB, Cakir T, et al. The rationality of resectional surgery and palliative interventions in the management of patients with gallbladder cancer. Am Surg. 2015;81:591–599.

23. Kosuge T, Sano K, Shimada K, et al. Should the bile duct be preserved or removed in radical surgery for gallbladder cancer? Hepatogastroenterology. 1999;46:2133–2137.

24. Chijiiwa K, Tanaka M. Indications for and limitations of extended cholecystectomy in the treatment of carcinoma of the gall bladder. Eur J Surg. 1996;162:211–216.

25. Tsukada K, Hatakeyama K, Kurosaki I, et al. Outcome of radical surgery for carcinoma of the gallbladder according to the TNM stage. Surgery. 1996;120:816–821.

26. Choi SB, Han HJ, Kim WB, et al. Surgical strategy for T2 and T3 gallbladder cancer: Is extrahepatic bile duct resection always necessary? Langenbeck's Arch Surg. 2013;398:1137–1144.

PART III Novel Treatments

CHAPTER 11

Intrahepatic Cholangiocarcinoma: Current Perspectives

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is the second most common malignancy arising from the liver. ICC makes up about 10% of all cholangiocarcinomas. It arises from the peripheral bile ducts within the liver parenchyma, proximal to the secondary biliary radicals. Histologically, the majority of ICCs are adenocarcinomas. Only a minority of patients (15%) present with resectable disease, with a median survival of less than 3 years.

Multidisciplinary management of ICC is complicated by large differences in disease course for individual patients both across and within tumor stages. Risk models and nomograms have been developed to more accurately predict survival of individual patients based on clinical parameters. Predictive risk factors are necessary to improve patient selection for systemic treatments. Molecular differences between tumors, such as in the epidermal growth factor gene (EGFR) status, are promising, but their clinical applicability should be validated.

For patients with locally advanced disease, several treatment strategies are being evaluated. Both hepatic arterial infusion chemotherapy with floxuridine and yttrium-90 embolization (Y-90) aim to downstage locally advanced ICC. Selected patients have resectable disease after downstaging, other patients might benefit because of postponing widespread dissemination and biliary obstruction.

Incidence and Risk Factors

The incidence of intrahepatic cholangiocarcinoma (ICC) in the Western world is approximately 1-2 per 100,000.[1-3] ICC is the second most common malignancy arising from the liver, accounting for 3% of all cases of gastro-intestinal cancer.[4,5] ICC makes up about 10% of all cholangiocarcinomas. It arises in peripheral bile ducts within the liver parenchyma, proximal to the secondary biliary radicals (Figure 1).[6] It should be distinguished from perihilar cholangiocarcinoma arising near the biliary confluence and distal cholangiocarcinoma arising near the head of the pancreas. Only a minority (15%) of ICC patients presents with resectable disease at the time of diagnosis. Complete surgical resection remains the only option for cure with an estimated median survival ranging from 27 to 36 months (Figure 2).[5,7-10]

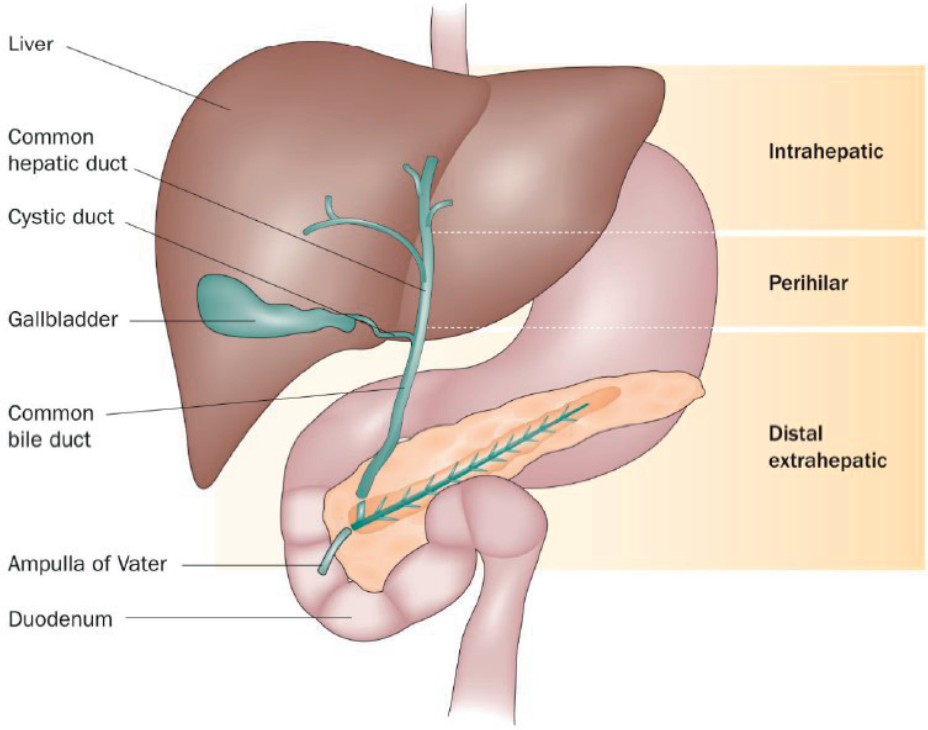

Figure 1. Types of cholangiocarcinoma (From: Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nature reviews Gastroenterology & hepatology. 2011;8(9):512-522.)

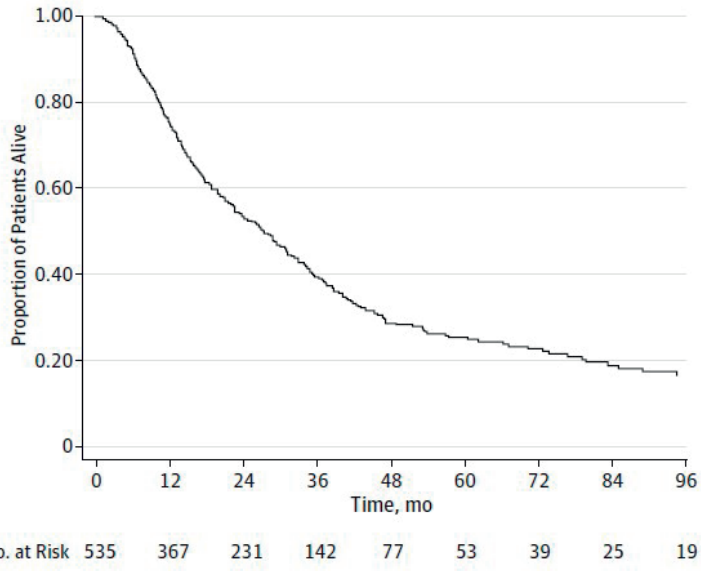

Figure 2. Overall survival in a large cohort of ICC patients (From Spolverato G, Kim Y, Ejaz A, et al. Conditional Probability of Long-term Survival After Liver Resection for Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis of 535 Patients. JAMA Surg. 2015;150(6):538-545.)

Over three quarters of patients are older than 65 years of age at initial diagnosis[3] and ICC is slightly more common in men.[11] ICC is more common in East-Asia; in China an incidence 10 per 100,000 persons has been reported, while in Thailand the incidence is 71 per 100,000, higher than for hepatocellular carcinoma (HCC).[1,12]

In general, ICC has similar risk factors to hepatocellular carcinoma (HCC). A correlation with diseases causing biliary inflammation and fibrosis, such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), has been noted.[13,14] Other risk factors for ICC are congenital malformations of the bile duct (ie choledochal cysts), hepatolithiasis, hepatitis B and C virus, alcoholic liver cirrhosis, and smoking.[13] In East-Asia hepatic parasite infections, in particular *Opisthorchis viverrini* and *Clonorchis sinensis*, are significant risk factors.[15,16] The reasons for the vast difference in incidence between the east and west is not fully understood, as it cannot be attributed completely to the spread of the infectious risk-factors.[1,12]

Histology

ICC mostly develops as a well-differentiated adenocarcinoma.[17,18] Its formation is frequently caused by mutations of the KRAS oncogene, a protein normally involved in the cell proliferation, in combination with the deletion of the p53 tumor suppressor gene.[19] A critical signaling protein downstream of KRAS and p53 mutations is interleukin 6 (IL-6), which is a serum biomarker for ICC.[20-22] Further downstream, ROS1 fusion proteins, regulated by KRAS/IL-6 pathways, have been associated with an aggressive phenotype and metastatic disease at diagnosis.[23,24]

Based on their histological appearance, ICC can be divided into three histological growth types: the mass-forming, intraductal infiltrating, and periductal pattern.[25,26] The most common of these growth patterns is the mass-forming pattern, of which the clinical symptoms may be similar to HCC as both involve the formation of a mass in the liver.[27,28] On imaging (ie computed tomography [CT] and magnetic resonance imaging [MRI]) these tumors are clearly visible and well-delineated.[26] Mass-forming ICC typically has a diameter of 5 to 10 centimeters at the time of diagnosis.[29,30] Intraductal ICC is a slowly growing papillary tumor and has a favorable prognosis compared to the other two types.[26] On imaging it is a 1 to 2 centimeter mass within the bile duct with proximal ductal dilatation. The mass is usually confined to the bile duct wall.[26,31,32] Periductal infiltrating cholangiocarcinoma is characterized by growth along the bile duct without mass formation, which radiologically presents as a small lesion or diffuse bile duct thickening.[33] This type of tumor is a rare form of ICC and is commonly seen in combination with mass-forming ICC.[34,35] The different histological appearances of cholangiocarcinoma necessitate different surgical strategies, since tumors growing along the bile duct (intraductal and periductal ICC) often require extrahepatic bile duct resection in addition to hepatic resection[26,36]

ICC and HCC may occur simultaneously in the same patient or even in the same lesion.[37,38] Combined HCC and ICC tumors mostly follow the more aggressive behavior of ICC.[37] Because of similar allelic losses in both HCC-like and ICC-like cells, these tumors are thought to have a monoclonal origin with bidirectional phenotype differentiation.[38,39] In concordance with this hypothesis, a Korean group recently suggested that the acquisition of ICC characteristics is a leading cause of atypically aggressive HCC behavior.[40] Further research in the fields of imaging and molecular analysis are required to improve early diagnosis.[38]

Staging

The most commonly used classification system to qualify advancement and resectability of ICC is the American Joint Committee on Cancer (AJCC) TNM staging system, currently in its 7th edition, consisting of four stages (Table 1).[41] Prior to this edition there was no separate staging system for ICC and these tumors were classified with HCC.[42] The T-stage is determined by the number of liver tumors, the presence of vascular invasion, and direct extrahepatic invasion. The T4 stage is reserved for tumors with a periductal growth pattern. N1 indicates the presence of regional lymph node metastases, and M1 disease distant metastatic disease.[42] Recent research suggests the AJCC staging system performs poorly in differentiating between various prognoses, with vast inter-patient survival differences within TNM stages.[43,44] Additional independent prognostic factors have been identified to improve staging, including: elevated serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), lympho(neuro)vascular invasion, and serum alkaline phosphatase (ALP).[44]

A genomic biomarker profile can also help in differentiating patients with ICC.[45-47] A genomic study of 149 patients with ICC identified two molecular subgroups, an inflammation and a proliferation group, with distinct clinical outcomes. The inflammation subclass (40%) showed increased activation of inflammation pathways, over-expression of IL-6, IL-10, and IL-17, and constitutive activation of immune system transcription factor STAT3.[47,48] The proliferation subclass (60%) showed increased activation of oncogenic pathways RAS/MAPK and MET, specific DNA mutations and risk factors for poor clinical outcome.[13,48]

In a recent meta-analysis we identified several immunohistochemistry biomarkers for patients with ICC.[45] An example of a diagnostic and prognostic biomarker is fascin, an actin cross-linked protein found in the cell membrane of the biliary duct cells.[49] The epidermal growth factor receptor (EGFR) also plays an important role in prognostics and is a potential treatment target.[50,51] Mucin 1, cell surface associated (MUC1) and Mucin 4, cell surface associated (MUC4) are two membrane proteins that have been shown to be associated with patient prognosis.[52-54] Lastly, p27, Cyclin-dependent kinase inhibitor 1B, is a protein involved in the cell cycle, which also has predictive capabilities in relation to postoperative survival.[55-57] In addition to these biomarkers, several other biomarkers have been shown to have an impact on diagnostics, prognostics, and treatment efficacy; HSP27, Akt, HDGF, MUC6, p16, p-4EBP1, S100A4, alpha-SMA, keratin 903, and TROP2.[45] A composite biomarker profile could improve prognosis and guide treatment selection.[47]

Table 1. AJCC TNM Classification 7th Edition

T - Stage	Definition
Tx	No description of the tumor's extent is possible because of incomplete information
T0	There is no evidence of a primary tumor.
T1	There is a single tumor that has grown into deeper layers of the bile duct wall, but it is still only in the bile duct. The cancer has not grown into any blood vessels.
T2a	There is a single tumor that has grown through the wall of the bile duct and into a blood vessel.
T2b	There are 2 or more tumors, which may (or may not) have grown into blood vessels.
T3	The cancer has grown into nearby structures such as the intestine, stomach, common bile duct, abdominal wall, diaphragm (the thin muscle that separates the chest from the abdomen), or lymph nodes around the portal vein.
T4	The cancer is spreading through the liver by growing along the bile ducts.
N - Stage	**Definition**
Nx	Nearby (regional) lymph nodes cannot be assessed.
N0	The cancer has not spread to nearby lymph nodes.
N1	The cancer has spread to nearby lymph nodes.
M- Stage	
M0	The cancer has not spread to tissues or organs far away from the bile duct.
M1	The cancer has spread to tissues or organs far away from the bile duct.
Stage Grouping	**Definition**
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0
Stage IVa	T4, N0, M0 / Any T, N1, M0
Stage IVb	Any T, any N, M1

Diagnosis and Preoperative Workup

The initial diagnosis of ICC is mostly made when the tumor is not eligible for resection because of locally advanced or metastatic disease.[13,14,58] Typically a very large mass has developed in the periphery of the liver with few clinical symptoms.[19] Most patients present with nonspecific symptoms, such as pain in the right upper abdominal quadrant, weight loss and high serum ALP levels. Some

patients present with painless jaundice, when the tumor grows towards the biliary confluence.[14,58] Small ICCs are found in screening programs for early detection of HCC.[59]

Transabdominal ultrasound is often the first imaging modality that detects a liver mass with or without dilatation of the biliary tract.[60] The number of lesions and vascular involvement are determined using a dual-phase multi-detector-CT (MDCT). Typical appearance of ICC on CT is a hypodense mass with irregular margins on unenhanced scans, peripheral rim enhancement in the arterial contrast-enhancement phase, and progressive contrast uptake in the (portal-) venous and delayed contrast-enhancement phase.[61] Small ICCs can be difficult to distinguish from HCC. Biliary drainage (if needed) should be performed *after* imaging, because the presence of stents and drains hamper accurate assessment of the extent of the tumor.[62]

Both magnetic resonance cholangiopancreatography (MRCP) and positron emission tomography (PET) have a good accuracy for diagnosis and assessment of the extent of the tumor. MRCP has a diagnostic accuracy of up to 93% and is recommended for visualization of the tumor extension in the ductal system and vascular structures.[47,63] Clinical utility of PET for diagnosing ICC in the liver when CT or MRI imaging has been performed is limited.[47] However, preoperative PET scanning may be considered to help rule out occult metastatic disease, as PET changes surgical decision making in up to 30% of patients.[64-66] Despite these imaging modalities, as many as a third of patients with resectable disease on imaging have occult metastatic or locally advanced disease during diagnostic laparoscopy.[67,68] Therefore, better imaging is needed to avoid surgery in these patients.[14,67,68]

Biliary drainage and portal vein embolization

ICC may cause biliary obstruction when the tumor grows towards the liver hilum. Biliary drainage may be required in the preoperative setting with resectable disease and in the palliative setting. Biliary drainage aims to improve liver function and increase appetite.[69] Moreover, preoperative biliary drainage may improve liver regeneration and decrease the risk of postoperative liver failure .[70,71] The main drawback of biliary drainage is colonization of the bile duct that often results in cholangitis.[72] Patients with a future liver remnant of at least 50% should probably undergo a resection without preoperative biliary drainage.[73,74] Drainage can be performed endoscopically (ERCP) or percutaneously (PTCD) Biliary drainage can reduce symptoms and improve quality of life in the palliative setting.[75,76]

A resection of more than 75% of the total liver volume in a healthy liver and more than 65% of the total liver volume in a compromised liver (eg, due to cirrhosis or fibrosis) is an indication for portal vein embolization (PVE).[77] PVE results in hypertrophy of the future liver remnant by preoperatively embolizing the liver that will be resected.[77] In a total of 1,791 patients with different hepatic tumors, PVE had a technical success of 96.1%.[77]

Surgical Management

Resection

Surgical treatment is the only potentially curative treatment in patients with ICC. ICC is an aggressive cancer, when compared to other primary hepatic neoplasms.[4,14,58] A large study (n=584) demonstrated that even after curative-intent resection the probability of cure is only about 10%.[78] Because of the large size as well as intraductal and periductal spread, major hepatectomies are required to obtain negative resection margins.[4] With regards to prognosis, resection is only useful when a complete resection (R0) with negative resection margins is anticipated. Moreover, the liver remnant should be adequate in size and function, with or without prior PVE.[8,77,79,80] Extrahepatic disease, including lymph node metastases beyond the regional basin (N2), are a contra-indication for curative-intent surgery.[41] Multifocal ICC is considered unresectable by some experts.[79-83] Nevertheless, other experts report favorable long-term outcomes in selected patients with typically 2-3 lesions, with a 5-year overall survival (OS) of 20%.[84,85] A 2015 cure model confirms the possibility of cure, albeit at a chance of only 4%.[78] Recent studies have reported favorable outcomes of portal vein reconstructions.[86-88] However, tumor invasion of the main hepatic artery or bilateral hepatic artery involvement remain contra-indications for resection in most Western centers. Hepatic artery reconstruction is associated with a high risk of postoperative mortality as well as poor oncologic outcomes.[89,90]

A complete resection of ICC involves an (extended) hemihepatectomy in most (75%) of patients. Many patients (25%) also require a bile duct resection and reconstruction. Morbidity rates are often more than 1 in 5, and mortality rates vary from 1% to 6%.[8,9,91] Intraoperative and postoperative strategies, such as low central venous pressure, restricted fluid resuscitation, and enhanced recovery pathways, have improved recovery and decreased the risk of complications.[87,88,92] A recent article reviewed perioperative management of patients undergoing hepatic resection.[93] They noted that surgeons left an operative drain in almost

half of patients undergoing liver resection, even though most data suggest that routine operative drainage after liver resection (without a biliary anastomosis) is unnecessary and should generally be avoided.[94-96]

Whereas HCC is commonly treated with orthotopic liver transplantation (OLT), ICC as an indication for OLT is still controversial.[97] Historical evidence suggests poor outcomes for ICC in single center studies.[98-104] Outcomes of OLT for combined HCC and ICC were also predominantly unfavorable.[98,105] Five-year survival estimates in these studies ranged from 10%-18%, which is clearly inferior to the benchmark of OLT of about 70%.[97] More recent studies indicate that strictly selected patients might benefit from OLT, particularly patients with ICC smaller than 2 cm.[106]

Systemic chemotherapy

Preoperative Chemotherapy

Preoperative chemotherapy (pCT) can be administered for multiple purposes, although it is not routinely prescribed due to a lack of evidence.[107] Neoadjuvant therapy is employed to address occult metastatic disease or facilitate resection. We recently evaluated the role of pCT in a cohort of 1,057 patients, of whom 62 patients received chemotherapy. We found that patients receiving pCT had similar survival following curative-intent resection, regardless of more advanced disease.[107] No regimen is currently proven to have effect during the preoperative period. In light of the outcomes of the ABC-02 trial, discussed below, a combination of gemcitabine and cisplatin was offered most often.[108]

Adjuvant Chemotherapy

Adjuvant chemotherapy is aimed at decreasing the chance of tumor recurrence.[109] Chemotherapy consists of mainly nucleoside analogues, most commonly gemcitabine, sometimes in combination with cisplatin.[109] Systemic therapy is known to have a large impact on patient's quality of life, and form a large financial burden. The efficacy of chemotherapy regimens in ICC is usually poor, with only a small subgroup benefitting significantly in both quality of life and length of survival.[16,109] While a significant portion of US patients receive chemotherapy, no randomized trials have been completed.[42] A multicenter phase III trial is currently accruing patients to determine the effectiveness of adjuvant gemcitabine and cisplatin in patients with biliary cancer (Table 2).

Palliative Chemotherapy

A phase III trial, the ABC-02 trial, randomized 410 patients with biliary cancer (ie cholangiocarcinoma and gallbladder cancer) and found an improvement in overall survival of nearly four months with gemcitabine plus cisplatin compared to gemcitabine alone.[108] A combined analysis of the ABC-02 trial and the Japanese BT22 trial, conducted in a comparable setting, found a hazard ratio (HR) of 0.54 (95% confidence interval (CI) 0.36-0.81) for the subgroup of 108 patients with ICC.[110] Gemcitabine plus cisplatin has been the standard palliative regimen for locally advanced or metastatic ICC since. Best supportive care is recommended for patients with a poor performance status or a life expectancy of less than 6 months.[111-114]

Regional Treatments

Regional treatments rely on the dual blood supply of the liver, where the hepatic artery is mostly responsible for the blood supply of tumors, as illustrated by early arterial enhancement on imaging.[115] [116,117] Hepatic arterial infusion (HAI) chemotherapy using a subcutaneous pump has been investigated for patients with ICC at Memorial Sloan Kettering Cancer Center (MSKCC). It involves continuous infusion of floxuridine directly into the hepatic artery. Intra-arterial delivery allows for a 200 fold higher drug delivery to the tumor with little systemic toxicity, because of the 95% first pass effect of floxuridine in the liver.[5] HAI chemotherapy has been studied extensively in common malignancies, such as colorectal liver metastases.[5,118]

In a recent study from MSKCC, HAI with floxuridine was combined with systemic chemotherapy in patients with locally advanced (ie unresectable without extrahepatic disease) ICC (n=104). [119] Outcomes were compared with locally advanced patients receiving systemic chemotherapy alone.[5] Median OS was superior with HAI chemotherapy (30.8 months vs. 18.4 months; $p < 0.001$). Five-year OS was 20% in patients who received HAI chemotherapy compared with 5% in the systemic only group. In comparison, 5-year OS was 0% in the ABC-02 trial.[108] Moreover, the partial response rate (RECIST criteria) in the HAI chemotherapy group was 59%, with conversion to resectability in 8 of 104 patients (13%). Future prospective studies should be conducted in order to confirm these results. Currently, a phase 2 trial is recruiting patients for HAI chemotherapy in the adjuvant setting (NCT01312857).

Table 2. Currently Active Phase III and Phase IV Studies

Title	Collaborators	Country / Region	Interventions
Palliative Setting			
Photodynamic Therapy (PDT) for Palliation of Cholangiocarcinoma	Weill Medical College of Cornell University	United States	Photodynamic Therapy
Effect of Early Management on PAin and DEpression in Patients With PancreatoBiliary Cancer, EPADE-PB	National Cancer Center, Korea	Korea	Early Palliative care integrated with usual oncologic care
Active Symptom Control Alone or With mFOLFOX Chemotherapy for Locally Advanced/ Metastatic Biliary Tract Cancers	The Christie NHS Foundation Trust|Cancer Research UK	United Kingdom	mFOLFOX
Early Palliative Care With Standard Care or Standard Care Alone in Improving Quality of Life of Patients With Incurable Lung or Non-colorectal Gastrointestinal Cancer and Their Family Caregivers	Alliance for Clinical Trials in Oncology|National Cancer Institute (NCI)	United States	Early Palliative Care
RFA RCT for Pancreatic or Bile Duct Cancer	Weill Medical College of Cornell University	United States	Radiofrequency Ablation using EndoHPB Probe vs. Stenting only
Chemo Alone or in Combination With Radiation in Unresectable Cholangiocarcinoma	Tata Memorial Hospital	India	High Dose Radiation and Systemic Chemotherapy
Safety and Efficacy of Modified Folfirinox Versus Gemcis in Bile Duct Tumours	Centre Hospitalier Universitaire de Saint Etienne|Federation Francophone de Cancerologie Digestive	France	Gemcitabine & Cisplatin vs. mFOLFIRINOX
Study of SPARC1507 (Sun Pharma Advanced Research Company Limited Drug)	Sun Pharma Advanced Research Company Limited	India	SPARC1507

# of Patients	Outcome Measures	Recruitment Start	Completion Date	NCT Number
55	Efficacy Profile, Safety Profile	Feb-12	Dec-16	NCT01755013
288	Reduction in Pain Scale, Reduction in Depression Score, Quality of Life, Overall Survival	Apr-12	Jun-17	NCT01589328
162	Overall Survival, Progression Free Survival, Response Rate, Toxicity, Quality of Life, Cost-effectiveness	Feb-14	Jan-18	NCT01926236
700	Reduction in Depression, Ilness Understanding, Quality of Life, Rate of Referral, Lenght of Hospice Stay, Location of Death, ICU Visits, Number of Patients Treated with Chemotherapy, Overall Survival, Perceptions of Cure	Apr-15	-	NCT02349412
44	Clinical Success, Mutational Profile of DNA	Jun-14	Jun-17	NCT02166190
155	Overall Survival, Progression Free Survival, Toxicity, Quality of Life, Surgical Resectability Rates	May-15	Jun-22	NCT02773485
316	Progression Free Survival, Overall Survival, Response Rate, Toxicity	Nov-15	Jun-18	NCT02591030
198	Progression Free Survival, Overall Survival, Response Rate	Apr-16	Nov-19	NCT02597465

Table 2. Currently Active Phase III and Phase IV Studies (*continued*)

Title	Collaborators	Country / Region	Interventions
Early Palliative Care in Patients With Metastatic Upper Gastrointestinal Cancers Treated With First-line Chemotherapy	Centre Oscar Lambret|Canceropôle Nord Ouest	France	Early Palliative Care
Adjuvant Setting			
Adjuvant Chemotherapy With Gemcitabine and Cisplatin Compared to Observation After Curative Intent Resection of Biliary Tract Cancer, ACTICCA	Universitätsklinikum Hamburg-Eppendorf|Deutsche Krebshilfe e.V., Bonn (Germany)|medac GmbH|Cancer Research UK|AGITG Australasian Gastro Intestinal Trials Group|KWF Kanker Bestrijding The Netherlands	Europe and Oceania	Gemcitabine & Cisplatin
Oxaliplatin+Gemcitabine vs Capecitabine as Adjuvant Therapy for Intrahepatic Cholangiocarcinoma	Shanghai Zhongshan Hospital	China	Gemcitabine & Cisplatin

Abbreviations: FOLFOX, chemotherapy regimen consisting of folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of folonic acid (leucovorin), 5-fluorouracil (5-FU), irinotecan, and oxaliplatin.

# of Patients	Outcome Measures	Recruitment Start	Completion Date	NCT Number
558	Overall Survival, Quality of Life, Reduction in Depression Score, Time Until Definitive Deterioration, Advanced Directives, Number of Patients Treated with Chemotherapy	Aug-16	Aug-20	NCT02853474
440	Disease Free Survival, Overall Survival, Toxicity, Quality of Life, Function Biliodigestive Anastomosis, Infections.	Apr-14	Apr-22	NCT02170090
286	Recurrence Free Survival, Overall Survival	Jul-15	Dec-18	NCT02548195

Other hepatic artery–based treatments for locally advanced ICC include transarterial chemoembolization (TACE) and radio-embolization with Yttrium-90 (Y-90).[115] TACE affects the blood flow to the tumor in addition to locally releasing cytotoxic agents. It causes ischemic tumor necrosis and facilitates intracellular transit of chemotherapeutic agents.[115,117] In a study of 41 prospectively followed patients, one group described a median OS of 11.7 months from first treatment, after treatment with irinotecan TACE.[120] One patient successfully underwent resection following TACE.[120] Another prospective study reported a median survival of 17.5 months in 24 patients, with 3 patients being adequately down staged to undergo resection.[121] Despite the encouraging results no phase III trial has been performed.[115]

Y-90 radio-embolization therapy also aims to improve life expectancy in patients with unresectable HCC and colorectal liver metastases.[115] The technique is based on administration of beads filled with the radioactive isotope yttrium Y-90 microspheres into the hepatic artery branch responsible for the lobes of the liver beset by tumor.[122,123] Prior to treatment, embolization of the non-target vessels and injection of Technetium-99mm-labeled macro-aggregated albumin is performed, in order to exclude extrahepatic accumulation.[115,122,123] Several small studies indicate that Y-90 is tolerated well in patients with a good performance status.[124-129] In intrahepatic cholangiocarcinoma patients, Y-90 was associated with improved survival, when compared with patients undergoing best supportive care only.[124-129] Estimates ranged from 9 months post-treatment in a cohort of 25 Australian patients,[128] to 22 months in a cohort of 33 German patients.[127] Randomized trials are required to determine the effectiveness of Y-90 therapy.

Prognostic Models and Nomograms

Several prognostic models have been developed in addition to the AJCC staging. More accurate prediction of individual patient outcome may provide better individual survival estimates, as well as improve identification of high-risk groups who may benefit from adjuvant therapy.[11] While the AJCC staging concerns all ICC patients, other models pertain only to patients who have undergone a complete resection. A Chinese nomogram predicts individual OS after resection of ICC (Figure 3).[43] Prognostic factors in this model included CEA, CA19-9, vascular invasion, presence of lymph node metastases, direct invasion and local metastases, number of tumors, and tumor diameter. A similar model was developed with a multinational dataset without tumor markers. Risk factors for survival after resection were; age, number of tumors, tumor diameter, cirrhosis, lymph node

metastases, and macrovascular invasion.[130] The Chinese nomogram had superior discrimination at external validation.[43,44]

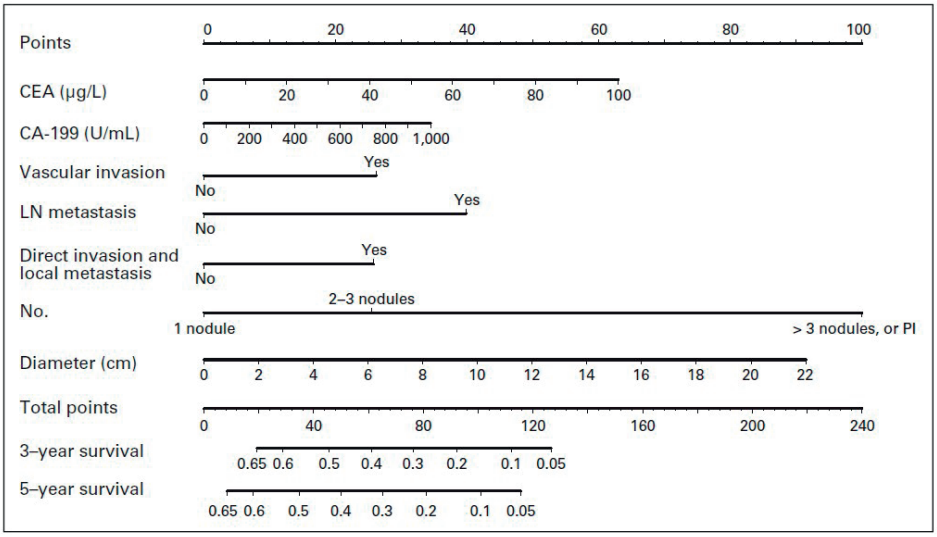

Figure 3. Validated ICC nomogram predicting overall survival (From Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31(9):1188-1195.)

Other prognostic models were developed for conditional survival, accounting for the years that a patient had already survived after surgery.[84,131,132] Conditional survival was found to be the most important prognostic factor, when predicting future survival time.[84,131,132] Overall survival in this study decreased over time to 16% at 8 years, while the three-year conditional survival at 5 years, ie the chance of surviving to year 8 after having survived to year 5, was 65%.[84]

Personalized Treatments

Personalized treatments for ICC patients could improve the overall outcomes, mainly by withholding treatments from patients who are unlikely to benefit from surgery or chemotherapy. For example, patients with a very poor predicted survival after surgery (eg, 3-year OS below 5% based on the Chinese nomogram in Figure 3) are unlikely to benefit from surgery. Unfortunately, predictive biomarkers for response to systemic chemotherapy are not available.[45] Future studies should further improve prognostic models and identify predictive biomarkers to determine the response to chemotherapy.[44,133]

Future Perspectives

ICC is a complex disease, with a dismal prognosis. ICC is typically diagnosed with metastatic or locally advanced disease. Surgery may improve both survival and quality of life, but comes with a substantial risk postoperative morbidity and mortality. The benefit of palliative systemic treatment is real but small. The merits of (neo)adjuvant therapy still need to be explored in phase 3 trials. Targeted therapies (e.g., targeting IDH 1 or 2 mutations) are promising but require further evaluation.[134] Hepatic arterial infusion, TACE, and radio-embolization are promising locoregional techniques. Appropriate allocation of all locoregional and systemic treatments may further improve with better knowledge of histopathology and biological behavior.

Ideally, low-cost diagnostic biomarkers could reliably detect ICC in patients presenting with vague symptoms of the upper abdomen or screened for liver cancer. Furthermore, predictive biomarkers are required to determine in advance , which patients will benefit from chemotherapy.

References

1. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma--focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010; **11**(5): 1159-66.
2. Singal AK, Vauthey JN, Grady JJ, Stroehlein JR. Intra-hepatic cholangiocarcinoma--frequency and demographic patterns: thirty-year data from the M.D. Anderson Cancer Center. *J Cancer Res Clin Oncol* 2011; **137**(7): 1071-8.
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009; **136**(4): 1134-44.
4. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**(5): 755-62.
5. Konstantinidis IT, Koerkamp BG, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2015.
6. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer* 2016.
7. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery* 2002; **132**(4): 555-63; discission 63-4.
8. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 2008; **248**(1): 84-96.
9. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011; **29**(23): 3140-5.
10. Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol* 2014; **110**(2): 163-70.
11. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011; **54**(1): 173-84.
12. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)* 2008; **10**(2): 77-82.
13. Brito AF, Abrantes AM, Encarnacao JC, Tralhao JG, Botelho MF. Cholangiocarcinoma: from molecular biology to treatment. *Med Oncol* 2015; **32**(11): 245.
14. Dodson RM, Weiss MJ, Cosgrove D, et al. Intrahepatic cholangiocarcinoma: management options and emerging therapies. *J Am Coll Surg* 2013; **217**(4): 736-50 e4.
15. Casper FW, Seufert RJ. Atrial natriuretic peptide (ANP) in preeclampsia-like syndrome in a rat model. *Exp Clin Endocrinol Diabetes* 1995; **103**(5): 292-6.
16. Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004; **9**(1): 43-57.
17. Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. *Oncology* 2004; **66**(3): 167-79.

18. Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. *World J Hepatol* 2010; **2**(12): 419-27.

19. O'Dell MR, Huang JL, Whitney-Miller CL, et al. Kras(G12D) and p53 mutation cause primary intrahepatic cholangiocarcinoma. *Cancer Res* 2012; **72**(6): 1557-67.

20. Fava G, Lorenzini I. Molecular pathogenesis of cholangiocarcinoma. *Int J Hepatol* 2012; **2012**: 630543.

21. Johnson C, Han Y, Hughart N, McCarra J, Alpini G, Meng F. Interleukin-6 and its receptor, key players in hepatobiliary inflammation and cancer. *Transl Gastrointest Cancer* 2012; **1**(1): 58-70.

22. Goydos JS, Brumfield AM, Frezza E, Booth A, Lotze MT, Carty SE. Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. *Ann Surg* 1998; **227**(3): 398-404.

23. Lee KH, Lee KB, Kim TY, et al. Clinical and pathological significance of ROS1 expression in intrahepatic cholangiocarcinoma. *BMC Cancer* 2015; **15**: 721.

24. Deng G, Hu C, Zhu L, et al. Downregulation of ROS-FIG inhibits cell proliferation, colonyformation, cell cycle progression, migration and invasion, while inducing apoptosis in intrahepatic cholangiocarcinoma cells. *Int J Mol Med* 2014; **34**(3): 661-8.

25. Lazaridis KN, Gores GJ. Cholangiocarcinoma. *Gastroenterology* 2005; **128**(6): 1655-67.

26. Chung YE, Kim MJ, Park YN, et al. Varying appearances of cholangiocarcinoma: radiologic-pathologic correlation. *Radiographics* 2009; **29**(3): 683-700.

27. Yusuhn K, Jeong Min L, Seung Ho K, Joon Koo H, Byung Ihn C. Intrahepatic Mass-forming Cholangiocarcinoma: Enhancement Patterns on Gadoxetic Acid–enhanced MR Images. *Radiology* 2012; **264**(3): 751-60.

28. Okabayashi T, Yamamoto J, Kosuge T, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. *Cancer* 2001; **92**(9): 2374-83.

29. Kim SJ, Lee JM, Han JK, Kim KH, Lee JY, Choi BI. Peripheral mass-forming cholangiocarcinoma in cirrhotic liver. *AJR Am J Roentgenol* 2007; **189**(6): 1428-34.

30. Mamone G, Marrone G, Caruso S, et al. Intrahepatic mass-forming cholangiocarcinoma: enhancement pattern on Gd-BOPTA-MRI with emphasis of hepatobiliary phase. *Abdominal Imaging* 2015; **40**(7): 2313-22.

31. Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR Am J Roentgenol* 2003; **181**(3): 819-27.

32. Lim JH, Yi CA, Lim HK, Lee WJ, Lee SJ, Kim SH. Radiological spectrum of intraductal papillary tumors of the bile ducts. *Korean J Radiol* 2002; **3**(1): 57-63.

33. Mittelstaedt CA. Ultrasound of the bile ducts. *Semin Roentgenol* 1997; **32**(3): 161-71.

34. Park HS, Lee JM, Kim SH, et al. CT Differentiation of cholangiocarcinoma from periductal fibrosis in patients with hepatolithiasis. *AJR Am J Roentgenol* 2006; **187**(2): 445-53.

35. Lim JH, Park CK. Pathology of cholangiocarcinoma. *Abdom Imaging* 2004; **29**(5): 540-7.

36. Sasaki A, Aramaki M, Kawano K, et al. Intrahepatic peripheral cholangiocarcinoma: mode of spread and choice of surgical treatment. *Br J Surg* 1998; **85**(9): 1206-9.

37. Jarnagin WR, Weber S, Tickoo SK, et al. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. *Cancer* 2002; **94**(7): 2040-6.

38. Maximin S, Ganeshan DM, Shanbhogue AK, et al. Current update on combined hepatocellular-cholangiocarcinoma. *Eur J Radiol Open* 2014; **1**: 40-8.

39. Wu PC, Fang JW, Lau VK, Lai CL, Lo CK, Lau JY. Classification of hepatocellular carcinoma according to hepatocellular and biliary differentiation markers. Clinical and biological implications. *Am J Pathol* 1996; **149**(4): 1167-75.

40. Woo HG, Lee JH, Yoon JH, et al. Identification of a cholangiocarcinoma-like gene expression trait in hepatocellular carcinoma. *Cancer Res* 2010; **70**(8): 3034-41.

41. Edge S., Byrd D.R., Compton C.C., Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual 7th Edition.; 2010.

42. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; **17**(8): 669-80.

43. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 2013; **31**(9): 1188-95.

44. Doussot A, Groot-Koerkamp B, Wiggers JK, et al. Outcomes after Resection of Intrahepatic Cholangiocarcinoma: External Validation and Comparison of Prognostic Models. *J Am Coll Surg* 2015; **221**(2): 452-61.

45. Ruys AT, Groot Koerkamp B, Wiggers JK, Klumpen HJ, ten Kate FJ, van Gulik TM. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21**(2): 487-500.

46. Wiggers JK, Ruys AT, Groot Koerkamp B, Beuers U, ten Kate FJ, van Gulik TM. Differences in immunohistochemical biomarkers between intra- and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; **29**(8): 1582-94.

47. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; **60**(6): 1268-89.

48. Sia D, Hoshida Y, Villanueva A, et al. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. *Gastroenterology* 2013; **144**(4): 829-40.

49. Iguchi T, Aishima S, Taketomi A, et al. Fascin overexpression is involved in carcinogenesis and prognosis of human intrahepatic cholangiocarcinoma: immunohistochemical and molecular analysis. *Hum Pathol* 2009; **40**(2): 174-80.

50. Shafizadeh N, Grenert JP, Sahai V, Kakar S. Epidermal growth factor receptor and HER-2/neu status by immunohistochemistry and fluorescence in situ hybridization in adenocarcinomas of the biliary tree and gallbladder. *Hum Pathol* 2010; **41**(4): 485-92.

51. Herberger B, Berger W, Puhalla H, et al. Simultaneous blockade of the epidermal growth factor receptor/mammalian target of rapamycin pathway by epidermal growth factor receptor inhibitors and rapamycin

results in reduced cell growth and survival in biliary tract cancer cells. *Mol Cancer Ther* 2009; **8**(6): 1547-56.

52. Higashi M, Yamada N, Yokoyama S, et al. Pathobiological implications of MUC16/CA125 expression in intrahepatic cholangiocarcinoma-mass forming type. *Pathobiology* 2012; **79**(2): 101-6.

53. Park SY, Roh SJ, Kim YN, et al. Expression of MUC1, MUC2, MUC5AC and MUC6 in cholangiocarcinoma: prognostic impact. *Oncol Rep* 2009; **22**(3): 649-57.

54. Yeh CN, Pang ST, Wu RC, Chen TW, Jan YY, Chen MF. Prognostic value of MUC4 for mass-forming intrahepatic cholangiocarcinoma after hepatectomy. *Oncol Rep* 2009; **21**(1): 49-56.

55. Hashimoto N, Yachida S, Okano K, et al. Immunohistochemically detected expression of p27(Kip1) and Skp2 predicts survival in patients with intrahepatic cholangiocarcinomas. *Ann Surg Oncol* 2009; **16**(2): 395-403.

56. Jarnagin WR, Klimstra DS, Hezel M, et al. Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. *J Clin Oncol* 2006; **24**(7): 1152-60.

57. Fiorentino M, Altimari A, D'Errico A, et al. Low p27 expression is an independent predictor of survival for patients with either hilar or peripheral intrahepatic cholangiocarcinoma. *Clin Cancer Res* 2001; **7**(12): 3994-9.

58. Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; **383**(9935): 2168-79.

59. Brown KM, Parmar AD, Geller DA. Intrahepatic cholangiocarcinoma. *Surg Oncol Clin N Am* 2014; **23**(2): 231-46.

60. Yamasaki M, Miyata H, Miyazaki Y, et al. Evaluation of the nodal status in the 7th edition of the UICC-TNM classification for esophageal squamous cell carcinoma: Proposed modifications for improved survival stratification - Impact of lymph node metastases on overall survival after esophagectomy. *Ann Surg Oncol* 2014; **21**(9): 2850-6.

61. Valls C, Guma A, Puig I, et al. Intrahepatic peripheral cholangiocarcinoma: CT evaluation. *Abdom Imaging* 2000; **25**(5): 490-6.

62. Weber A, Schmid RM, Prinz C. Diagnostic approaches for cholangiocarcinoma. *World J Gastroenterol* 2008; **14**(26): 4131-6.

63. Suthar M, Purohit S, Bhargav V, Goyal P. Role of MRCP in Differentiation of Benign and Malignant Causes of Biliary Obstruction. *J Clin Diagn Res* 2015; **9**(11): TC08-12.

64. Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. *J Gastrointest Surg* 2004; **8**(1): 90-7.

65. Kim YJ, Yun M, Lee WJ, Kim KS, Lee JD. Usefulness of 18F-FDG PET in intrahepatic cholangiocarcinoma. *Eur J Nucl Med Mol Imaging* 2003; **30**(11): 1467-72.

66. Corvera CU, Blumgart LH, Akhurst T, et al. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. *J Am Coll Surg* 2008; **206**(1): 57-65.

67. Weber SM, Jarnagin WR, Klimstra D, DeMatteo RP, Fong Y, Blumgart LH. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. *J Am Coll Surg* 2001; **193**(4): 384-91.

68. Goere D, Wagholikar GD, Pessaux P, et al. Utility of staging laparoscopy in subsets of biliary cancers : laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 2006; **20**(5): 721-5.

69. van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. *J Gastrointest Surg* 2009; **13**(4): 814-20.

70. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). *HPB (Oxford)* 2008; **10**(2): 130-3.

71. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. *Ann Surg* 2003; **238**(1): 84-92.

72. Iacono C, Ruzzenente A, Campagnaro T, Bortolasi L, Valdegamberi A, Guglielmi A. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg* 2013; **257**(2): 191-204.

73. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. *J Am Coll Surg* 2016; **223**(2): 321-31 e1.

74. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013; **100**(2): 274-83.

75. van Delden OM, Lameris JS. Percutaneous drainage and stenting for palliation of malignant bile duct obstruction. *Eur Radiol* 2008; **18**(3): 448-56.

76. Gamanagatti S, Singh T, Sharma R, Srivastava DN, Dash NR, Garg PK. Unilobar Versus Bilobar Biliary Drainage: Effect on Quality of Life and Bilirubin Level Reduction. *Indian J Palliat Care* 2016; **22**(1): 50-62.

77. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol* 2013; **36**(1): 25-34.

78. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer* 2015; **121**(22): 3998-4006.

79. Ribero D, Pinna AD, Guglielmi A, et al. Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis of 434 Patients. *Arch Surg* 2012; **147**(12): 1107-13.

80. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 2013; **153**(6): 811-8.

81. Luo X, Yuan L, Wang Y, Ge R, Sun Y, Wei G. Survival outcomes and prognostic factors of surgical therapy for all potentially resectable intrahepatic cholangiocarcinoma: a large single-center cohort study. *J Gastrointest Surg* 2014; **18**(3): 562-72.

82. Sulpice L, Rayar M, Boucher E, Pracht M, Meunier B, Boudjema K. Treatment of recurrent intrahepatic cholangiocarcinoma. *Br J Surg* 2012; **99**(12): 1711-7.

83. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg* 2011; **254**(5): 824-29; discussion 30.

84. Spolverato G, Kim Y, Ejaz A, et al. Conditional probability of long-term survival after liver resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 535 patients. *JAMA Surg* 2015; **150**(6): 538-45.

85. Spolverato G, Kim Y, Alexandrescu S, et al. Is Hepatic Resection for Large or Multifocal Intrahepatic Cholangiocarcinoma Justified? Results from a Multi-Institutional Collaboration. *Ann Surg Oncol* 2015; **22**(7): 2218-25.

86. Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in Hospital Volume and Failure to Rescue for Pancreatic Surgery. *J Gastrointest Surg* 2015; **19**(9): 1581-92.

87. Gurusamy KS, Li J, Vaughan J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database Syst Rev* 2012; **5**: CD007338.

88. Kim Y, Ejaz A, Gani F, et al. Crystalloid administration among patients undergoing liver surgery: Defining patient- and provider-level variation. *Surgery* 2016; **159**(2): 389-98.

89. Hartog H, Ijzermans JN, van Gulik TM, Groot Koerkamp B. Resection of Perihilar Cholangiocarcinoma. *Surg Clin North Am* 2016; **96**(2): 247-67.

90. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)* 2013; **15**(7): 492-503.

91. Giuliante F, Gauzolino R, Vellone M, Ardito F, Murazio M, Nuzzo G. Liver resection for intrahepatic cholangiocarcinoma. *Tumori* 2005; **91**(6): 487-92.

92. Gurusamy KS, Li J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database Syst Rev* 2009; (4): CD007338.

93. Spolverato G, Ejaz A, Kim Y, et al. Patterns of care among patients undergoing hepatic resection: a query of the National Surgical Quality Improvement Program-targeted hepatectomy database. *J Surg Res* 2015; **196**(2): 221-8.

94. Fong Y, Brennan MF, Brown K, Heffernan N, Blumgart LH. Drainage is unnecessary after elective liver resection. *Am J Surg* 1996; **171**(1): 158-62.

95. Butte JM, Grendar J, Bathe O, et al. The role of peri-hepatic drain placement in liver surgery: a prospective analysis. *HPB (Oxford)* 2014; **16**(10): 936-42.

96. Brooke-Smith M, Figueras J, Ullah S, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. *HPB (Oxford)* 2015; **17**(1): 46-51.

97. Sapisochin G, Fernandez de Sevilla E, Echeverri J, Charco R. Liver transplantation for cholangiocarcinoma: Current status and new insights. *World J Hepatol* 2015; **7**(22): 2396-403.

98. DeOliveira ML. Liver transplantation for cholangiocarcinoma: current best practice. *Curr Opin Organ Transplant* 2014; **19**(3): 245-52.

99. Robles R, Figueras J, Turrion VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004; **239**(2): 265-71.

100. Casavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma. *J Am Coll Surg* 1997; **185**(5): 429-36.

101. Jan YY, Yeh CN, Yeh TS, Chen TC. Prognostic analysis of surgical treatment of peripheral cholangiocarcinoma: two decades of experience at Chang Gung Memorial Hospital. *World J Gastroenterol* 2005; **11**(12): 1779-84.

102. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; **69**(8): 1633-7.

103. Ghali P, Marotta PJ, Yoshida EM, et al. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. *Liver Transpl* 2005; **11**(11): 1412-6.

104. Weimann A, Varnholt H, Schlitt HJ, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. *Br J Surg* 2000; **87**(9): 1182-7.

105. Groeschl RT, Pappas SG, Christians KK, et al. Are we justified in excluding combined hepatocellular-cholangiocarcinoma from transplantation? *J Clin Oncol* 2012; **30**(4_suppl): 256.

106. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013; **145**(6): 1215-29.

107. Buettner S, Groot Koerkamp B, Ejaz A, et al. The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients—A multi-institutional analysis. *J Surg Oncol* 2016; **In Press**.

108. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**(14): 1273-81.

109. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012; **30**(16): 1934-40.

110. Valle JW, Furuse J, Jitlal M, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; **25**(2): 391-8.

111. Goenka MK, Goenka U. Palliation: Hilar cholangiocarcinoma. *World J Hepatol* 2014; **6**(8): 559-69.

112. Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. *Liver Transpl* 2000; **6**(3): 302-8.

113. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**(8938): 1655-60.

114. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**(8): 1132-5.

115. Seidensticker R, Ricke J, Seidensticker M. Integration of chemoembolization and radioembolization into multimodal treatment of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 2015; **29**(2): 319-32.

116. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; **30**(5): 969-77.

117. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**(9319): 1734-9.

118. McAuliffe JC, Qadan M, D'Angelica MI. Hepatic resection, hepatic arterial infusion pump therapy, and genetic biomarkers in the management of hepatic metastases from colorectal cancer. *J Gastrointest Oncol* 2015; **6**(6): 699-708.

119. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2016; **122**(5): 758-65.

120. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol* 2012; **24**(4): 437-43.

121. Schiffman SC, Metzger T, Dubel G, et al. Precision hepatic arterial irinotecan therapy in the treatment of unresectable intrahepatic cholangiocellular carcinoma: optimal tolerance and prolonged overall survival. *Ann Surg Oncol* 2011; **18**(2): 431-8.

122. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012; **35**(5): 1066-73.

123. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**(3): 868-78.

124. Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. *J Vasc Interv Radiol* 2014; **25**(2): 256-65.

125. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol* 2013; **24**(8): 1227-34.

126. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol* 2013; **36**(2): 440-8.

127. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol* 2012; **35**(1): 105-16.

128. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol* 2010; **17**(2): 484-91.

129. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer* 2008; **113**(8): 2119-28.

130. Hyder O, Marques H, Pulitano C, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014; **149**(5): 432-8.

131. Kim Y, Ejaz A, Spolverato G, et al. Conditional survival after surgical resection of gastric cancer: a multi-institutional analysis of the us gastric cancer collaborative. *Ann Surg Oncol* 2015; **22**(2): 557-64.

132. Nathan H, de Jong MC, Pulitano C, et al. Conditional Survival after Surgical Resection of Colorectal Liver Metastasis: An International Multi-Institutional Analysis of 949 Patients. *J Am Coll Surg* 2010; **210**(5): 755-64.

133. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. *J Surg Oncol* 2014; **110**(5): 585-91.

134. Merla A, Liu KG, Rajdev L. Targeted Therapy in Biliary Tract Cancers. *Curr Treat Options Oncol* 2015; **16**(10): 48.

CHAPTER 12

The Effect of Preoperative Chemotherapy Treatment in Surgically Treated Intrahepatic Cholangiocarcinoma Patients - A Multi-Institutional Analysis

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Abstract

Introduction: While preoperative chemotherapy (pCT) is utilized in many intra-abdominal cancers, the use of pCT among patients with intrahepatic cholangiocarcinoma (ICC) remains ill defined. As such, the objective of the current study was to examine the impact of pCT among patients undergoing curative-intent resection for ICC.

Methods: Patients who underwent hepatectomy for ICC were identified from a multi-institutional international cohort. The association between pCT with peri-operative and long-term clinical outcomes was assessed.

Results: Of the 1,057 patients who were identified and met the inclusion criteria, 62 patients (5.9%) received pCT. These patients were noticed to have more advanced disease. Median OS (pCT:46.9 months vs. no pCT:37.4 months; p=0.900) and DFS (pCT: 34.1 months vs. no pCT: 29.1 months; p=0.909) were similar between the two groups. In a subgroup analysis of propensity-score matched patients, there was longer OS (pCT:46.9 months vs. no pCT:29.4 months) and DFS (pCT:34.1 months vs. no pCT:14.0 months), however this did not reach statistical significance (both p>0.05).

Conclusion: In conclusion, pCT utilization among patients with ICC is higher among patients with more advanced disease. Short-term post-operative outcomes were not affected by pCT use and receipt of pCT resulted in equivalent OS and DFS following curative-intent resection.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, accounting for 3% of all cases of gastro-intestinal cancer.[1,2] ICC makes up about 5% to 10% of all cholangiocarcinomas and originates from bile ducts within the liver parenchyma.[2,3] Histologically, the majority of advanced ICC tumors are adenocarcinoma, which are typically treated with a combination of cytotoxic nucleoside analogs and platins.[4,5] When feasible, complete surgical resection of ICC remains the only possible option for cure with an estimated median survival ranging from 27 to 36 months.[6-9] However, only a minority of patients with ICC present with surgically resectable disease at the time of diagnosis. Even with complete surgical resection, recurrence can be as high as 50% within 24 months of surgical resection.[10] In addition, nearly 1 in 5 patients undergoing curative-intent resection are left with microscopic disease following surgery.[11] As such, there has been interest in using preoperative chemotherapy (pCT) to improve patient selection, increase the incidence of margin negative surgical resection and potentially improve disease-free (DFS) and overall survival (OS).

Preoperative chemotherapy is utilized in many intra-abdominal cancers to reduce local disease burden and the incidence of micrometastatic disease prior to surgical resection. In patients with perihilar cholangiocarcinoma (PHC), recent trials have shown that pCT may be effective in increasing DFS.[12] Furthermore, in patients with PHC, pCT can down-size locally advanced tumors in order to help facilitate surgical resection.[12] Despite this, the use of pCT among patients with ICC has not been well-studied.[5,12] As such, the objective of the current study was to determine the impact of pCT on OS and DFS in a large, multi-institutional international cohort of patients who underwent curative-intent resection for ICC. Furthermore, we sought to characterize current practice patterns regarding the use of pCT among patients undergoing curative-intent resection for ICC.

Methods

All patients undergoing curative-intent resection for ICC between January 1, 1990, and July 1, 2016 at one of 12 participating major hepatobiliary institutions in the United States, Asia, Oceania and Europe were identified (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia; Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal;

Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Ottowa General Hospital, Ottowa, Canada; Royal Prince Alfred Hospital, Sydney, Australia; San Raffaele Hospital, Milan, Italy; Erasmus University Medical Centre Rotterdam, Rotterdam, the Netherlands). Sociodemographic and clinicopathologic data were collected and include age, sex and race, tumor size, AJCC stage, histologic grade, presence of nodal metastases, final resection margin and the presence of vascular and/or perineural invasion.

A minor hepatectomy was defined as a hepatic resection of less than 3 Couinaud segments. Suspected lymph node metastases on preoperative scans were considered suspicious preoperative lymph nodes, while only pathologically proven metastases were considered proven metastases. Patients with suspected lymph nodes preoperatively, and confirmed lymph node metastases during pathological examination of the resection specimen, were considered to have lymph node disease preoperatively and postoperatively, respectively. Patients with suspected lymph node disease preoperatively, but no evidence in the resection specimen, were considered to only have lymph node metastases preoperatively.

The American Joint Committee on Cancer (AJCC) 7th edition staging was used to stratify patients by extent of disease.[13] Margin status was categorized as R0 for a negative margin, R1 when the margin was microscopically positive and R2 when the margin was macroscopically positive. Only patients undergoing a curative intent surgery for histologically confirmed ICC were included in the final study population; patients who did not undergo resection were excluded. Patients who underwent transplantation were also excluded. The respective institutional review boards of each participating institution approved this study.

Statistical analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. Percentages for each variable were calculated based on available data, excluding missing values. Univariable comparison of categorical variables was performed using the Pearson chi-square test. Univariable comparison of continuous variables was performed using the Mann-Whitney U-test. The primary outcome of the study was 5-year OS. OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up; OS was estimated using the Kaplan-Meier method. DFS was calculated from the date of surgery to the date of first-known radiographically or pathologically confirmed metastasis. Logistic regression analysis was conducted in order to determine factors associated with

receipt of pCT in a multivariable model. Based on this regression model, a propensity score was calculated to determine the likelihood of receiving pCT. Patients were matched based on this propensity score and OS was compared between the groups. All analyses were performed using SPSS 22.0 (IBM, New York). All tests were 2-sided and $p<0.05$ defined statistical significance.

Results

Clinical and pathologic description of patient cohort receiving pCT

1,057 patients who underwent curative-intent resection for ICC and met the inclusion criteria were identified; 62 patients (5.9%) received pCT (Table 1). Among the patients who received pCT, 18 (29.0%) patients were treated with intra-arterial chemotherapy, while the remaining 44 patients (71.0%) were treated with systemic chemotherapy. Median patient age among patients who received pCT was 60 years (IQR 52, 69) and the majority of the patients were male (n=37, 59.7%). Most patients had an ASA classification of II or III (n=51, 92.7%).

Based on preoperative imaging and/or biopsy, over one-third of patients had suspected or proven lymph node metastases (n=21, 39.6%). We observed that patients who received systemic chemotherapy more frequently had suspected or confirmed lymph node metastases (n=17, 44.7%), compared to patients who received intra-arterial chemotherapy (n=4, 26.7%). However this difference did not reach statistical significance (p=0.226). At the time of surgery, approximately one-half of patients underwent a major hepatectomy involving more than 3 Couinaud segments (n=29, 52.7%). The majority of patients underwent a formal portal lymphadenectomy (n=39, 70.9%), with a median of 3 lymph nodes (IQR: 1, 6) examined. On final pathology, the majority of patients had an R0 resection (n=42, 73.7%). Lymph node metastasis was noted in 24.2% of patients (n=15). Twelve patients (25.5%) who had lymph node metastases on the preoperative work-up did not have lymph node metastasis on final pathology.

Receipt of preoperative chemotherapy

The majority of patients who received pCT (n=50) were treated within the past 10 years, however the rate of pCT remained stable over the study period (p=0.632). Several clinicopathologic features were associated with receipt of pCT (Table 2). Preoperatively, patients with suspected or biopsy-proven lymph nodes more likely received pCT (39.6% vs. 18.5%, $p<0.001$). Patients who received pCT were also more likely to have advanced disease compared with patients who did not receive

Table 1. Characteristics of the Preoperative Chemotherapy Group (n=62)

Variable	n (%) / median (IQR)
Gender	
Male	37 (59.7)
Female	25 (40.3)
Age, years	60 (52-69)
Race	
Caucasian	49 (79.0)
African-American	8 (12.9)
Other	5 (8.0)
ASA	
I	3 (5.5)
II	24 (43.6)
III	27 (49.1)
IV	1 (1.8)
BMI	25.8 (23.5-29.0)
Period of Treatment	
1990-2000	3 (5.3)
2001-2005	4 (7.0)
2006-2010	20 (35.1)
2011-2016	30 (52.6)
Preoperative Chemotherapy Type	
Intra-Arterial Therapy	18 (29.0)
Systemic Therapy	44 (71.0)
Preoperative Lymph Node Metastases	
No	32 (60.4)
Suspicious	12 (22.6)
Proven	9 (17.0)
Type of Resection	
Minor Hepatectomy (<3 segments)	6 (10.9)
Right Hepatectomy	9 (16.4)
Left Hepatectomy	8 (14.5)
Extended Right Hepatectomy	18 (32.7)
Extended Left Hepatectomy	11 (20.0)
Central Hepatectomy	3 (5.5)
Lymphadenectomy	39 (70.9)
Lymph Nodes Harvested	3 (1-6)
Lymph Node Metastases	15 (24.2)
Extrahepatic Metastases	8 (12.9)
Margin Status	
R0	42 (73.7)
R1	14 (24.6)
R2	1 (1.8)

Table 2. Comparison of Disease Characteristics Across Treatment Groups

Variable	No Preoperative Chemotherapy (n=995)	Preoperative Chemotherapy (n=62)	*P-value*
Preoperative Lymph Node Metastases			< 0.001
No	699 (81.2)	32 (60.4)	
Suspicious	121 (14.1)	12 (22.6)	
Proven	38 (4.4)	9 (17.0)	
Type of Resection			< 0.001
Minor Hepatectomy (<3 segments)	413 (42.6)	6 (10.9)	
Right Hepatectomy	158 (16.3)	9 (16.4)	
Left Hepatectomy	185 (19.1)	8 (14.5)	
Extended Right Hepatectomy	110 (11.4)	18 (32.7)	
Extended Left Hepatectomy	85 (8.8)	11 (20.0)	
Central Hepatectomy	18 (1.9)	3 (5.5)	
Number of tumors	1 (1-1)	1 (1-1)	0.207
Tumor size (cm)	6.0 (4.2-8.8)	7.1 (5.0-10.2)	0.069
Major vascular Invasion	95 (9.8)	5 (8.9)	0.832
Microvascular Invasion	232 (24.4)	25 (48.1)	< 0.001
Perineural invasion	137 (15.6)	15 (30.6)	0.006
Invasion of Adjacent Organs	72 (7.4)	5 (8.9)	0.676
Satellite Lesions	216 (22.2)	17 (29.8)	0.181
Intrahepatic metastases	69 (7.1)	6 (10.7)	0.308
Lymphadenectomy	424 (43.7)	39 (70.9)	< 0.001
Lymph Nodes Harvested	2 (0-5)	3 (1-6)	0.074
Lymph Node Metastases	169 (17.0)	15 (24.2)	0.146
Extrahepatic Metastases	32 (3.2)	8 (12.9)	< 0.001
Margin Status			0.010
R0	840 (87.1)	42 (73.7)	
R1	120 (12.4)	14 (24.6)	
R2	4 (0.4)	1 (1.8)	
AJCC Stage			< 0.001
I	282 (48.0)	7 (24.1)	
II	160 (27.2)	6 (20.7)	
III	22 (3.7)	6 (20.7)	
IVA	112 (19.0)	8 (27.6)	
IVB	12 (2.0)	2 (6.9)	

pCT. Specifically, patients with microvascular invasion (pCT: n=25, 48.1% vs. no pCT: n=232, 24.4%; p<0.001) and perineural invasion (pCT: n=15, 30.6% vs. no pCT: n=137, 15.6%; p=0.006) more commonly received pCT. Furthermore, based on the AJCC 7th edition staging system, patients who received pCT more commonly had stage III or IV disease (pCT: n=16, 55.2% vs. no pCT: n=146, 24.7; p<0.001). The presence of extrahepatic disease was also associated with receipt of pCT (pCT: n=8, 12.9% vs. no pCT: n=32, 3.2; p<0.001). On final pathology, patients who received pCT also more often had microscopic R1 (pCT: n=14, 24.6% vs. no pCT: n=120, 12.4%; or macroscopic R2 (pCT: n=1, 1.8% vs. no pCT: n=4, 0.4%; p=0.010) resections.

On multivariable analysis, after controlling for all measurable confounders, factors associated with receipt of pCT included major hepatic resection (OR: 3.88, 95%CI 1.43-10.49, p=0.008) and the presence of microvascular invasion (OR: 2.93, 95%CI 1.43-6.02, p=0.003).

Perioperative Morbidity

Overall morbidity among all patients who underwent resection for ICC was 40.2% (n=420) with a higher incidence of complications occurring among patients who received pCT (pCT: n=36, 59.0% vs. no pCT: n=384, 39.0%; P=0.002); major morbidity, however, did not differ between the two groups (p=0.568) (Table 3). Median length of stay (pCT: 9 days, IQR 6,15 vs. no pCT: 12 days, IQR 7,17; p=0.080) and perioperative mortality within 90 days of surgery (pCT: n=1, 2.2%

Table 3. Comparison of Postoperative Course and Follow-up Across Treatment Groups

Variable	No Preoperative Chemotherapy (n=995)	Preoperative Chemotherapy (n=62)	*P-value*
Complication	384 (39.0)	36 (59.0)	0.002
Clavien Dindo Grade			0.568
I-II	239 (58.0)	23 (53.5)	
III-V	173 (42.0)	20 (46.5)	
Length of Stay (days)	12 (7-17)	9 (6-15)	0.080
Readmission within 30 days	39 (4.8)	8 (15.7)	0.001
Postoperative Mortality	35 (3.9)	1 (2.2)	0.569
Adjuvant Therapy			
Adjuvant Intra-arterial therapy	102 (14.1)	7 (14.6)	0.921
Adjuvant Chemotherapy	270 (29.0)	30 (50.8)	0.001
Adjuvant Radiotherapy	56 (6.4)	6 (10.7)	0.203

vs. no pCT: n=35, 3.9%; p=0.569) also did not differ between the two groups. Readmission within 30 days from surgery, however, was more common among patients who received pCT (pCT: n=8, 15.7% vs. no pCT: n=39, 4.8%; p=0.001). Post-operatively, patients in the pCT group more often received adjuvant chemotherapy (50.8% vs. 29.0%, p=0.001).

Impact of preoperative chemotherapy on overall and disease-free survival

At a median follow-up of 27.6 months, mortality occurred in 522 (49.7%) patients. Median OS among the entire cohort was 37.4 months (95%CI 32.5-42.3 months) with 1, 3-, and 5-year OS being 78.9%, 51.4%, and 39.2%, respectively. Stratified by receipt of pCT, median OS was similar between the two groups (pCT: 46.9 months, 95%CI 28.5-65.2 months vs. no pCT: 37.4 months, 95%CI 32.3-42.5 months; p=0.900; Figure 1). Disease recurrence occurred in 454 (43.0%) patients. Median DFS among the entire cohort was 29.6 months (95% CI 17.2-42.0 months) with 1-, 3-, and 5-year DFS being 64.7%, 46.6%, and 44.4%, respectively. Stratified by receipt of pCT, median DFS was also similar between the two groups (pCT: 34.1 months, 95%CI 2.5-65.7 months vs. no pCT: 29.1 months, 95%CI 16.0-42.2 months; p=0.909; Figure 2).

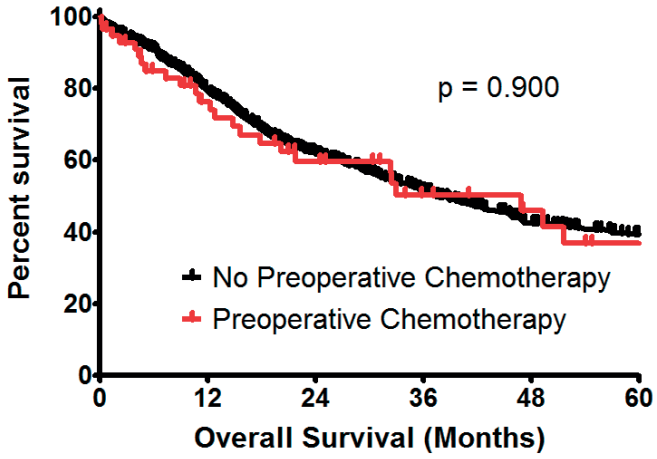

Figure 1 Overall Survival Stratified by Preoperative Chemotherapy (p = 0.900)

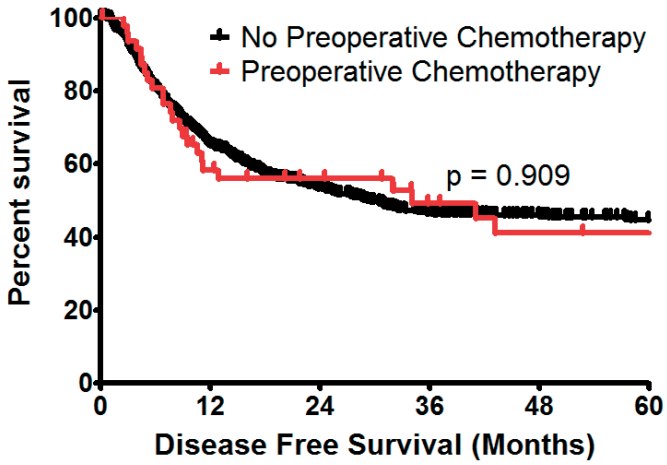

Figure 2 Disease Free Survival Stratified by Preoperative Chemotherapy (p = 0.909)

In a subgroup analysis of propensity-score matched patients based on the factors associated with receipt of pCT (n=100), there was longer OS in the pCT group (pCT: 46.9 months, 95%CI 24.3-69.4 months vs. no pCT: 29.4 months, 95%CI 14.5-44.4 months), however this did not reach statistical significance (p=0.136; Figure 3). Similarly, there was suggestion of an improved DFS in the pCT group (pCT: 34.1 months, 95%CI 0-70.2 months vs. no pCT:14.0 months, 95%CI 7.0-20.9 months; p=0.551).

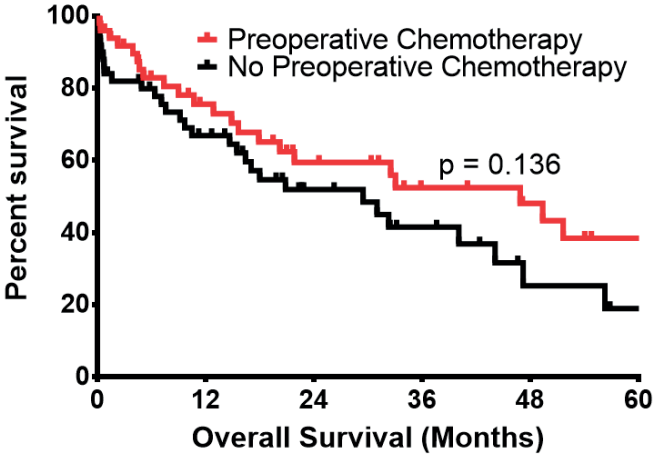

Figure 3 Overall Survival Propensity Score-Matched Patients for Resection and Microvascular Invasion (p=0.136)

Discussion

Preoperative therapy is used in several intra-abdominal cancers to reduce local and micrometastatic tumor burden prior to complete surgical resection. Some benefits of pCT include the potential to down-size tumors to increase resectability rates among patients who are initially deemed unresectable. Furthermore, pCT can potentially improve completeness of surgical resection, as well as help select patients with a better tumor biology, thereby improving OS and DFS. In the current study, we examined a large, multi-institutional international cohort of patients receiving pCT for ICC. As the use of pCT among patients with ICC has not been well-studied, this represents to our knowledge the largest study to date analyzing the impact of pCT among patients undergoing curative-intent resection for ICC. We noted that patients with more advanced disease were more likely to receive pCT. Of note, the use of pCT did result in higher overall but not major perioperative morbidity. Furthermore, in the propensity score-matched cohort, there was a suggestion that pCT improved OS and DFS, however these differences did not reach statistical significance perhaps due to a small sample size.

The use of pCT has not been examined among patients with ICC in any prospective clinical trial to date. Likely due to the overall low incidence of ICC, patients with ICC are often grouped in clinical trials with other patients with biliary tract cancers. As such, the benefit of pCT in patients with ICC is ill-defined and not commonly utilized.[2,14-16] In fact, in the current multi-institutional international cohort, the overall utilization of pCT was only 5.9%. This is likely due to the fact that analyses from available studies have been unable to show a reproducible benefit with the use of pCT among patients with ICC.[2,16] Among patients with pancreatic adenocarcinoma, however, pCT has been used in patients with locally advanced tumors to define the tumor biology.[17] In the current cohort, patients with more advanced disease were more likely to receive pCT – suggesting that physicians were using pCT, in part, to help define the natural history of the disease. Specifically, patients with more preoperative suspected or biopsy-proven lymph node metastasis, as well as those patients with worse pathological tumor features more commonly received pCT. Unfortunately, as the current cohort only included patients undergoing curative-intent hepatic resection for ICC, we were unable to determine the rate of resectability among patients with locally advanced disease. Of note, on final pathology, the use of pCT did not improve complete R0 resection rates. This is likely multifactorial, but largely be due to the selection of pCT use for patients with tumors characterized by worse pathological features.

Patients who received pCT had increased minor, but not major perioperative morbidity or mortality rates versus patients who did not receive pCT. This is similar to previously published data regarding the safety of pCT among patients undergoing resection for intra-abdominal cancer.[18,19] Despite having more advanced disease and undergoing larger hepatic resections, patients who received pCT had equivalent peri-operative mortality and LOS. While long-term OS and DFS were comparable among patients who did and did not receive pCT, propensity score-matched analysis suggested a possible benefit of pCT regarding both OS and DFS – although the association did not reach statistical significance. While it is difficult to know, the lack of significance, despite the considerable differences in the point estimates, was likely due to a type II statistical error given the very low utilization of pCT in the current cohort. Nelson et al. had reported that the use of pCT combined with radiation therapy improved survival outcomes among patients with extrahepatic cholangiogcarcinoma.[20] In a different study, Tamandl et al. reported on 10 patients with ICC who were treated with pCT and noted no survival benefit.[21] While the current study was one of the largest series to examine ICC patients to receive pCT (n=62), we similarly failed to find an effect of pCT on long-term outcomes. As noted, however, the sample size was still relatively small and therefore future prospective studies are needed.

In this study, we included 18 patients who received preoperative intra-arterial chemotherapy, as opposed to the 44 patients who received systemic chemotherapy. Intra-arterial therapy consists of the delivery of high doses of chemotherapy directly to the arterial circulation.[9] This results in high first pass extraction rates and minimizes systemic toxicity, as tumors derive most of their supply from the arterial circulation.[9,22] The effects of intra-arterial therapy have been described in 2 clinical trials and a retrospective analysis, which showed promising results in patients with liver-confined disease in a palliative setting.[9,23,24] In our cohort, the lower percentage of patients with preoperatively confirmed lymph node metastases in the intra-arterial chemotherapy group (26.7% vs. 44.7%), suggests that intra-arterial therapy was most often used preoperatively in patients with suspected borderline resectable disease, as opposed to patients with suspected micrometastatic disease. Although our finding is in line with current literature on patients with irresectable disease, future studies are needed to confirm the validity of this approach prior to a curative resection.

Results of the current study should be interpreted in the context of several limitations. As noted, the number of patients treated with pCT was small as the overall utilization was only 5.9%. Therefore, the lack of statistical significance was likely

related to a type II error. Additionally, inherent to all retrospective analyses, there may have been a selection bias regarding the diagnosis and treatment of patients. The inclusion of multiple centers also did not allow for the standardization of operative approach or protocols related to the use of pCT or adjuvant chemotherapy. The multi-center nature of the study adds to the generalizability of the study, allowing the finding to be applied across a wide range of patient populations.

Conclusions

In conclusion, pCT utilization among patients with ICC is higher among patients with more advanced disease. In this large, multi-institutional cohort, the use of pCT did not impact short-term peri-operative outcomes such as morbidity or LOS. While OS and DFS following resection were not significantly different across treatment groups, propensity matching suggested possible improved outcomes in patients treated with pCT. Further prospective trials are needed, however, to better define the role of pCT and to identify the subset of patients who might yield the most clinical benefit from the use of pCT.

References

1. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**(5): 755-62.
2. Cillo U, Spolverato G, Vitale A, et al. Liver Resection for Advanced Intrahepatic Cholangiocarcinoma: A Cost-Utility Analysis. *World journal of surgery* 2015; **39**(10): 2500-9.
3. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer* 2016.
4. Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. *Oncology* 2004; **66**(3): 167-79.
5. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; **143**(1): 88-98 e3; quiz e14.
6. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery* 2002; **132**(4): 555-63; discission 63-4.
7. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 2008; **248**(1): 84-96.
8. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(23): 3140-5.
9. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2016; **122**(5): 758-65.
10. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 2013; **153**(6): 811-8.
11. Spolverato G, Yakoob MY, Kim Y, et al. The Impact of Surgical Margin Status on Long-Term Outcome After Resection for Intrahepatic Cholangiocarcinoma. *Annals of surgical oncology* 2015; **22**(12): 4020-8.
12. Wagner A, Wiedmann M, Tannapfel A, et al. Neoadjuvant Down-Sizing of Hilar Cholangiocarcinoma with Photodynamic Therapy--Long-Term Outcome of a Phase II Pilot Study. *Int J Mol Sci* 2015; **16**(11): 26619-28.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. Chicago, IL: Springer; 2009.
14. Tran TB, Bal CK, Schaberg K, Longacre TA, Chatrath BS, Poultsides GA. Locally Advanced Intrahepatic Cholangiocarcinoma: Complete Pathologic Response to Neoadjuvant Chemotherapy Followed by Left Hepatic Trisectionectomy and Caudate Lobectomy. *Dig Dis Sci* 2015; **60**(11): 3226-9.
15. Walker EJ, Simko JP, Nakakura EK, Ko AH. A patient with cholangiocarcinoma demonstrating pathologic complete response to chemotherapy: exploring the role of neoadjuvant therapy in biliary tract cancer. *J Gastrointest Oncol* 2014; **5**(6): E88-95.

16. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; **17**(8): 669-80.

17. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. *Ann Surg* 2016; **264**(3): 457-63.

18. Ejaz A, Spolverato G, Kim Y, et al. Impact of External-Beam Radiation Therapy on Outcomes Among Patients with Resected Gastric Cancer: A Multi-institutional Analysis. *Annals of surgical oncology* 2014; **21**(11): 3412-21.

19. Parikh AA, Gentner B, Wu TT, Curley SA, Ellis LM, Vauthey JN. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2003; **7**(8): 1082-8.

20. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *International journal of radiation oncology, biology, physics* 2009; **73**(1): 148-53.

21. Tamandl D, Herberger B, Gruenberger B, Puhalla H, Klinger M, Gruenberger T. Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. *Annals of surgical oncology* 2008; **15**(10): 2787-94.

22. Collins JM. Pharmacologic rationale for regional drug delivery. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1984; **2**(5): 498-504.

23. Jarnagin WR, Schwartz LH, Gultekin DH, et al. Regional chemotherapy for unresectable primary liver cancer: results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. *Ann Oncol* 2009; **20**(9): 1589-95.

24. Kemeny NE, Schwartz L, Gonen M, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: does the addition of systemic bevacizumab improve results? *Oncology* 2011; **80**(3-4): 153-9.

CHAPTER 13

Assessing Trends in Palliative Surgery for Extrahepatic Biliary Malignancies: A 15-year Multi-center Study

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Abstract

Introduction: Extrahepatic biliary malignancies are often diagnosed at an advanced stage. We compared patients with unresectable peri-hilar cholangiocarcinoma (PHCC) and gallbladder cancer (GBC) who underwent a palliative procedure versus an aborted laparotomy.

Methods: 777 patients who underwent surgery for PHCC or GBC between 2000-2014 were identified. Uni- and multivariable analyses were performed to identify factors associated with outcome.

Results: Utilization of preoperative imaging increased over time (CT use: 80.1% pre-2009 vs. 90% post-2009) ($p<0.001$). The proportion of patients undergoing curative-intent resection also increased (2000-2004:67.0% vs. 2005-2009:74.5% vs. 2010-2014:78.8%; $p=0.001$). The planned surgery was aborted in 106 (13.7%) patients, and 94 (12.1%) had a palliative procedure. A higher incidence of postoperative complications (19.2% vs. 3.8%, $p=0.001$) including deep surgical site infections (8.3% vs. 1.1%), bleeding (4.8% vs. 0%), bile leak (6.0% vs. 0%) and longer length-of-stay (7 vs. 4.5 days) were observed among patients who underwent a palliative surgical procedure versus an aborted non-therapeutic, non-palliative laparotomy (all $p<0.05$). OS was comparable among patients who underwent a palliative procedure (8.7 months) versus an aborted laparotomy (7.8 months) ($p=0.23$).

Conclusion: Increased use of advanced imaging modalities was accompanied by increased curative-intent surgery. Compared with patients in whom surgery was aborted, patients who underwent surgical palliation demonstrated an increased incidence of postoperative morbidity with comparable survival.

Introduction

Extrahepatic biliary malignancies represent up to 3% of all cancers in the United States with a dramatic rise in the incidence of these malignancies noted over the last several decades.[1,2] Despite recent advances in diagnostic tools, peri-operative therapy and surgical approach, prognosis following resection of these malignancies remains poor. Given their diffuse and sclerotic nature, extrahepatic biliary tumors tend to invade local structures and a subset have an increased propensity for distant metastasis. As a consequence, many patients are either diagnosed at advanced stages of disease when curative resection is no longer feasible or are found to have unresectable or metastatic disease at the time of surgery.[2,3] For example, in a recent report of patients with hilar cholangiocarcinoma, only 36% of patients were amenable to surgery at the time of diagnosis due to metastatic or locally advanced disease.[4] Under such circumstances, rather than cure, efforts are often aimed at palliating symptoms of biliary obstruction including jaundice, pruritis, nausea and weight loss. However, procedures for biliary drainage including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiography (ERC) are invasive and complications following their use may compromise further management and quality of life.[1,2,4]

Currently, there is disagreement about what constitutes the most appropriate method for palliation. Non-operative management is typically recommended among patients with a life expectancy of less than 6 months who present with malignant obstructive jaundice, while the best course of treatment among patients found to have unresectable disease at the time of surgery is debated.[5-8] Data evaluating the utilization patterns and outcomes of palliative surgery are scarce, with most reports coming from small cohorts at single centers. As such, these reports are limited and may not be generalizable. With an increasing number of patients diagnosed with extrahepatic malignancies each year, data on the use of palliative surgical procedures may help inform the management of these difficult to treat patients. Given this, the aim of the current study was to analyze trends in operative approach among patients undergoing non-curative operations for extrahepatic biliary malignancies. Specifically, using a large, multi-institutional cohort of patients, we sought to compare short- and long-term outcomes of patients with unresectable peri-hilar cholangiocarcinoma (PHCC) and gallbladder cancer (GBC) who underwent a palliative procedure versus an aborted non-therapeutic, non-palliative exploratory laparotomy.

Methods

Data Sources and Patient Population

Patients presenting with PHCC or GBC between January 1, 2000 and December 31, 2014 were identified using the Extrahepatic Biliary Malignancy Consortium database from 2000-2014. Collected at and maintained by 10 academic centers in the United States (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina), the Extrahepatic Biliary Malignancy Consortium database records sociodemographic and clinicopathologic characteristics for all patients presenting with a primary extrahepatic biliary malignancy. Specifically, sociodemographic variables including age, sex and race, as well as clinicopathologic characteristics such as the American Society of Anesthesiology (ASA) physical classification score, presence of preoperative comorbidity, preoperative imaging, preoperative serum CA-19-9, preoperative peak serum bilirubin and type of cancer were recorded for each patient record. Tumor size, tumor grade, margin status as well as the presence of nodal disease and / or invasion of adjacent structures was determined using the final histopathology report. Additionally, intraoperative characteristics including the type and extent of surgery, completion of the procedure as well as the nature of the procedure (curative vs. palliative) were also recorded for each patient. Palliative procedures included both biliary bypass and cholecystectomy, both of which have been previously reported as palliative procedures to help improve quality of life.[9-11] Perioperative morbidity was classified according to the Clavien-Dindo classification system while other short-term perioperative outcomes recorded for each patient included index hospitalization length-of-stay (LOS), perioperative mortality, and 30-day readmission.[12] Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up, as appropriate. The institutional review board of each participating institutional approved this study.

Statistical Analysis

Continuous variables were described as means with standard deviation or medians with interquartile range (IQR) while categorical variables were reported as whole numbers and proportions. For ease of interpretation, patients were categorized into one of three groups based on year of diagnosis: 2000-2004, 2005-2009 and 2010-2014.[13] Differences in patient, disease and treatment-specific characteristics

were compared among these groups using the Pearson's Chi-squared test or a Kruskal-Wallis test, as appropriate. OS was estimated using the Kaplan-Meier method and differences in OS were compared between patient groups using the Mantel-Haenszel test. Uni- and multivariable Cox proportional hazard regression analysis was performed to identify clinicopathologic characteristics predictive of a poor postoperative survival. All variables with a corresponding $p<0.20$ on univariable analysis were entered into the multivariable model. Results from multivariable analysis were presented as hazard ratios (HR) with corresponding 95% confidence intervals (95%CI). All analyses were performed using STATA version 13.0 (StataCorp, College Station, TX) and $p<0.05$ (two-tailed) was used to define statistical significance.

Results

Baseline sociodemographic and clinicopathologic characteristics

A total of 777 patients who underwent surgery for hilar cholangiocarcinoma (n=328, 42.2%) or gallbladder carcinoma (n=449, 57.8%) between January 1, 2000 and December 31, 2014 were identified (Table 1). The median age of patients was 66.6 years (IQR 57.6-73.1) and a majority of patients were female (n=429, 55.2%). Nearly two-thirds of patients presented with an ASA score of 3 or 4 (n=364, 64.2%). The median CA-19-9 among all patients was 63.8 (18.0-281.0) U/mL while the median peak and final preoperative bilirubin for all patients was 1.6 (0.6-8.4) mg/dL and 0.9 (0.5-2.3) mg/dL, respectively. Preoperative clinical jaundice was observed in 350 patients (48.4%). Preoperatively, 405 patients had no biliary drainage or stent (52.9%), while 191 (25.0%) underwent endoscopic drainage, 95 (12.4%) were drained percutaneous and 74 (9.7%) underwent both types of drainage. Neoadjuvant therapy was administered to 43 patients; 30 (3.9%) patients received preoperative chemotherapy and 13 (1.7%) patients received neoadjuvant radiotherapy.

At the time of surgery, a diagnostic laparoscopy was performed in 211 (27.2%) patients. Among all patients who underwent surgery, the planned surgery was aborted in 106 (13.7%) due to the presence of either locally advanced disease (n=22, 20.8%) or the presence of metastatic disease (n=84, 79.3%). In contrast, 94 (12.1%) patients who had unresectable disease underwent a palliative surgical procedure (cholecystectomy, n=47, 63.5%; bile duct resection, n=14, 18.9%).

Table 1. Trends in Indication and Outcomes after Surgery for Hilar Cholangio- and Gallbladder Carcinoma.

Variable	2000-2004 (n=203, 26.1%)	2005-2009 (n=271, 34.9%)	2010-2014 (n=303, 39.0%)	*p*-value	Total (n=777)
Median Age (years)	65.0 (55.3-72.9)	66.2 (58.3-72.9)	68.0 (59.0-73.8)	0.102	66.6 (57.6-73.1)
Gender				0.429	
Female	120 (59.1)	146 (53.9)	163 (53.8)		429 (55.2)
Male	83 (40.9)	125 (46.1)	140 (46.2)		348 (44.8)
ASA				<0.001	
1-2	56 (50.0)	80 (36.9)	67 (28.2)		203 (35.8)
3-4	56 (50.0)	137 (63.1)	171 (71.9)		364 (64.2)
Clinical Jaundice	93 (52.8)	134 (52.8)	123 (42.0)	0.017	350 (48.4)
Type of Extrahepatic Malignancy				0.154	
Gallbladder Cancer	113 (55.7)	148 (54.6)	188 (62.1)		449 (57.8)
Hilar Cholangiocarcinoma	90 (44.3)	123 (46.4)	115 (38.0)		328 (42.2)
Biliary Drainage or Stent				0.03	
None	101 (50.5)	131 (49.4)	173 (57.7)		405 (52.9)
Endoscopic	44 (22.0)	72 (27.2)	75 (25.0)		191 (25.0)
Percutaneous	37 (18.5)	33 (12.5)	25 (8.3)		95 (12.4)
Endoscopic and percutaneous	18 (9.0)	29 (10.9)	27 (9.0)		74 (9.7)
Imaging					
CT	153 (80.1)	244 (90.7)	276 (91.1)	<0.001	673 (88.2)
MRI	48 (25.1)	94 (35.1)	161 (53.5)	<0.001	303 (39.9)
PET	9 (4.7)	38 (14.2)	43 (14.2)	0.002	90 (11.8)
Preoperative Chemo	2 (1.0)	9 (3.35)	19 (6.3)	0.009	30 (3.9)
Preoperative Radiation	1 (0.5)	6 (2.3)	6 (2.0)	0.310	13 (1.7)
Diagnostic Laparoscopy	48 (23.6)	59 (21.8)	104 (34.3)	0.002	211 (27.2)
Aborted Operation	34 (16.8)	28 (10.3)	44 (14.5)	0.112	106 (13.7)
Reason for Abortion of Operation				0.068	

Table 1. Trends in Indication and Outcomes after Surgery for Hilar Cholangio- and Gallbladder Carcinoma. (*continued*)

Variable	2000-2004 (n=203, 26.1%)	2005-2009 (n=271, 34.9%)	2010-2014 (n=303, 39.0%)	*p*-value	Total (n=777)
Locally Advanced Disease	6 (17.7)	10 (35.7)	6 (13.6)		22 (20.8)
Presence of Metastases	28 (82.4)	18 (64.3)	38 (86.4)		84 (79.3)
T-Stage Hilar	2b (2a-2b)	2b (2a-3)	2b (2a-2b)	0.191	2b (2a-3)
T-Stage Gallbladder	3 (2-3)	3 (2-3)	3 (2-3)	0.540	3 (2-3)
Lymph Node Metastases	57 (45.2)	85 (42.9)	107 (45.7)	0.833	249 (44.6)
Distant Disease	44 (21.7)	48 (17.7)	51 (16.8)	0.362	143 (18.4)
Palliative Operation	33 (16.3)	41 (15.1)	20 (6.6)	0.001	94 (12.1)
Reason for Palliation				0.218	
Locally Advanced Disease	21 (63.6)	20 (48.8)	14 (70.0)		55 (58.5)
Presence of Metastases	12 (36.4)	21 (51.2)	6 (30.0)		39 (41.5)
Extent of Palliative Surgery				0.425	
Bile Duct Resection	4 (13.3)	5 (35.7)	5 (31.3)		14 (18.9)
Cholecystectomy	19 (63.3)	20 (71.4)	8 (50.0)		47 (63.5)
Other	7 (23.3)	3 (10.7)	3 (18.8)		13 (17.6)
Length-of-Stay (days), mean ± SD	7 (5-11)	8 (6-12)	6 (4-10)	<0.001	7 (5-11)
Any Complication	74 (49.0)	132 (51.8)	154 (50.8)	0.865	360 (50.8)
# of Complications	0 (0-1)	1 (0-2)	1 (0-1)	0.540	1 (0-1)
Major Complication	31 (15.3)	71 (26.2)	76 (25.1)	0.010	178 (77.1)
Perioperative Mortality	6 (3.1)	16 (6.1)	11 (3.8)	0.241	33 (4.4)
Readmissions	36 (21.4)	57 (24.8)	79 (29.4)	0.166	172 (25.8)
Adjuvant Chemotherapy	57 (44.9)	123 (54.2)	142 (53.2)	0.206	322 (51.9)
Adjuvant Radiation	46 (37.4)	84 (37.8)	57 (22.4)	<0.001	187 (31.2)

Trends in patient, disease and operative characteristics over time

To compare trends in disease presentation and treatment over time, patients were divided into three categories based on the year of diagnosis. Marked differences were noted among these three patient groups. For example, the proportion of patients with an ASA score of 3 or 4 undergoing surgery was noted to increase over the study time, with 71.9% (n=171) of patients having an ASA score of 3 or 4 between 2010-2014 compared with 50.0% (n=56) and 63.1% (n=137) of patients between 2000-2004 and 2005-2009, respectively (p<0.001). Of note, the use of preoperative imaging also increased over the study period. Compared with 80.1% (n=153) of patients between 2000-2004 who had a preoperative computed tomography (CT) scan, over 90% (n=276, 91.1%) of patients underwent a preoperative CT scan in the last five years of the study (p<0.001). Similarly, the proportion of patients undergoing preoperative magnetic resonance imaging (MRI) increased from 25.1% (n=48) between 2000-2004 to 53.5% (n=161) between 2010-2015 (p<0.001). Patients undergoing surgery in the last five years of the study were also proportionally more likely to have received neoadjuvant therapies; specifically, the proportion of patients receiving neoadjuvant chemotherapy increased from 1.0% (n=2) between 2000-2004 to 6.3% (n=19) between 2010-2014 (p=0.009). A similar trend in the receipt of neoadjuvant radiation therapy was not observed (p=0.310). Interestingly, while the proportion of patients undergoing a curative-intent resection increased from 67.0% before 2005 to 78.8% in the last five years of the study, the proportion of patients undergoing a palliative procedure decreased from 16.3% between 2000-2004 to 6.6% between 2010-2014 (p=0.001). Of note, the number of aborted procedures (in which the surgery was ended due to the presence of unresectable disease upon surgical exploration of the abdomen) did not change over time (Figure 1, 2). Although the proportion of patients presenting with preoperative jaundice decreased from 52.8% between 2000-2004 to 42.0% between 2010-2014 (p=0.017), T-stage and the proportion of patients presenting with lymph node metastases and distal disease remained the same (all p>0.05).

Trends in diagnosis and treatment of patients with metastatic disease

In our cohort, 123 patients were found to have distant disease. Disease was located in the liver in 33 (27.7%) of these patients, while 53 (44.5%) patients had peritoneal carcinomatosis and 11 (9.2%) had both. The remainder of patients (22 (18.5%)), had distant disease elsewhere. Although our dataset is limited, it appears that distant disease was not noted on preoperative scans. More specifically, none of the patients in the cohort had any visible metastases on preoperative PET-CT, the image modality of choice for diagnosing distant metastases. Thirty-five patients with metastatic disease were diagnosed by laparoscopy. Of those 6 were

located in the liver, 22 were cases of peritoneal carcinomatosis, 6 were both liver and peritoneal carcinomatosis and 1 was located elsewhere. Four patients then went on to have a palliative resection. The remainder of patients with metastatic disease were diagnosed by laparotomy (88 (71.5%)). Of those metastases, 27 were located in the liver, 31 were cases of peritoneal carcinomatosis, 5 were both liver and peritoneal carcinomatosis, and 21 were located elsewhere. Thirty-five (39.7%) patients with distant disease diagnosed by laparotomy went on to have a palliative intent resection, while the remaining operations were aborted.

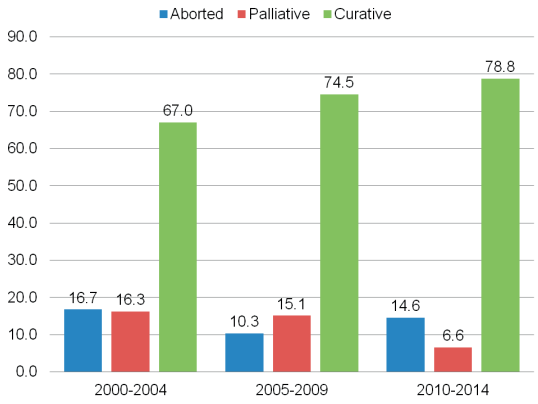

Figure 1. Aborted, palliative and curative-intent operations stratified by year of procedure (p=0.001).

Trends in postoperative outcomes over time

Among all patients identified, the total LOS was noted to decrease from an average of 7 days (IQR 5-11) before 2005 to 6 days (4-10) after 2009 (p<0.001). However, a similar trend in postoperative morbidity or mortality was not noted. In fact, the overall incidence of postoperative complications, the average number of postoperative complications and postoperative mortality was comparable across all time periods examined (p>0.05). Of note, patients who underwent a palliative procedure had worse postoperative outcomes compared with patients who had an aborted non-therapeutic, non-palliative exploratory laparotomy (Table 2). Specifically, a higher incidence of major postoperative complications (19.2% vs. 3.8%, p=0.001), including deep surgical site infections (8.3% vs. 1.1%, p=0.025), bleeding (4.8% vs. 0%, p=0.039) and bile leak (6.0% vs. 0%, p=0.020) were observed among patients who underwent a palliative surgical procedure. Similarly, the median LOS was higher among patients who underwent a palliative procedure (7 days (IQR 5-10) vs. 4.5 days (IQR 2-7); p<0.001). Readmission rates and perioperative mortality, however, were not different between groups (p>0.05).

Table 2. Comparison between Aborted Resection and Palliative Resection.

Variable	N (%)	Aborted (n = 106)	Palliative Surgery (n = 94)	*p-value*
Perioperative Mortality	10 (5.1)	4 (3.8)	6 (6.7)	0.349
Complications	76 (38.0)	32 (30.2)	44 (46.9)	0.031
Minor Complication	54 (27.0)	28 (26.4)	26 (27.7)	0.843
Major Complication	22 (11.0)	4 (3.8)	18 (19.2)	0.001
# of Complications	0 (0-1)	0 (0-1)	1 (0-1)	0.010
Clavien Dindo Grade	II (I-IIIa)	I (I-II)	II (I-IIIa)	0.012
Specific Complications				
Superficial Surgical Site Infection	12 (7.0)	5 (5.7)	7 (8.3)	0.495
Deep Surgical Site Infection	8 (4.7)	1 (1.1)	7 (8.3)	0.025
Intra-abdominal Infection	4 (2.3)	2 (2.3)	2 (2.4)	0.962
Bleeding	4 (2.3)	0	4 (4.8)	0.038
Bile Leak	5 (2.9)	0	5 (6.0)	0.020
Anastomotic Leak	1 (0.6)	0	1 (1.2)	0.305
New Post-op Ascites	3 (1.8)	1 (1.15)	2 (2.4)	0.533
Reoperation	5 (2.5)	2 (1.9)	3 (3.23)	0.554
Peak Postop Bilirubin	1.9 (0.8-5.4)	1.8 (0.8-4.9)	2 (0.8-6.2)	0.627
Length-of-Stay (days)	6 (3-8)	4.5 (2-7)	7 (5-10)	<0.001
Readmission	55 (29.4)	32 (31.7)	23 (26.7)	0.460
Time to Readmission	17.5 (7-37)	14.5 (7.5-37.5)	24.5 (7-37)	0.481
Location of Readmission				
Participating Center	53 (98.2)	31 (96.9)	22 (100)	0.403
Other	1 (1.9)	1 (3.1)	0	

Trends in OS and factors associated with OS

The median OS among all patients was 17.3 months (IQR 8.2-43.7, figure 3) with 1-year OS being 64.1% (95%CI 60.4-67.6). Of note, OS increased across the time periods examined, varying from 15.5 months (IQR 6.9-41.0) among patients undergoing surgery between 2000-2004 to 19.2 months (IQR 10.1-53.1) among patients undergoing surgery after 2009 (p=0.069). Similarly, estimates for 1-year OS increased from 58.2% (95%CI 50.8-64.9) to 69.9% (95%CI 63.7-75.3) across the study period (p<0.001). In contrast, median OS among patients who underwent a palliative procedure or a procedure that was aborted was noted to be 8 months (IQR 4.0-16.1) and was comparable among patients who underwent a palliative procedure (8.7 months) versus patients who had an aborted non-therapeutic, non-palliative exploratory laparotomy (7.8 months) (p=0.23) (Figure 4).

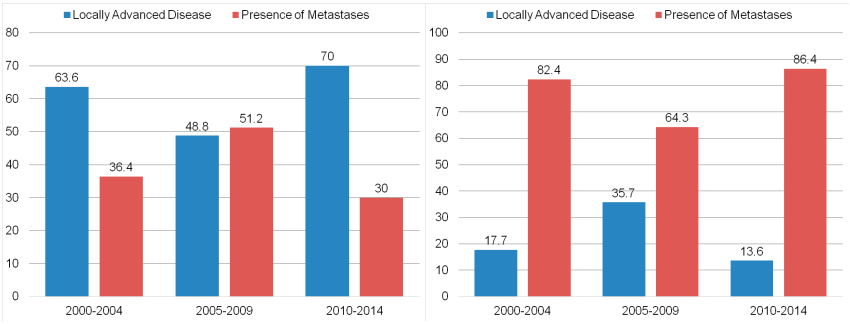

Figure 2. Reason for (a) palliative and (b) aborted, non-therapeutic, non-palliative laparotomy stratified by year of procedure.

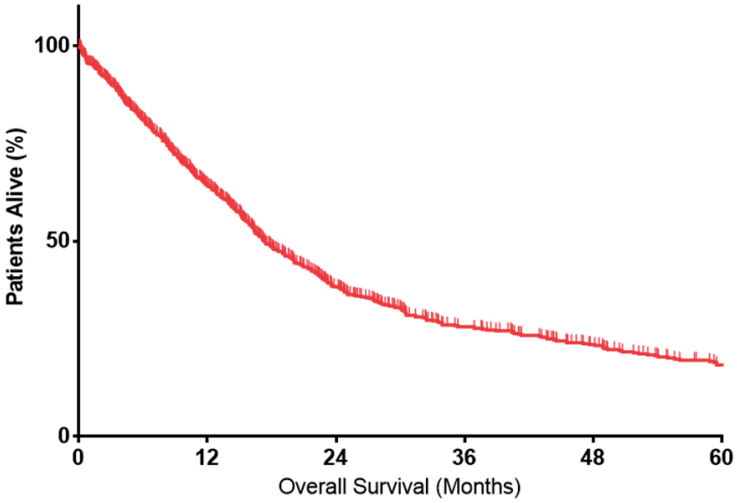

Figure 3. Overall Survival.

Cox proportional hazards regression was performed to identify potential risk factors for a worse OS. Increasing patient age (HR 1.01, 95%CI 1.00-1.03, p=0.063), a higher peak preoperative bilirubin level (HR 1.02, 95%CI 1.00-1.04, p=0.131) and a positive diagnostic laparoscopy (HR 1.54, 95% CI 1.12-2.12, p=0.008) were associated with a worse OS (Table 3). After adjusting for these competing risk factors risk factors on multivariable analysis, a higher peak preoperative bilirubin (HR 1.02, 95%CI 1.00-1.04, p=0.045) and a positive diagnostic laparoscopy (HR 1.52. 95%CI 1.09-2.13, p=0.015) were noted to be independently associated with a worse overall survival.

Table 3. Univariable and Multivariable Cox Regression Model of Overall Survival after Resections with Non-Curative intent.

Variable Name	Univariable Analysis			Multivariable Analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Age	1.01	1.00-1.03	0.063	1.01	0.99-1.03	0.215
Male Gender	0.91	0.67-1.23	0.542			
Race						
White	Ref	-	-			
Black	1.00	0.56-1.78	0.999			
Other	1.15	0.73-1.82	0.541			
BMI	0.99	0.96-1.02	0.367			
ASA Score 3-4	1.14	0.78-1.66	0.501			
CA 19-9	1.00	1.00-1.00	0.940			
Peak Bilirubin	1.02	1.00-1.04	0.131	1.02	1.00-1.04	0.045
Last Bilirubin	1.01	0.98-1.04	0.453			
Biliary Drainage or Stent						
None	Ref	-	-			
Endoscopic	1.17	0.82-1.67	0.398			
Percutaneous	1.28	0.79-2.08	0.317			
Endoscopic and percutaneous	1.01	0.62-1.65	0.953			
Preoperative Chemotherapy	0.86	0.35-2.10	0.739			
Preoperative Radiation	1.50	0.47-4.71	0.492			
Diagnostic Laparoscopy	1.54	1.12-2.12	0.008	1.52	1.09-2.13	0.015
Palliative Resection	0.84	0.62-1.14	0.274			
Reason for Palliation						
Locally Advanced Disease	Ref	-	-			
Presence of Metastases	1.15	0.85-1.57	0.365			

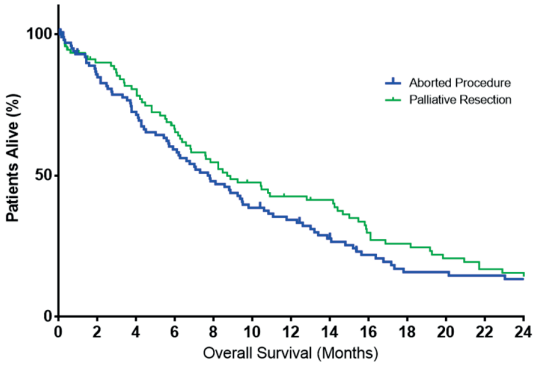

Figure 4. Overall survival stratified by receipt of palliative procedure vs. aborted, non-therapeutic, non-palliative laparotomy (p=0.23).

Discussion

Extrahepatic biliary malignancies represent a heterogeneous group of malignancies accounting for 3% of all cancers within the United States.[1,2] Given their aggressive nature and propensity for early metastasis, less than a third of patients are amenable to cure.[14-18] Given this, palliative surgical resection is often the only option to relieve the symptoms of biliary obstruction including jaundice, pruritis, nausea and weight loss.[19] Data evaluating the patterns of use and prognosis following palliative surgery remain limited with most data collected at single, specialized centers.[5-8] The current study is important in that it represents one of the largest studies to assess the patterns of use and trends of non-curative surgery for extrahepatic biliary malignancies. Using a multi-centric cohort of 777 patients, we noted a decreasing trend in the use of palliative surgery with an increasing number of curative-intent resections being performed over the study time period. Further, the current study noted an increase in the use of imaging modalities for preoperative assessment / planning with the number of patients undergoing a preoperative CT or MRI scan increasing with time. Perhaps of greater interest, postoperative clinical outcomes were also noted to improve with time as overall survival and estimated 1-year OS both were better over time. Specifically, patients who underwent surgery before 2004 demonstrated an OS of 15.5 months compared with an OS of 19.2 months among those undergoing surgery after 2009.

The observed increased trend in the number of curative-intent resections being performed is likely multifactorial and may be a consequence of improvements in diagnostic imaging and surgical technique in recent years. Studies assessing the efficacy of diagnostic imaging for biliary cancers have demonstrated that newer imaging modalities such as MRCP and PET scans can achieve an accuracy of up to 84.9% and 77.9% in assessing T and N staging, as well as a sensitivity of 78% in detecting portal vein invasion and a sensitivity ranging from 58-73% in detecting hepatic artery invasion.[20,21] In the current study, we noted the use of CT, MRI and PET for preoperative planning increased from 80.1%, 25.1% and 4.7% before 2005 to 91.1%, 53.5% and 14.2% in the years following 2009. As such, the increased use of MRI and PET scans may have contributed to the greater proportion of patients being identified with resectable disease and a greater proportion of patients amenable to curative resection. Of note, patients did not, however, present with an earlier stage of disease, as T-stage, nodal metastases and distant disease status were equal among the three time periods (Table 1). Only clinical jaundice declined over time from 52.8% (n=93) between 2000-2004 to 42.0% (n=123) between 2010-2014 (p=0.017). The increase in curative resections in a population in which the stage of the disease is unchanged may also indicate

a trend towards a more aggressive surgical approach over time. Furthermore, the proportion of aborted non-therapeutic, non-palliative exploratory laparotomy procedures was not observed to change over time. This suggests that advancements in diagnostic imaging still cannot fully delineate whether all extrahepatic biliary tract tumors are resectable based on preoperative cross-sectional imaging, and remain inadequate at diagnosing low volume disease such as peritoneal carcinomatosis. Due to the aggressive nature of many extrahepatic biliary malignancies, it is also possible that disease may spread significantly during the time between imaging and operation. In order to continue the trend toward increased curative resections while limiting the number of non-therapeutic laparotomies, we recommend utilizing laparoscopy, whenever possible, to diagnose the extent of disease in these patients. Although our data does show a significant increase in the use of laparoscopy over time from 23.6% to 34.3% of cases (p=0.002), the majority of patients underwent laparotomies, even in the most recent tercile.

Another interesting finding of the current study was a decreasing LOS among patients following surgery despite an increasing trend in the proportion of patients with a high ASA score (ASA score III or IV) undergoing resection. Specifically, LOS was noted to decrease from 7 days before 2005 to 6 days after 2009 while the numbers of patients with an ASA score of III or IV increased from 50.0% in 2004 to over 71% after 2010. These observed differences are likely due to advances in surgical technique and improvements in the perioperative management of patients. For example, recent studies have reported an increased utilization of portal vein reconstruction with favorable outcomes, which in turn allows for the resection of more challenging tumors.[13,22,23] Additionally, intraoperative and postoperative practices such as restricted fluid resuscitation strategies and enhanced recovery pathways have facilitated a better perioperative recovery and an overall decreased risk for complications.[21-23] Further highlighting improvement in peri-operative practices was our finding of a decreased number of patients who underwent a palliative procedure over time. Specifically, the proportion of patients undergoing palliative surgery decreased from 16.3% during the first five years to 6.6% over the last five years. In contrast, the proportion of patients undergoing a non-operative biliary decompression and in particular the proportion of patients undergoing an endoscopic biliary decompression increased over time (Table 1). Of note, patients who underwent a palliative surgical procedure demonstrated an increased incidence of postoperative complications with major complications such as bleeding and bile leaks more often noted following surgery. While endoscopic palliation with self-expanding metal stents remains a good treatment option for patients with preoperatively identified unresectable disease,

our data demonstrated comparable postoperative bilirubin levels among patients who underwent surgical biliary decompression suggesting that this approach is an effective palliative surgical option.[24] Results from the current study, as well as previous reports, highlight the potential benefits of biliary decompression among patients with unresectable disease. Surgical palliation did come at a cost, however, as these patients had an increased risk of complications and a longer LOS.

In addition to short-term perioperative clinical outcomes, the current study also sought to compare long-term clinical outcomes among patients with biliary cancers. The median overall survival for all patients was 17.3 months and was noted to be lower among patients undergoing non-curative intent surgery. Perhaps of greater interest, median OS among patients who underwent a palliative surgery was 8.7 months compared with 7.8 months for patients in whom surgery was aborted due to metastatic or locally advanced disease. Consistent with the results of the current study, Conner et al. in a review of patients with hilar cholangiocarcinoma, as well as Ercan and colleagues in a separate study of patients with gallbladder cancer, demonstrated comparable long-term survival among patients undergoing surgical palliation versus a non-therapeutic laparotomy.[25,26] It is also important to note that, according to recent literature, median survival in patients receiving chemotherapy without surgical resection for locally advanced or metastatic biliary tract cancers ranges from 8 to 12 months depending upon the type of chemotherapy used. Therefore, palliative resection does not appear to provide survival benefit in comparison to medical treatment alone.[27, 28]

Results of the current study should be interpreted with the following limitations. First, the data used in the current analysis were collected at 10 large, academic centers each with their own patient case mix, clinical practices and protocols. As such, differences among centers could not be controlled for and may have resulted in some residual confounding. However, the use of a large, multi-centric cohort of patients facilitated more generalizable results and an adequate sample size to assess trends over time. Second, we were unable to account for any selection bias given the retrospective nature of the study. For example, patients who underwent a palliative resection may have been more amenable to surgery compared with patients who had an aborted non-therapeutic, non-palliative laparotomy. Since this is a retrospective study, we were unable to determine all the specific circumstances related to the surgeon's decision to pursue a palliative procedure at the time of surgery, or specific information on the type of palliative procedure performed. For this reason, we were unable to make data-driven comparisons between those undergoing surgical biliary bypass versus endoscopic or percutaneous biliary

drainage, which would have helped in making recommendations for the treatment of patients with biliary obstruction.

Conclusion

In conclusion, the current study noted an increase in the number of patients undergoing curative intent surgery for gallbladder carcinomas and hilar cholangiocarcinomas over time. The observed increase in curative surgery was associated with an increased use of advanced imaging modalities preoperatively, which may have led to better identification of patients with resectable disease, and therefore a decrease in surgical palliation that was observed over time. Compared with patients in whom surgery was aborted, patients who underwent a surgical palliation demonstrated an increased incidence of postoperative morbidity with comparable survival. These data should help inform decisions around intraoperative management of patients with unresectable PHCC or GBC.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**(12): 2893-917.
2. Velu LKP, Chandrabalan V, Carter R, et al. The Glasgow whipple risk score to predict pancreas-specific complications after pancreaticoduodenectomy. *J Clin Oncol* 2015; **33**(3).
3. Wakabayashi H, Ishimura K, Hashimoto N, Otani T, Kondo A, Maeta H. Analysis of prognostic factors after surgery for stage III and IV gallbladder cancer. *Eur J Surg Oncol* 2004; **30**(8): 842-6.
4. Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5. *Eur J Cancer* 2015.
5. Goenka MK, Goenka U. Palliation: Hilar cholangiocarcinoma. *World J Hepatol* 2014; **6**(8): 559-69.
6. Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. *Liver Transpl* 2000; **6**(3): 302-8.
7. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**(8938): 1655-60.
8. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**(8): 1132-5.
9. Lee SE, Kim KS, Kim WB, et al. Practical guidelines for the surgical treatment of gallbladder cancer. *J Korean Med Sci* 2014; **29**(10): 1333-40.
10. Pradeep R, Kaushik SP, Sikora SS, Bhattacharya BN, Pandey CM, Kapoor VK. Predictors of survival in patients with carcinoma of the gallbladder. *Cancer* 1995; **76**(7): 1145-9.
11. Cunningham SC, Choti MA, Bellavance EC, Pawlik TM. Palliation of hepatic tumors. *Surg Oncol* 2007; **16**(4): 277-91.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**(2): 205-13.
13. Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in Hospital Volume and Failure to Rescue for Pancreatic Surgery. *J Gastrointest Surg* 2015; **19**(9): 1581-92.
14. Ishihara S, Miyakawa S, Takada T, et al. Status of surgical treatment of biliary tract cancer. *Dig Surg* 2007; **24**(2): 131-6.
15. de Aretxabala X, Roa I, Hepp J, et al. Early gallbladder cancer: is further treatment necessary? *J Surg Oncol* 2009; **100**(7): 589-93.
16. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. *Cancer* 2007; **110**(3): 572-80.
17. Guglielmi A, Ruzzenente A, Campagnaro T, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg* 2009; **33**(6): 1247-54.

18. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011; **29**(23): 3140-5.

19. Muller BG, De Aretxabala X, Gonzalez Domingo M. A review of recent data in the treatment of gallbladder cancer: what we know, what we do, and what should be done. *Am Soc Clin Oncol Educ Book* 2014: e165-70.

20. Sanchez JA, Newman KD, Eichelberger MR, Nauta RJ. The papillary-cystic neoplasm of the pancreas. An increasingly recognized clinicopathologic entity. *Arch Surg* 1990; **125**(11): 1502-5.

21. Gurusamy KS, Li J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database Syst Rev* 2009; (4): CD007338.

22. Gurusamy KS, Li J, Vaughan J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database Syst Rev* 2012; **5**: CD007338.

23. Kim Y, Ejaz A, Gani F, et al. Crystalloid administration among patients undergoing liver surgery: Defining patient- and provider-level variation. *Surgery* 2016; **159**(2): 389-98.

24. Mukai T, Yasuda I, Nakashima M, et al. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2013; **20**(2): 214-22.

25. Connor S, Barron E, Redhead DN, et al. Palliation for suspected unresectable hilar cholangiocarcinoma. *Eur J Surg Oncol* 2007; **33**(3): 341-5.

26. Ercan M, Bostanci EB, Cakir T, et al. The rationality of resectional surgery and palliative interventions in the management of patients with gallbladder cancer. *Am Surg* 2015; **81**(6): 591-9.

CHAPTER 14

Yttrium-90 Radioembolization in Intrahepatic Cholangiocarcinoma: A Multicenter Retrospective Analysis

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Abstract

Background Radioembolization with yttrium-90 microspheres (^{90}Y) is a promising technique for extending intrahepatic cholangiocarcinoma patient survival in those patients ineligible for surgical resection.

Methods Patients who underwent ^{90}Y radioembolization were retrospectively included from five tertiary care centers. In all hospitals, prospectively maintained databases were supplemented with information from electronic patient charts.

Results A total of 89 patients met our inclusion criteria. Of these patients, 69 were treated with resin microspheres (77.5%), while 19 patients were treated with glass microspheres (n = 19; 21.3%), and one patient was treated with both. Toxicity was observed in 55 patients (80%) in the resin group and 11 patients (58%) in the glass group. On average, glass seemed to have lower grade toxicity (p = 0.007). Complications according to the SIR-definition were noted in 18 patients (26.5%) in the resin group and 4 patients (21.1%) in the glass group (p = 0.631). Median overall survival (OS) from diagnosis was 29.2 months (95%CI: 18.6-39.8) for patients treated with resin microspheres, and 1-, 3- and 5-year OS were 82.8%, 32.9% and 8.0%. Median OS after treatment with resin microspheres was 9.5 months (95%CI: 6.1-12.8) and 1- and 3- year OS were 37.1% and 6.8%. These estimates were not significantly different in the glass group. Five patients were able to undergo curative intent resection after ^{90}Y (5.9%), two of these patients died of the complications of their surgery.

Discussion This study shows the potential of ^{90}Y radioembolization, as well as its safety and effectiveness.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy in the West, with an incidence of about 2 per 100,000.[1-3] Although surgical resection is the only curative treatment for proximal bile duct malignancies, only 15% of patients are eligible for operation at the time of presentation.[4-8] In patients who are not eligible for resection, a median survival of 3 to 8 months is observed.[9,10] It is possible to extend this period up to twelve months with a chemotherapy regimen of gemcitabine and cisplatin.[11] However, almost half of these patients develop significant clinical toxicities and adverse events.[11-13] In order to extend life and increase the quality of life, numerous non-surgical approaches are currently being utilized in intrahepatic cholangiocarcinoma, one of the most notable being radioembolization with yttrium-90 (^{90}Y) microspheres.

Radioembolization has been shown to extend life and suppress tumor sequelae in large cohorts for unresectable HCC and colorectal liver metastases.[14,15] It has been pioneered in a number of small series in proximal bile duct malignancies. These studies indicate that ^{90}Y radioembolizations are tolerated well in relatively healthy patients, as measured by their low Eastern Cooperative Oncology Group (ECOG) performance status.[9,16-20] In addition, ^{90}Y radioembolization was correlated with longer survival, when compared with patients undergoing best supportive care only.[9,16-20] Further comparisons with other treated groups and eventually prospective trials are required to truly evaluate the potential of ^{90}Y radioembolization therapy.

In this study we describe survival after diagnosis, and after ^{90}Y radioembolization. Furthermore, we detail and compare the rate and severity of complications after ^{90}Y radioembolization treatment for two currently used types of microspheres.

Methods

All patients undergoing radioembolization with ^{90}Y microspheres between January 1, 2000 and January 1, 2016 in five tertiary care centers (University Medical Center Utrecht, Utrecht, the Netherlands; Johns Hopkins Hospital, Baltimore, Maryland; Vanderbilt University Medical Center, Nashville, Tennessee; MD Anderson Cancer Center, Houston, Texas; Stanford University Medical Center, Stanford, California) were included in this study.

In all hospitals, prospectively maintained databases were supplemented with information from electronic patient charts. Sociodemographic and clinicopathologic variables were collected for all patients and included age, sex, baseline hepatobiliary disease,

lab values, clinical work-up and prior / other treatments including chemotherapy and resection. Details on the ^{90}Y radioembolization treatment were collected, including the activity calculation method, administered activity, targeted volume and treatment sessions. Post-intervention complications were reported following the SIR definition and grading system[21] and biochemical toxicity was assessed using the Common Terminology Criteria for Adverse Events 4.0 based on post-intervention alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin.[22] Follow-up was retrieved from the electronic patient records. The respective institutional review boards of each participating institution approved this study.

Pretreatment mesenteric angiography and technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scanning were performed according to previously published guidelines.[23] This method was also used to calculate the pulmonary shunt fraction (PSF). Devices used were TheraSphere® glass microspheres (BTG, London, United Kingdom) and SIR-Spheres® resin microspheres (Sirtex, Lane Cove, New South Wales, Australia). The United States Food and Drug Administration (FDA) approved TheraSphere® for hepatocellular carcinoma (HCC). This device was used off-label for the treatment of the patients included in this study. SIR-Spheres® have been FDA-approved as a brachytherapy treatment for unresectable liver tumors. For the purpose of this study post-intervention outcomes for resin microspheres and glass microspheres were compared, with regard to toxicity, and complications. A preliminary analysis of long-term outcomes was performed. Dose was calculated using the body surface area (BSA) method for resin and using the Medical Internal Radiation Dose (MIRD) method for glass. The exception was Stanford University Medical Center, where the MIRD method was utilized post 2011 for all patients, including resin. Patients with bilobar disease were treated in a sequential lobar fashion. Patients were evaluated at regular intervals after treatment. After treatment, best tumor response was assessed by post-intervention contrast-enhanced computed tomography (CT) according to the Response Evaluation Criteria in Solid Tumors (RECIST).[24]

Statistical analysis

Continuous variables were described as medians with interquartile range (IQR). Categorical variables were described as totals and frequencies. Differences in groups were assessed using the χ^2 test for categorical and the Mann-Whitney U-test for continuous variables. Survival was estimated using the Kaplan-Meier method, and differences between survival were examined with the log-rank test. All analyses were carried out with SPSS 22 (International Business Machines Corporation, NY) and R 3.3.3 (https://cran.r-project.org/), and a P value of <0.05 (two tailed) was considered statistically significant.

Results

A total of 89 patients met our inclusion criteria and were included into this study (Table 1). Sixty-nine patients were treated with resin microspheres (77.5%), while 19 patients were treated with glass microspheres (n = 19; 21.3%). Two patients presented with portal vein thrombosis and were therefore treated with glass microspheres, as resin microspheres were considered too embolic. One patient was treated with both glass and resin microspheres and was disregarded for the purpose of comparison. A majority of patients were female (n = 50; 57.2%) and most patients had an ECOG/WHO status of 0 or 1 (n = 83; 93.3%). Patients had an average BMI of 26.2 (Interquartile range [IQR]: 22.9-30.4). Eight patients had a prior medical history of cirrhosis (10.1%). Nine patients had cholangitis (10.5%), and 7 patients presented with clinical jaundice (7.9%). In all patients, pre-intervention imaging was acquired and in the vast majority of patients this consisted of CT with or without further imaging techniques (n = 83; 93.3%). Median CA 19-9 was heightened at 107.0 U/mL (IQR: 27.1-683.4), as were liver markers AST and ALT. Alkaline Phosphatase, a marker of biliary damage, was elevated as well. The average tumor diameter was 6.2 cm (IQR: 4.7-8.0) and most patients had multiple tumors (n = 61; 68.5%). Suspicious lymph nodes were identified in 32 patients (37.6%), and distant metastases in 22 patients (25.6). Vascular involvement was reported in 33 patients (38.8%).

Table 1. Baseline Characteristics

Characteristic	Resin microspheres (n = 69)	Glass microspheres (n = 19)	Total (n = 89)
Total	69 (100.0)	19 (100.0)	89 (100.0)
Male Gender	31 (44.9)	8 (42.1)	39 (43.8)
ECOG / WHO			
0	28 (40.6)	11 (57.9)	39 (43.8)
1	36 (52.2)	7 (36.8)	44 (49.4)
2	4 (5.8)	1 (5.3)	5 (5.6)
3	1 (1.4)	0 (0.0)	1 (1.1)
Body Mass Index	26.2 (22.9-30.2)	29.5 (22.9-31.0)	26.2 (22.9-30.4)
Baseline Hepatobiliary Disease			
Biliary Stone	4 (6.0)	1 (5.6)	5 (5.8)
Cholangitis	7 (10.4)	2 (11.1)	9 (10.5)
Hepatitis B	3 (5.1)	0 (0.0)	3 (3.9)
Hepatitis C	4 (6.8)	1 (6.3)	5 (6.6)
Cirrhosis	6 (8.7)	3 (15.8)	9 (10.1)

Table 1. Baseline Characteristics (*continued*)

Characteristic	Resin microspheres (n = 69)	Glass microspheres (n = 19)	Total (n = 89)
Lab			
CA 19-9, kU/L	107.0 (27.1-744.0)	52.0 (18.8-2245.5)	107.0 (27.1-684.4)
Carcinoembryonic antigen, µg/L	3.0 (1.0-15.6)	2.4 (2.0-3.5)	3.0 (1.5-8.5)
Alkaline Phosphatase, U/L	174.0 (129.3-263.5)	125.0 (89.0-151.0)	156.5 (117.8-247.0)
Hemoglobin, g/dL	12.2 (10.7-13.7)	12.4 (10.1-13.4)	12.2 (10.6-13.7)
Platelets x 10^9/L	210 (129-281)	189 (129-249)	208 (129-265)
ALT, U/L	34.0 (22.0-48.0)	22.0 (20.0-42.0)	33.0 (21.2-47.2)
AST, U/L	38.0 (29.0-50.0)	38.0 (24.0-62.0)	38.0 (27.0-50.0)
Albumin, g/dL	3.9 (3.4-4.1)	3.8 (3.5-4.1)	3.9 (3.5-4.1)
Bilirubin, mg/dL	0.5 (0.4-0.8)	0.6 (0.3-0.9)	0.5 (0.3-0.8)
Clinical Jaundice	6 (8.7)	1 (5.3)	7 (7.9)
Imaging Techniques			
CT	68 (98.6)	14 (73.7)	83 (93.3)
MRI	29 (42.0)	7 (36.8)	36 (40.4)
Ultrasound	33 (48.5)	6 (31.6)	39 (44.3)
PET	35 (50.7)	9 (47.4)	45 (50.6)
Tumor Diameter in Imaging, cm	7.0 (4.6-9.2)	6.9 (3.9-10.5)	6.2 (4.7-8.0)
Multiple Tumors	53 (76.8)	8 (42.1)	61 (68.5)
Bilobar Localization	51 (73.9)	11 (61.1)	63 (71.6)
Lobar Atrophy	2 (2.9)	3 (17.6)	5 (5.8)
Vascular Involvement	24 (36.4)	9 (50.0)	33 (38.8)
Suspicious Lymph Nodes	25 (37.9)	7 (38.9)	32 (37.6)
Suspected Distant Metastases	17 (25.4)	5 (27.8)	22 (25.6)

Continuous variables were described as medians with interquartile range (IQR). Categorical variables were described as totals and frequencies. ECOG/WHO: Eastern Cooperative Oncology Group/World Health Organization performance status. CA 19-9: cancer antigen 19-9. ALT: alanine aminotransferase. AST: aspartate aminotransferase.

At the time of radiological intervention, 12 patients (15.7%) had undergone prior resection with curative intent (Table 2). In 40% of cases, these resections consisted of a major liver resection >3 Couinaud segments (n = 6; 42.9%). Most patients undergoing resection had a negative margin (n = 9; 64.3%); one patient (7.1%) had macroscopic disease left at the resection margin and one patient underwent margin re-excision during surgery. Prior chemotherapy was given in 66 patients (74.2%) and consisted of gemcitabine and cisplatin in most cases. Median fraction of pulmonary shunting was 5.3% (IQR: 3.1-8.7) in patients treated with

resin microspheres and 5.6% (3.1-9.1) in patients with glass microspheres. The median administered activity was 1.7 GBq (IQR: 1.2-2.3) for resin microspheres and 2.4 GBq (IQR: 1.2-3.8) for glass microspheres. The whole liver was targeted in 49 (55.1%) of patients.

Table 2. Treatment Details

Characteristic	Resin microspheres (n = 69)	Glass microspheres (n = 19)	Total (n = 89)
Prior Resection	12 (17.4)	2 (10.5)	14 (15.7)
Palliative Drainage	7 (10.1)	2 (14.3)	9 (10.7)
Prior Chemotherapy	54 (78.3)	12 (63.2)	66 (74.2)
Pulmonary Shunt (%)	5.3 (3.1-8.7)	5.6 (3.1-9.1)	5.3 (3.1-8.7)
Activity Delivered, GBq	1.7 (1.2-2.3)	2.4 (1.2-3.8)	1.72 (1.24-2.72)
Treatment Sessions			
1	59 (85.5)	14 (77.8)	73 (83.0)
2	9 (13.0)	4 (22.2)	14 (15.9)
3	1 (1.4)	0 (0.0)	1 (1.1)
Tumor Volume			
Selected Targeting (≤ 2 segments)	3 (4.3)	1 (5.3)	4 (4.5)
Single-Lobe	23 (33.3)	12 (63.2)	36 (40.4)
Whole-Liver	43 (62.3)	6 (31.6)	49 (55.1)

Continuous variables were described as medians with interquartile range (IQR). Categorical variables were described as totals and frequencies.

Post-intervention Results

The median follow-up of patients treated with resin microspheres was 10.5 months (IQR: 3.3-22.3), and the median follow-up of patients treated with glass microspheres was 14.4 months (IQR:8.2-16.1). Technical success after the procedure was noted in all patients (Table 3). No patients died within 90 days of their intervention, but two patients treated with glass microspheres developed permanent adverse sequelae in the form of radioembolization-induced liver disease (REILD),[25] one of whom eventually passed away. Toxicity was observed in the laboratory values of 55 patients (80%) in the resin microspheres group and 11 patients (58%) in the glass group. On average, glass microspheres treatment seemed to cause less overall toxicity, as well as lower grade toxicity (p = 0.007). Complications according to the SIR-definition were noted in 18 patients (26.5%) in the resin group and 4 patients (21.1%) in the glass group (p = 0.631). The average complication grade was C (IQR: B-C), equaling therapy requirement and

minor hospitalization (<48 hours) in the resin group, whereas it was D (major therapy requirement and hospitalization >48 hours; IQR: C-E) in the glass group. According to the RECIST criteria, partial response was noted in 21.4% of patients who underwent embolization with glass microspheres, vs. 2.2% of patients who were treated with resin spheres (p = 0.021). In the resin microspheres group, 50 patients (72.5%) experienced recurrence during follow-up. This was the case for 11 patients (57.9%) in the glass group. Five patients were able to undergo curative intent resection after ^{90}Y radioembolization (5.9%), two of whom died of the complications of their surgery.

Table 3. Postintervention Outcomes

Characteristic	Resin microspheres (n = 69)	Glass microspheres (n = 19)	*P* - value
Technical Success	69 (100.0)	19 (100.0)	
CTC Adverse Events			0.007
Grade 1	37 (63.8)	6 (35.3)	
Grade 2	13 (22.4)	3 (17.6)	
Grade 3	5 (8.6)	2 (11.8)	
SIR Complication	18 (26.5)	4 (21.1)	0.631
Grade A	2 (12.5)	0 (0.0)	
Grade B	7 (43.8)	0 (0.0)	
Grade C	7 (43.8)	2 (50.0)	
Grade D	0 (0.0)	0 (0.0)	
Grade E	0 (0.0)	2 (50.0)	
RECIST criteria			
Progressive disease	12 (26.1)	5 (35.7)	0.021
Stable disease	33 (71.3)	6 (42.9)	
Partial response	1 (2.2)	3 (21.4)	
Progression within Follow-up	50 (72.5)	11 (57.9)	

Variables were described as totals and frequencies. Differences between groups were assessed using the $\chi 2$ test.

Survival Analysis

Most patients died during follow-up (n = 65; 73.0%). Median overall survival (OS) from diagnosis was 29.2 months (95%CI: 18.6-39.8) after resin microsphere treatment, and 1-, 3- and 5-year OS were 82.8%, 32.9% and 8.0%. Median OS after treatment with resin microspheres was 9.5 months (95%CI: 6.1-12.8) and 1- and 3- year OS were 37.1% and 6.8%. Progression free survival (PFS) after resin microsphere treatment was 4.4 months (95%CI: 1.9-6.9) and 1-year

freedom from progression was 26.6%. For liver-specific recurrence, median PFS was 5.5 months (95%CI 0.9-10.1). Freedom from liver progression at one year was observed in 35.0% of patients (Figure 2A & B).

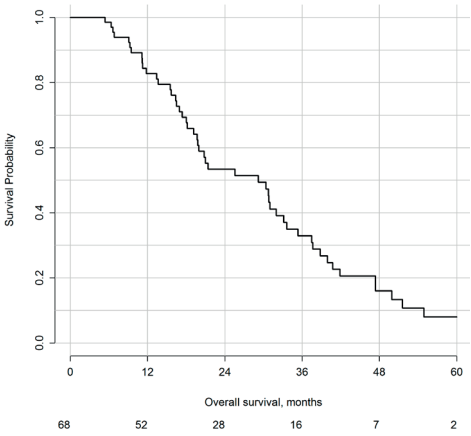

Figure 1A Overall survival after diagnosis with resin-microspheres

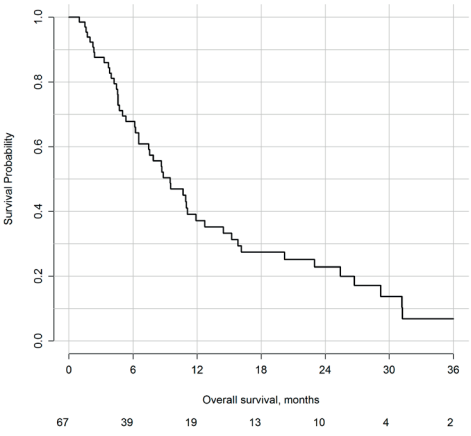

Figure 1B Overall survival after Yttrium-90 radio-embolization with resin-microspheres

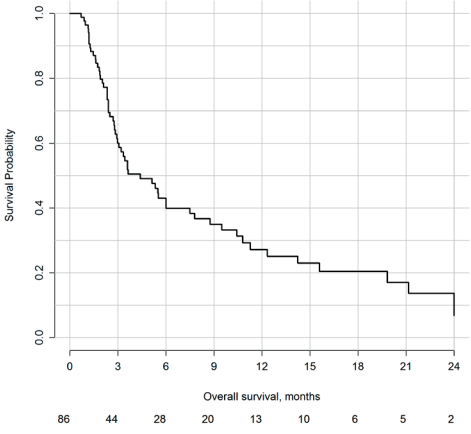

Figure 2A Progression-free survival after Yttrium-90 radio-embolization with resin-microspheres

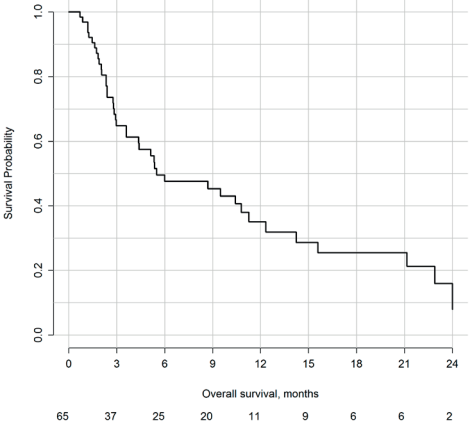

Figure 2B Liver-specific progression-free survival after Yttrium-90 radio-embolization with resin-microspheres

For patients with glass microspheres, median OS after diagnosis was 21.2 months (95%CI: 19.6-22.7). This estimate did not differ significantly from the estimate of resin microspheres (p = 0.876). The same was the case for median OS after treatment (14.8 months; 95%CI: 2.2-27.4; p = 0.811), PFS (median 3.3 months;

95%CI: 2.9-3.7; p = 0.601), and liver-specific PFS (median 4.8 months; 95%CI: 0.15-9.4; p = 0.997).

We separately evaluated outcomes in patients without prior chemotherapy who were treated with resin microspheres, in whom median survival from diagnosis was 30.8 months (95%CI: 26.8-34.9), and 1- and 3-year OS were 70.0%, and 28.0% (Figure 3). Overall survival after treatment was 16.2 months (95%CI: 13.9-18.4). Time to overall progression was 10.8 months (95%CI: 9.8-11.7), and time to liver-specific progression was 10.8 months (95%CI: 9.9-11.7). This analysis was not performed for patients who underwent glass microsphere ^{90}Y radioembolization, as they were too few in number.

Discussion

In this study, a large cohort of ICC patients who underwent ^{90}Y radioembolization treatment was investigated. Most patients underwent resin microspheres ^{90}Y radioembolization, as opposed to glass microspheres treatment, and had a relatively low ECOG/WHO status. Few patients underwent primary resection, as most tumors were unresectable at diagnosis. At the time of radiological intervention most patients underwent whole liver irradiation. A comparatively low number of one in four patients developed a complication according to the SIR criteria and no patients died shortly post-treatment, attesting the safety of ^{90}Y radioembolization. Less than 10% experienced grade 3 or 4 toxicity, compared to up to 70% in currently used chemotherapy regimens.[11] A partial response rate of 20% for glass microspheres and 2% for resin microspheres was achieved. Despite these modest response figures, a post-treatment OS of 10 months was observed, with a 6% chance of curative intent resection.

Regional treatments rely on the dual blood supply of the liver, where the hepatic artery is mostly responsible for the blood supply of tumors.[26 27,28] Radioembolization was first utilized in colorectal liver metastases and hepatocellular carcinoma.[26] The technique is based on administration of radioactive microspheres into the hepatic artery branch supplying the tumor.[14,15] Embolization of the non-target vessels and injection of technetium-99m (^{99m}Tc)-labeled macro-aggregated albumin (MAA) is performed before treatment, in order to exclude extrahepatic accumulation.[14,15,26] In this study we concluded that radioembolization is tolerated well in patients with a good performance status, which is in line with current literature.[9,16-20] The survival estimates in this study are superior to those of patients undergoing best supportive care only.[9,11,16-20] The post-treatment survival

of 9.5 months was relatively low compared to existing literature, with estimates ranging from 9 months post-treatment in a cohort of 25 Australian patients,[9] to 22 months in a cohort of 33 German patients.[19] Despite being primarily unresectable, 5 out of the 89 patients went on to have a curative intent resection. This leads us to conclude that ^{90}Y radioembolization can successfully be utilized in patients with unresectable ICC to offer a chance to undergo curative resection.

Currently available literature shows a highly significant correlation between dose delivered to the tumor and response rate.[29-31] The radiation dose that is effectively delivered to the tumor tissue and the (unwanted) dose that is absorbed by healthy tissue should therefore be calculated when using radioembolization treatment.[29-31] Most clinical trials to date, however, do not calculate these metrics.[31] Instead, they use the most basic method of determining activity to be administered, in the form of the empirical model, based solely on the estimated tumor involvement of the liver,[32] or the BSA method, which builds on this principle by taking into account the size of the tumor and patient.[32] Using ^{99m}Tc-MAA SPECT images, it is possible to carry out provisional dosimetry before the ^{90}Y infusion.[29-32] Although imperfect, this method has been validated for both resin and glass microsphere treatments in hepatocellular carcinoma.[31,33,34] In the current study, dose calculation using the MIRD method was carried out for patients treated with glass microspheres and those treated with resin microspheres at Stanford post 2011. Additional prospective research into a personalized dosimetric approach, combined with currently ongoing trials of ^{90}Y-microspheres concurrent with chemotherapy, will allow for a more personalized treatment of patients with ICC in the future. This approach would ideally lead to optimal efficacy with lower toxicity in individual patients.

TheraSphere® (glass) and SIR-Spheres® (resin), the two currently used types of ^{90}Y microspheres, demonstrate different biological properties.[35,36] These differences could theoretically lead to different safety and efficacy outcomes.[36] A recent systematic review of 38 articles, comparing glass to resin microspheres for the treatment of hepatocellular carcinoma, tentatively demonstrated a safety advantage for glass microspheres.[35] In this study, we observed a trend towards lower toxicity in patients with glass microspheres too. Post-intervention RECIST criteria also seemed to favor the glass group, in which relatively more patients exhibited partial response. Complications according to the SIR definition were not differently distributed. Long term outcomes did not differ. These tentative results are difficult to verify in a head-to-head comparison, as the low accrual rate of a study specifically aiming at ICC patients necessitates a large, and prolonged multi-center cooperation.

Although ^{90}Y radioembolization studies, including the present, show a relatively favorable response, OS and DFS, as well as a relatively low incidence of adverse effects, there are several liver-directed techniques aiming to achieve the same goals. In a recent study, hepatic arterial infusion (HAI) with floxuridine was combined with systemic chemotherapy in 78 patients with locally advanced ICC (n=104). This treatment requires a small operation; implanting an arterial pump. Median OS of this method was superior to systemic chemotherapy alone (31 months vs. 18 months).[5] Five-year OS was 20% in patients who received HAI chemotherapy. Currently, a phase 2 trial is recruiting patients for HAI chemotherapy in the adjuvant setting. Another liver-directed technique, transarterial chemo-embolization (TACE) affects the blood flow to the tumor in addition to locally releasing cytotoxic agents. It causes ischemic tumor necrosis and facilitates intracellular transit of chemotherapeutic agents.[26,28] In a study of 41 prospectively followed patients, one group described a median OS of 11.7 months from first treatment after treatment with irinotecan TACE in ICC patients.[37] One patient successfully underwent resection following TACE.[37] Another prospective study on TACE reported a median survival of 18 months in 24 patients, with 3 patients being adequately downstaged to undergo resection.[38] Again, these results appear similar to those observed in our cohort. The costs of TACE, however, are significantly lower than those of ^{90}Y radioembolization, with an average treatment costing about $8,000.[39] Prospective head-to-head studies need to be conducted to compare treatment outcomes.

The results of this study should be viewed in the light of several limitations. First and foremost, the retrospective nature of this study precludes definitive conclusions about post-therapy disease progression, because no follow-up schedule was predetermined. However, due to the large proportion of patients returning to the hospital in which they were treated and due to the high early progression rate, we believe we can still draw some tentative conclusions on this issue. Additionally, the treatment method, dose calculation method, and device used, differed between patients. Although this prevents us from drawing conclusions favoring one method over the other, this does add to the generalizability of our results. Finally, for a formal treatment benefit analysis, weighing advantages against adverse events, and a formal cost-effectiveness analysis, weighing advantages against financial aspects, future prospective studies need to be performed.

This study shows the potential of ^{90}Y radioembolization, as well as its safety and effectiveness.

References

1. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma--focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev.* 2010;11(5):1159-1166.
2. Singal AK, Vauthey JN, Grady JJ, Stroehlein JR. Intra-hepatic cholangiocarcinoma--frequency and demographic patterns: thirty-year data from the M.D. Anderson Cancer Center. *J Cancer Res Clin Oncol.* 2011;137(7):1071-1078.
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology.* 2009;136(4):1134-1144.
4. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery.* 2002;132(4):555-563; discission 563-554.
5. Konstantinidis IT, Koerkamp BG, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer.* 2015.
6. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg.* 2008;248(1):84-96.
7. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol.* 2011;29(23):3140-3145.
8. Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol.* 2014;110(2):163-170.
9. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol.* 2010;17(2):484-491.
10. Park J, Kim MH, Kim KP, et al. Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study. *Gut Liver.* 2009;3(4):298-305.
11. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-1281.
12. Harder J, Riecken B, Kummer O, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. *Br J Cancer.* 2006;95(7):848-852.
13. Jang JS, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. *Cancer Chemother Pharmacol.* 2010;65(4):641-647.
14. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol.* 2012;35(5):1066-1073.

15. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology.* 2011;54(3):868-878.

16. Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. *J Vasc Interv Radiol.* 2014;25(2):256-265.

17. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol.* 2013;24(8):1227-1234.

18. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol.* 2013;36(2):440-448.

19. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol.* 2012;35(1):105-116.

20. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer.* 2008;113(8):2119-2128.

21. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology Clinical Practice Guidelines. *Journal of Vascular and Interventional Radiology.* 2003;14(9, Part 2):S199-S202.

22. Health USDo, Human S. Common terminology criteria for adverse events (CTCAE) version 4.0. *National Cancer Institute.* 2009(09-5410).

23. Salem R, Lewandowski RJ, Sato KT, et al. Technical aspects of radioembolization with 90Y microspheres. *Tech Vasc Interv Radiol.* 2007;10(1):12-29.

24. Duffaud F, Therasse P. New guidelines to evaluate the response to treatment in solid tumors. *Bulletin du cancer.* 2000;87(12):881-886.

25. Braat MN, van Erpecum KJ, Zonnenberg BA, van den Bosch MA, Lam MG. Radioembolization-induced liver disease: a systematic review. *Eur J Gastroenterol Hepatol.* 2017;29(2):144-152.

26. Seidensticker R, Ricke J, Seidensticker M. Integration of chemoembolization and radioembolization into multimodal treatment of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol.* 2015;29(2):319-332.

27. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol.* 1954;30(5):969-977.

28. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359(9319):1734-1739.

29. Garin E, Lenoir L, Rolland Y, et al. Dosimetry based on 99mTc-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with 90Y-loaded glass microspheres: preliminary results. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 2012;53(2):255-263.

30. Garin E, Rolland Y, Lenoir L, et al. Utility of Quantitative (99m)Tc-MAA SPECT/CT for (90)yttrium-Labelled Microsphere Treatment Planning: Calculating Vascularized Hepatic Volume and Dosimetric Approach. *International Journal of Molecular Imaging*. 2011;2011:398051.

31. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90)Y-loaded glass microsphere radioembolization. *Liver International*. 2017;37(1):101-110.

32. Mosconi C, Cappelli A, Pettinato C, Golfieri R. Radioembolization with Yttrium-90 microspheres in hepatocellular carcinoma: Role and perspectives. *World Journal of Hepatology*. 2015;7(5):738-752.

33. Strigari L, Sciuto R, Rea S, et al. Efficacy and toxicity related to treatment of hepatocellular carcinoma with 90Y-SIR spheres: radiobiologic considerations. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2010;51(9):1377-1385.

34. Chiesa C, Maccauro M, Romito R, et al. Need, feasibility and convenience of dosimetric treatment planning in liver selective internal radiation therapy with (90)Y microspheres: the experience of the National Tumor Institute of Milan. *The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So*. 2011;55(2):168-197.

35. Kallini JR, Gabr A, Thorlund K, et al. Comparison of the Adverse Event Profile of TheraSphere® with SIR-Spheres® for the Treatment of Unresectable Hepatocellular Carcinoma: A Systematic Review. *CardioVascular and Interventional Radiology*. 2017;40(7):1033-1043.

36. Pieper CC, Willinek WA, Thomas D, et al. Incidence and risk factors of early arterial blood flow stasis during first radioembolization of primary and secondary liver malignancy using resin microspheres: an initial single-center analysis. *European Radiology*. 2016;26(8):2779-2789.

37. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol*. 2012;24(4):437-443.

38. Schiffman SC, Metzger T, Dubel G, et al. Precision hepatic arterial irinotecan therapy in the treatment of unresectable intrahepatic cholangiocellular carcinoma: optimal tolerance and prolonged overall survival. *Ann Surg Oncol*. 2011;18(2):431-438.

39. Porter C, Friese J, Fleming C, Andrews J. Cost Analysis of Yttrium-90 Radioembolization vs Hepatic Artery Chemoembolization (HACE) in Patients with Hepatocellular Carcinoma. Radiological Society of North America 2009 Scientific Assembly and Annual Meeting; 2009; Chicago IL.

Discussion and Future Perspectives

DISCUSSION

Besides etiology and anatomy, the main similarity of biliary tract cancers (BTC) is their guarded prognosis. Only for a small number of patients can curative resection be considered and perioperative outcomes are often complicated by biliary leakage and infection.[1] In order to provide optimal health care to patients with hepatobiliary malignancies, it is of great importance to treat the right patients with the right treatment modalities. Where some patients might benefit from expansive surgical resection, other patients, either because of their disease status or other aspects of their physique, might be more adequately treated by chemotherapy or one of the emergent targeted treatment strategies. The personalization of treatment provides the best chance of improving postoperative and long-term outcomes, and can be divided in three general principles: selecting the correct patients for appropriate procedures, determining prognosis after treatment, and developing novel treatments as alternatives or as addition to surgery.

Patient Selection

Part I aimed to determine which patients are best selected for the different treatment modalities. More specifically, which patients should be considered eligible for surgery and which patients should rather be treated non-surgically. Surgery for BTC is highly specialized care and treatment at high volume hospitals has been associated with better outcomes.[2-5] In **Chapter 1**, the importance of hospital and surgery volume for individual patient outcomes was assessed in the United States (U.S.) in the National Inpatient Sample (NIS). A total of 5,075 patients underwent liver surgery for primary or secondary malignancies and were included in the study. Mortality and failure to rescue (FTR: mortality after a major complication) were noted to be lowest among high volume hospitals and surgeons. On multivariable analysis, compared with high volume surgeons, lower volume surgeons demonstrated greater odds for FTR. Interestingly, even within high volume centers, high volume surgeons reported lower complications and lower FTR. This led to the conclusion that, although both hospital volume and surgeon volume have a positive effect on postoperative outcome, surgeon volume, rather than hospital volume was accountable for most variability in these outcomes. Because this study was conducted in a national database lacking necessary details, further research should explore the microsystems within hospitals and surgeons that potentially drive variations in post-operative outcomes such as mortality and FTR.[6]

A dreaded postoperative complication after surgery for BTC is post-hepatectomy liver failure (PHLF). The incidence of postoperative liver failure is currently re-

ported to be between 0.7% and 34% and mortality following PHLF is reported as high as 1 in 3.[7-11] **Chapter 2** reviewed the different definitions of post-hepatectomy liver failure, with a particular focus on detailing predictive patient-specific factors. Preoperative models utilized for predicting PHLF, include the Child-Pugh-Turcotte and MELD scores.[12-14] Both these scores are also used postoperatively, in addition to the often-cited 50-50 criteria and the ISGLS definition.[8,15] Although all scores were adequate predictors in their derivation study, often with areas under the receiver operating characteristic (ROC) curve of over 0.9, scores performed considerably worse in validation studies. For example, in one validation of the 50-50 criteria, only 50% of the patients who experienced postoperative mortality had PHLF according to the criteria.[16] The conclusion of this literature review was that future studies should be aimed at understanding the mechanisms and risk factors of PHLF, as no definitive definition and cure have been found.

In order to decrease the chance of postoperative complications, including PHLF, in patients who do not benefit from surgery, adequate patient selection is vitally important. In previous studies, lymph node metastases have been reported as a major determinant of survival after resection.[17-19] Presence of lymph node metastases can be determined with reasonable accuracy preoperatively, using radiological modalities and Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS/FNA).[20,21] In **Chapter 3** a retrospective analysis of PHC patients was conducted, in order to try and answer the question whether it is prudent to resect PHC in patients with lymph node metastases. Patients who underwent resection for PHC with lymph node metastases were compared with patients who did not undergo resection because of locally advanced disease at exploratory laparotomy. Resected patients had a survival benefit of 7 months, although patients in the comparison group were more likely to have more advanced disease. The actual survival benefit, therefore, is likely to be smaller. Conclusions inferred from this analysis were that the decision to resect should be weighed against considerable postoperative morbidity and mortality, especially in the presence of other risk factors for disease recurrence.

One of the major determinants of postoperative outcomes is physiologic age.[22-24] In an increasingly aging population, the concept of frailty has been introduced to give an indication of physiologic fitness.[25,26] Frailty has different definitions, but a major recognized component is low muscle mass, or sarcopenia.[27] Sarcopenia in **Chapter 4 & Chapter 5** was defined as low muscle mass, volume or density of the psoas muscle at the level of the third lumbar vertebra.[28-31] In two large cohorts of patients who underwent hepato-pancreato-biliary or colorectal surgery

the impact of sarcopenia was reported. On multivariable analysis, independent risk factors for 1-year mortality included increasing age, preoperative anemia, and preoperative low muscle mass. Using these variables, a 28-point weighed composite score was able to stratify patients based on their risk for mortality 1 year after surgery. For elderly patients a separate 25-point composite score was constructed to predict 1-year mortality. This score included comorbidities, malignant disease, and sarcopenia measured by density.

Prognosis after Surgery

In *Part II*, prognosis after surgery was discussed. Prognostic and predictive tools for BTC were reviewed, which can be used for both patient information and treatment allocation. **Chapter 6** provided an overview of the current literature in hepato-pancreato-biliary model building, discussing current practices and shortcomings in validated models. Conclusions of this review were that basic requirements for prognostic studies are met in the field of malignant HPB surgery, yet many of the most often used models were constructed using dated methods. These models need to be updated, using validation and improvement studies. Subsequently, models for survival after resection for ICC were validated in a large international cohort in **Chapter 7**.[32-38] Although the risk factors included in the models were significantly associated with overall and disease-free survival, discrimination between good prognosis versus worse prognosis in the new population was disappointing. Only the Wang nomogram had reasonable discrimination.[32] Large cohorts should be used to derive models, using appropriate statistical methods. The validation and updating of models is essential for external validity.[39] Further research into the optimization of ICC prognostic models, possibly with inclusion of specific biomarkers, is warranted.

In **Chapter 8** the concept of conditional survival was applied to a large cohort of patients with PHC. Conditional survival is based on the notion that accrued survival time is the most important prognostic factor for further survival, especially after a long period has elapsed since operative resection.[40-44] This study showed that the chance of surviving an additional year could increase to 90% after surviving seven years. Additionally, known risk factors of worse outcome, such as age, margin status, disease stage, lymph node metastases and perineural invasion, became less impactful after time elapsed.[18,45,46] This led to the conclusion that use of conditional survival can serve as a more valuable estimate in predicting long-term survival, as follow-up accrues. Therefore, it can help in directing decisions pertaining to clinical decision making, surveillance and palliation.[41,42]

As in PHC, overall survival after resection of GBC is limited, making the concept of survival conditional on the accrued survival time an interesting concept for long-term survivors.[47] **Chapter 9** gave conditional survival estimates for patients with GBC. Three hundred and twelve patients who underwent curative resections for GBC were included, with a median survival of 25 months. Conditional survival improved as time after surgery elapsed, resulting in a 90% chance of living another year when 7 years had passed. Furthermore, marked differences in conditional and actuarial survival were also observed when patients were categorized based on the observed risk factors. Interestingly, while conditional survival was consistently higher than actuarial survival among all patient subgroups, the effect was most pronounced among patients in those subgroups characterized by high risk factors.

Finally, **Chapter 10** questions the prognostic impact of routine resection of the common bile duct in patients with GBC. Although radical re-resection for GBC has been advocated after incidental findings of GBC, the optimal extent of re-resection remains unknown and the role of routine excision of the common bile duct is controversial.[48-50] This study aimed to assess the impact of common bile duct resection on survival among patients undergoing surgery for GBC. Among the 449 included patients, 30% underwent a concomitant CBD resection. After adjusting for potential confounders, common bile duct resection did not impact overall survival. An increase in lymph node yield was not observed either, although common bile duct resection was associated with more aggressive underlying disease such as advanced tumor stage and lymph node metastases. These outcomes correspond with literature from other Western centers.[50] The conclusion drawn from this data was that the use of common bile duct resection should likely be reserved for that subgroup of patients who require it to extirpate all disease in the biliary tree.

Novel Treatments

In *Part III,* non-surgical techniques and their efficacy in the treatment of BTC were further explored. A general overview of treatments, prediction and prognostication of ICC was given in **Chapter 11**. ICC is the second most common malignancy arising from the liver, with an incidence of 1-2 per 100,000.[51-55] It develops mostly as a well-differentiated adenocarcinoma and also occurs in combination with hepatocellular carcinoma, and might be responsible for worse prognosis in some of the patients with that disease.[56] The mostly used staging system is the American Joint Committee on Cancer TNM staging, although new staging systems are being developed.[57] Most notably, a prognostic model by Wang

et al. performed reasonably in external validation.[32] The mainstay of treatment remains surgery, even though new techniques are being pioneered. These new techniques include hepatic arterial infusion, transarterial chemo-embolization and Y-90 radio-embolization.[55,58] The conclusion of this review was that advances still need to be made in personalized treatment of ICC patients, and future studies should further improve prognostic models and identify predictive biomarkers to determine the response to chemotherapy.[19,59]

Chapter 12 discussed the effect of preoperative chemotherapy (pCT) in ICC patients. Despite the successful use of preoperative chemotherapy to downstage tumors and treat micrometastases prior to operation in other malignancies, the use of pCT among patients with ICC has not been well-studied.[60,61] Sixty-two patients who underwent pCT were identified in a population of 1,057 ICC patients. In this retrospective analysis, no difference between disease free and overall survival was observed, despite the fact that pCT patients had significantly worse disease characteristics. After propensity score matching, the group receiving pCT had a survival advantage of 17 months, albeit this difference was non-significant. Further prospective trials are needed to better define the role of pCT and to identify the subset of patients who might have the most clinical benefit from the use of pCT, although this is made difficult by the low incidence of ICC.

As mentioned previously, many patients with BTC are either diagnosed at advanced stages of disease when curative resection is no longer feasible or are found to have unresectable or metastatic disease at the time of surgery.[62,63] Non-operative management is typically recommended among patients with a life expectancy of less than 6 months who present with malignant obstructive jaundice, while the best course of treatment among patients found to have unresectable disease at the time of surgery is debated.[64-67] **Chapter 13** assesses the outcomes and effects of palliative surgery in GBC and PHC in a large U.S. cohort, accrued over 15 years of practice. Of the 777 patients identified, resection was aborted in 106 patients and 94 patients had a palliative procedure. Median OS among patients who underwent a palliative procedure or a procedure that was aborted was noted to be 8 months and was comparable between patients in both groups. A higher incidence of major complications was noted amongst patients undergoing palliative resection.

A promising novel technique is Yttrium-90 (Y-90) radio-embolization. This technique is based on administration of beads filled with Y-90 microspheres into the hepatic artery branch supplying the tumor.[68,69] Several small studies indicate

that Y-90 is tolerated well in patients with a good performance status.[70-75] In ICC patients, Y-90 was associated with improved survival, when compared with patients undergoing best supportive care only.[70-75] Estimates ranged from 9 months post-treatment in a cohort of 25 Australian patients,[74] to 22 months in a cohort of 33 German patients.[73] **Chapter 14** presented an overview of utilization of Y-90 for radio-embolization of the liver in patients with cholangiocarcinoma in the largest cohort to date, discussing its safety and efficacy. In total, 89 patients were analyzed. Median survival after Y-90 treatment was 10 months, survival after diagnosis was 29 months. This is longer than the survival of similar patients who receive best supportive care. Progression-free survival was 4 months and 6% of patients were eligible for curative intent treatment after Y-90 treatment. Although these results were promising, randomized trials are required to definitively determine the effectiveness of Y-90 therapy.

FUTURE PERSPECTIVES

Prognostication and prediction models are still insufficiently capable of delineating individual patients' disease course. Although many improvements have been made in recent years, truly individualized care for BTC will still require significant scientific advances.

The rise of multi-center consortia such as the ENSCCA, the Extrahepatic Biliary Malignancy Consortium, in conjunction with more detailed national databases, such as those maintained by the Dutch Institute for Clinical Auditing, will bring a generation of databases of adequate size to enable derivation of models.[76,77] Increased awareness amongst peer-reviewers with regard to optimism, overfitting, and the merits of (external) validation, will most likely enhance the methods of derivation studies.[39,78] The guidelines, currently being developed by the Cochrane Prognostic Study Group, will further increase reporting and quality.[79]

In addition to better derived models, the recent increase in use of mobile phones and tablets allow computerized models to be used in daily practice. The main advantage of these innovations is that models no longer need to be simplified into integer risk scores or paper nomograms. The ease of use in the form of apps and web-pages will most likely also promote an increase in the use of prognostic and predictive models. Finally, computer interfaces enable the use of more complex model-building, e.g. recursive partitioning and artificial neural networking.[80]

Even with the use of new possibilities and techniques, the predictive and prognostic ability of models based on a relatively small number of clinical predictors is limited. In order to improve the predictive ability of current and new prognostic models, new determinants of biological processes in the form of biomarkers will be required. Biomarkers such as CEA and CA19-9 have previously been correlated with BTC formation and clinical outcomes.[81,82] To this end, e.g. Wang et al. have proposed that a composite biomarker profile that combines clinical factors (CEA and CA19-9) with pathological biomarkers may improve the accuracy of prognostic models and guide treatment in patients with resected ICC.[32] This nomogram proved to have the best discriminative ability in chapter 11. The potential of this approach has been proven with the recent successes of biomarker-based prediction in breast cancer and colorectal cancer.[83,84]

Predictive and prognostic biomarkers are not readily available.[85] A means of better differentiating individual tumors is determining a biomarker profile, by means of immunohistochemistry.[85] A recent meta-analysis identified several biomarkers that have prognostic value in patients with BTC.[85] An example of a proven diagnostic and prognostic biomarker, is fascin, an actin cross-linked protein found in the cell membrane of the biliary duct cells.[86] The epidermal growth factor receptor (EGFR) also plays an important role in prognostics and forms a potential treatment target.[87,88] Mucin 1, cell surface associated (MUC1) and Mucin 4, cell surface associated (MUC4) are two membrane proteins that have been shown to have an impact on patient prognosis.[89-91] Lastly, p27, Cyclin-dependent kinase inhibitor 1B, is a protein involved in the cell cycle which also has predictive capabilities.[92-94] In addition to these biomarkers, several other biomarkers have been shown to have an impact on diagnostics, prognostics and treatment efficacy, including HSP27, Akt, HDGF, MUC6, p16, p-4EBP1, S100A4, alpha-SMA, keratin 903, and TROP2.[85] From a number of these biomarkers a composite biomarker profile can be determined for each individual patient, indicating both prognosis and treatment efficacy.

Because of a rapidly growing knowledge of BTC biomarkers, treatment efficiency can still be vastly improved. A diagnostic biomarker could be a fast, relatively low-cost test, to rule out the possibility of BTC in patients presenting with vague symptoms of the upper abdomen. A marker predicting medium and long-term survival could improve identification of patients eligible for major liver resections. Finally, a marker indicating susceptibility for certain chemotherapeutics could have a large impact on medical treatment efficacy. A composite of multiple markers would allow treatment specifically designed for each patient.

REFERENCES

1. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)* 2013; **15**(7): 492-503.
2. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**(15): 1128-37.
3. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011; **364**(22): 2128-37.
4. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**(22): 2117-27.
5. Nathan H, Cameron JL, Choti MA, Schulick RD, Pawlik TM. The volume-outcomes effect in hepato-pancreato-biliary surgery: hospital versus surgeon contributions and specificity of the relationship. *J Am Coll Surg* 2009; **208**(4): 528-38.
6. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Ann Surg* 2009; **250**(6): 1029-34.
7. van den Broek MA, Olde Damink SW, Dejong CH, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 2008; **28**(6): 767-80.
8. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**(5): 713-24.
9. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy Liver Failure. *Digestive Surgery* 2012; **29**(1): 79-85.
10. Ribeiro HSC, Costa WL, Diniz AL, et al. Extended preoperative chemotherapy, extent of liver resection and blood transfusion are predictive factors of liver failure following resection of colorectal liver metastasis. *Eur J Surg Oncol* 2013; **39**(4): 380-5.
11. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. *Hepatogastroenterology* 2012; **59**(115): 782-4.
12. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). *Hepatology* 2007; **45**(3): 797-805.
13. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964; **1**: 1-85.
14. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**(8): 646-9.
15. Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005; **242**(6): 824-8, discussion 8-9.
16. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007; **204**(5): 854-62; discussion 62-4.
17. Buettner S, van Vugt JL, Gani F, et al. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. *J Gastrointest Surg* 2016.

18. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 2015; **26**(9): 1930-5.

19. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. *J Surg Oncol* 2014; **110**(5): 585-91.

20. Lee HY, Kim SH, Lee JM, et al. Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. *Radiology* 2006; **239**(1): 113-21.

21. Engelbrecht MR, Katz SS, van Gulik TM, Lameris JS, van Delden OM. Imaging of perihilar cholangiocarcinoma. *AJR Am J Roentgenol* 2015; **204**(4): 782-91.

22. Farquharson SM, Gupta R, Heald RJ, Moran BJ. Surgical decisions in the elderly: the importance of biological age. *J R Soc Med* 2001; **94**(5): 232-5.

23. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes* 2012; **5**(2): 222-8.

24. Sawhney R, Sehl M, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part I. *Cancer J* 2005; **11**(6): 449-60.

25. Berger NA, Savvides P, Koroukian SM, et al. Cancer in the Elderly. *Transactions of the American Clinical and Climatological Association* 2006; **117**: 147-56.

26. Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. *Age Ageing* 2012; **41**(2): 142-7.

27. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**(4): 412-23.

28. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB* 2011; **13**(7): 439-46.

29. Amini N, Spolverato G, Gupta R, et al. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. *J Gastrointest Surg* 2015; **19**(9): 1593-602.

30. Peng P, Hyder O, Firoozmand A, et al. Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2012; **16**(8): 1478-86.

31. Joglekar S, Asghar A, Mott SL, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. *J Surg Oncol* 2015; **111**(6): 771-5.

32. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 2013; **31**(9): 1188-95.

33. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. Chicago, IL: Springer; 2009.

34. Hyder O, Marques H, Pulitano C, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014; **149**(5): 432-8.

35. Sakamoto Y, Kokudo N, Matsuyama Y, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: Analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer* 2016; **122**(1): 61-70.

36. Uenishi T, Ariizumi S, Aoki T, et al. Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2014; **21**(7): 499-508.

37. Okabayashi T, Yamamoto J, Kosuge T, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. *Cancer* 2001; **92**(9): 2374-83.

38. Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2009; **16**(1): 14-22.

39. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating: Springer Science & Business Media; 2008.

40. Kurta ML, Edwards RP, Moysich KB, et al. Prognosis and conditional disease-free survival among patients with ovarian cancer. *J Clin Oncol* 2014; **32**(36): 4102-12.

41. Nathan H, de Jong MC, Pulitano C, et al. Conditional Survival after Surgical Resection of Colorectal Liver Metastasis: An International Multi-Institutional Analysis of 949 Patients. *J Am Coll Surg* 2010; **210**(5): 755-64.

42. Mayo SC, Nathan H, Cameron JL, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. *Cancer* 2012; **118**(10): 2674-81.

43. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. *J Clin Oncol* 2003; **21**(16): 3035-40.

44. Ploussard G, Shariat SF, Dragomir A, et al. Conditional survival after radical cystectomy for bladder cancer: evidence for a patient changing risk profile over time. *Eur Urol* 2014; **66**(2): 361-70.

45. Valero V, 3rd, Cosgrove D, Herman JM, Pawlik TM. Management of perihilar cholangiocarcinoma in the era of multimodal therapy. *Expert Rev Gastroenterol Hepatol* 2012; **6**(4): 481-95.

46. Mao K, Liu J, Sun J, et al. Patterns and prognostic value of lymph node dissection for resected perihilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2015.

47. Zabor EC, Gonen M, Chapman PB, Panageas KS. Dynamic prognostication using conditional survival estimates. *Cancer* 2013; **119**(20): 3589-92.

48. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. *Ann Surg Oncol* 2007; **14**(2): 833-40.

49. Sakamoto Y, Kosuge T, Shimada K, et al. Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. *J Surg Oncol* 2006; **94**(4): 298-306.

50. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009; **16**(4): 806-16.

51. Shin HR, Oh JK, Masuyer E, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma--focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010; **11**(5): 1159-66.

52. Singal AK, Vauthey JN, Grady JJ, Stroehlein JR. Intra-hepatic cholangiocarcinoma--frequency and demographic patterns: thirty-year data from the M.D. Anderson Cancer Center. *J Cancer Res Clin Oncol* 2011; **137**(7): 1071-8.

53. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009; **136**(4): 1134-44.

54. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**(5): 755-62.

55. Konstantinidis IT, Koerkamp BG, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2015.

56. Woo HG, Lee JH, Yoon JH, et al. Identification of a cholangiocarcinoma-like gene expression trait in hepatocellular carcinoma. *Cancer Res* 2010; **70**(8): 3034-41.

57. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology* 2010; **17**(6): 1471-4.

58. Seidensticker R, Ricke J, Seidensticker M. Integration of chemoembolization and radioembolization into multimodal treatment of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 2015; **29**(2): 319-32.

59. Doussot A, Groot-Koerkamp B, Wiggers JK, et al. Outcomes after Resection of Intrahepatic Cholangiocarcinoma: External Validation and Comparison of Prognostic Models. *J Am Coll Surg* 2015; **221**(2): 452-61.

60. Wagner A, Wiedmann M, Tannapfel A, et al. Neoadjuvant Down-Sizing of Hilar Cholangiocarcinoma with Photodynamic Therapy--Long-Term Outcome of a Phase II Pilot Study. *Int J Mol Sci* 2015; **16**(11): 26619-28.

61. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; **143**(1): 88-98 e3; quiz e14.

62. Chapman BC, Gleisner A, Rigg D, et al. Neoadjuvant FOLFIRINOX improves progression free survival compared to gemcitabine/abraxane in pancreatic adenocarcinoma. *Ann Surg Oncol* 2017; **24**(1): S105-S6.

63. Wakabayashi H, Ishimura K, Hashimoto N, Otani T, Kondo A, Maeta H. Analysis of prognostic factors after surgery for stage III and IV gallbladder cancer. *Eur J Surg Oncol* 2004; **30**(8): 842-6.

64. Goenka MK, Goenka U. Palliation: Hilar cholangiocarcinoma. *World J Hepatol* 2014; **6**(8): 559-69.

65. Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. *Liver Transpl* 2000; **6**(3): 302-8.

66. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**(8938): 1655-60.

67. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**(8): 1132-5.

68. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012; **35**(5): 1066-73.

69. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**(3): 868-78.

70. Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. *J Vasc Interv Radiol* 2014; **25**(2): 256-65.

71. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol* 2013; **24**(8): 1227-34.

72. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol* 2013; **36**(2): 440-8.

73. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol* 2012; **35**(1): 105-16.

74. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol* 2010; **17**(2): 484-91.

75. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer* 2008; **113**(8): 2119-28.

76. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 2016; **13**(5): 261-80.

77. de Groot S, van der Linden N, Franken MG, et al. Balancing the Optimal and the Feasible: A Practical Guide for Setting Up Patient Registries for the Collection of Real-World Data for Health Care Decision Making Based on Dutch Experiences. *Value Health* 2017; **20**(4): 627-36.

78. Thrift AP. Can we Accurately Predict Survival in Patients with Perihilar Cholangiocarcinoma? : Elsevier; 2017.

79. Bouwmeester W, Zuithoff NP, Mallett S, et al. Reporting and methods in clinical prediction research: a systematic review. *PLoS Med* 2012; **9**(5): 1-12.

80. Kattan MW, Hess KR, Beck JR. Experiments to determine whether recursive partitioning (CART) or an artificial neural network overcomes theoretical limitations of Cox proportional hazards regression. *Comput Biomed Res* 1998; **31**(5): 363-73.

81. Grobmyer SR, Wang L, Gonen M, et al. Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. *Ann Surg* 2006; **244**(2): 260-4.

82. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol* 2009; **16**(11): 3048-56.

83. Lech G, Slotwinski R, Slodkowski M, Krasnodebski IW. Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances. *World J Gastroenterol* 2016; **22**(5): 1745-55.

84. Le Du F, Ueno NT, Gonzalez-Angulo AM. Breast Cancer Biomarkers: Utility in Clinical Practice. *Curr Breast Cancer Rep* 2013; **5**(4).

85. Ruys AT, Groot Koerkamp B, Wiggers JK, Klumpen HJ, ten Kate FJ, van Gulik TM. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21**(2): 487-500.

86. Iguchi T, Aishima S, Taketomi A, et al. Fascin overexpression is involved in carcinogenesis and prognosis of human intrahepatic cholangiocarcinoma: immunohistochemical and molecular analysis. *Hum Pathol* 2009; **40**(2): 174-80.

87. Shafizadeh N, Grenert JP, Sahai V, Kakar S. Epidermal growth factor receptor and HER-2/neu status by immunohistochemistry and fluorescence in situ hybridization in adenocarcinomas of the biliary tree and gallbladder. *Hum Pathol* 2010; **41**(4): 485-92.

88. Herberger B, Berger W, Puhalla H, et al. Simultaneous blockade of the epidermal growth factor receptor/mammalian target of rapamycin pathway by epidermal growth factor receptor inhibitors and rapamycin results in reduced cell growth and survival in biliary tract cancer cells. *Mol Cancer Ther* 2009; **8**(6): 1547-56.

89. Higashi M, Yamada N, Yokoyama S, et al. Pathobiological implications of MUC16/CA125 expression in intrahepatic cholangiocarcinoma-mass forming type. *Pathobiology* 2012; **79**(2): 101-6.

90. Park SY, Roh SJ, Kim YN, et al. Expression of MUC1, MUC2, MUC5AC and MUC6 in cholangiocarcinoma: prognostic impact. *Oncol Rep* 2009; **22**(3): 649-57.

91. Yeh CN, Pang ST, Wu RC, Chen TW, Jan YY, Chen MF. Prognostic value of MUC4 for mass-forming intrahepatic cholangiocarcinoma after hepatectomy. *Oncol Rep* 2009; **21**(1): 49-56.

92. Hashimoto N, Yachida S, Okano K, et al. Immunohistochemically detected expression of p27(Kip1) and Skp2 predicts survival in patients with intrahepatic cholangiocarcinomas. *Ann Surg Oncol* 2009; **16**(2): 395-403.

93. Jarnagin WR, Klimstra DS, Hezel M, et al. Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. *J Clin Oncol* 2006; **24**(7): 1152-60.

94. Fiorentino M, Altimari A, D'Errico A, et al. Low p27 expression is an independent predictor of survival for patients with either hilar or peripheral intrahepatic cholangiocarcinoma. *Clin Cancer Res* 2001; **7**(12): 3994-9.

DISCUSSIE

Naast etiologie en anatomie, is de belangrijkste gelijkenis van galwegkankers (biliary tract cancers; BTC) hun infauste prognose. Slechts voor een klein aantal patiënten kan curatieve resectie overwogen worden en perioperatieve uitkomsten worden vaak gecompliceerd door gallekkage en infecties. Om optimale zorg te bieden aan patiënten met hepatobiliaire maligniteiten is het van groot belang om de juiste patiënten te behandelen met de juiste behandelingsmodaliteiten. Waar sommige patiënten baat hebben bij uitgebreide chirurgische resectie, kunnen andere patiënten door bijvoorbeeld comorbiditeiten beter behandeld worden door chemotherapie of een van de opkomende behandelingsstrategieën. De personalisatie van behandeling voor BTC biedt de beste kans om postoperatieve en lange termijnresultaten te verbeteren en kan worden ingedeeld in drie algemene principes: het selecteren van de juiste patiënten voor de juiste procedures, het kwantificeren wat de baten van behandeling zijn op het gebied van prognose en het ontwikkelen van nieuwe behandelingen als alternatief voor of als aanvulling op operatie.

Patiëntselectie

In deel I werd beoogd te bepalen welke patiënten het best geselecteerd kunnen worden voor de verschillende behandelingsmodaliteiten. Meer in het bijzonder, welke patiënten in aanmerking zouden moeten komen voor een operatie en welke patiënten niet-chirurgisch behandeld moeten worden. Chirurgie voor BTC is zeer gespecialiseerde zorg en de behandeling in gespecialiseerde centra is geassocieerd met betere resultaten. In **hoofdstuk 1** is het belang van ziekenhuis- en operatievolume voor individuele patiëntresultaten in de leverchirurgie beoordeeld in de Verenigde Staten (VS), middels het National In-Patient Sample (NIS). NIS is een database waarin een kwart van alle patiënten die een ingreep ondergaan in de VS worden opgenomen. Mortaliteit en *failure to rescue* (FTR: sterfte na een ernstige complicatie) bleek het laagst bij ziekenhuizen en chirurgen die grote aantallen patiënten behandelden. Bij multivariabele analyse hadden chirurgen met een lager operatievolume een grotere kans op FTR. Zelfs in hoog-volumecentra, hadden chirurgen met een hoog operatievolume lagere complicaties en lagere FTR. Dit leidde tot de conclusie dat het behandelvolume van de chirurg oorzaak is van de meeste variabiliteit in de postoperatieve uitkomsten. Omdat deze studie is uitgevoerd in een nationale database en hierbij weinig details per casus konden worden bepaald, moet verder onderzoek worden gedaan naar de processen binnen ziekenhuizen en de verschillen tussen chirurgen die potentieel variaties in postoperatieve uitkomsten veroorzaken.

Een gevreesde postoperatieve complicatie na operatie voor BTC is postoperatief leverfalen (PHLF). De incidentie van PHLF is tussen de 0,7% en 34% en sterfte na PHLF treedt in sommige studies op in één op de drie patiënten. In **hoofdstuk 2** zijn de verschillende definities van leverfalen na hepatectomie nader bekeken, met in het bijzonder aandacht voor de voorspellende patiënt-specifieke factoren. Preoperatieve modellen die worden gebruikt voor het voorspellen van PHLF, zijn de Child-Pugh-Turcotte en MELD scores. Beide scores worden ook postoperatief gebruikt, met ook de vaak gebruikte 50-50 criteria en de ISGLS definitie. Alle scores bleken voldoende voorspellend in de studies waarin ze ontwikkeld werden, terwijl dit in validatiestudies aanzienlijk slechter was. Bijvoorbeeld, bij een externe validatie van de 50-50 criteria, voldeed slechts de helft van de patiënten die stierven aan de 50-50 criteria. De conclusie van dit hoofdstuk was dat toekomstige studies zich meer moeten richten op de mechanismen en risicofactoren die aan PHLF ten grondslag liggen.

Om de kans op postoperatieve complicaties zoals PHLF te verminderen bij patiënten die geen baat bij chirurgie hebben, is adequate patiëntselectie van essentieel belang. In eerdere studies is aangetoond dat lymfekliermetastasen een belangrijke determinant zijn van overleving na resectie voor BTC. Aanwezigheid van lymfekliermetastasen kan met redelijke nauwkeurigheid preoperatief worden bepaald met behulp van radiologische modaliteiten en endoscopische echo-geleide dunne naald aspiratie (EUS / FNA). In **hoofdstuk 3** is een retrospectieve analyse van perihilair cholangiocarcinoom (PHC-)patiënten uitgevoerd om de vraag te beantwoorden of het in prognostisch opzicht zin heeft om PHC-patiënten met lymfekliermetastasen te opereren. Patiënten die een resectie ondergingen voor PHC met lymfekliermetastasen zijn vergeleken met patiënten die geen resectie konden ondergaan als gevolg van lokaal gevorderde ziekte. Gereseceerde patiënten hadden een overlevingsvoordeel van 7 maanden, hoewel patiënten in de vergelijkingsgroep waarschijnlijk meer gevorderde ziekte hadden. Het daadwerkelijke overlevingsvoordeel is daarom waarschijnlijk kleiner. Conclusies die uit deze analyse getrokken kunnen worden is dat de beslissing om een resectie uit te voeren afgewogen moet worden tegenover de aanzienlijke postoperatieve morbiditeit en mortaliteit. Met name de aanwezigheid van andere risicofactoren voor het ontwikkelen van een recidief is van belang.

Een van de belangrijkste determinanten van postoperatieve resultaten is de fysiologische leeftijd. In de literatuur is het begrip *frailty* geïntroduceerd om fysiologische leeftijd aan te duiden. Frailty heeft verschillende definities, maar een belangrijk onderdeel is lage spiermassa of sarcopenie. Sarcopenie werd in

hoofdstuk 4 en **hoofdstuk 5** gedefinieerd als lage spiermassa, volume of dichtheid van de psoas-spier op het niveau van de derde lumbale wervel. Bij twee grote cohorten patiënten die hepato-pancreato-biliaire of colorectale chirurgie ondergingen werd de invloed van sarcopenie onderzocht. Bij multivariabele analyse waren onafhankelijke risicofactoren voor 1-jaarsmortaliteit: toenemende leeftijd, preoperatieve bloedarmoede en preoperatieve lage spiermassa. Met behulp van deze variabelen werden twee preoperatieve scores samengesteld.

Prognose na chirurgie

In deel II werd de prognose na de operatie besproken. Prognostische en voorspellende modellen voor BTC werden beoordeeld. In **hoofdstuk 6** werd gepoogd een overzicht van de huidige literatuur te geven, op het gebied van prognostische modellen in de hepato-pancreato-biliaire chirurgie. Tekortkomingen van modellen die momenteel in gebruik zijn werden besproken. De conclusie uit dit literatuuroverzicht was dat de meest gebruikte modellen zijn gebouwd met behulp van gedateerde methoden. Deze modellen moeten bijgewerkt en vernieuwd worden, met behulp van validatie- en verbeterstudies. In **hoofdstuk 7** werden de in hoofdstuk 10 gevonden modellen voor intrahepatisch cholangiocarcinoom (ICC) toegepast op een groot internationaal cohort. Hoewel de risicofactoren die in de modellen waren opgenomen significant verband hielden met algehele en ziektevrije overleving, kon onderscheid tussen een goede en slechte prognose onvoldoende gemaakt worden. Alleen het Wang-nomogram had een redelijke discriminatie. Meer onderzoek naar de optimalisatie van prognostische ICC-modellen is noodzakelijk. Daarbij zou in het bijzonder gezocht moeten worden naar prognostische biomarkers.

In **hoofdstuk 8** werd het concept van *conditional survival* (CS) toegepast op een groot cohort van patiënten met PHC. CS is gebaseerd op het gegeven dat de tijd die iemand reeds overleefd heeft na operatie de belangrijkste voorspeller is voor de overleving. Uit deze studie bleek dat de kans op een additioneel jaar overleving zou kunnen toenemen tot 90 % na zeven jaar overleefd te hebben. In de aanwezigheid van bepaalde risicofactoren bleek dit effect nog meer uitgesproken te zijn. De schattingen van CS in dit hoofdstuk kunnen worden gebruikt bij de keuze van verdere behandeling van patiënten met bijvoorbeeld een recidief.

Net als bij PHC patiënten, is de overleving na diagnose van galblaascarcinoom (GBC) beperkt. In **hoofdstuk 9** werd *conditional survival* voor patiënten geopereerd voor GBC ingeschat. CS verbeterde in de tijd nadat de operatie was ondergaan, wat resulteerde in een 90% kans om nog een jaar te overleven nadat

7 jaar verstreken is. Net als bij PHC was dit effect het meest uitgesproken bij patiënten in subgroepen die gekenmerkt werden door hoge risicofactoren en slechte overleving. De gemaakte schattingen van CS kunnen ook hier worden gebruikt bij de keuze voor verdere behandeling van patiënten met bijvoorbeeld een recidief.

Ten slotte werd in **hoofdstuk 10** de prognostische invloed van routinematige verwijdering van de ductus choledochus bij patiënten met GBC besproken. Hoewel reeds is aangetoond dat re-resectie bij toevallige vondst van GBC de overleving bevordert, blijft de optimale mate van re-resectie onbekend en is de rol van routinematige excisie van de ductus choledochus controversieel. Uit de data van een groot Amerikaans cohort werd in deze studie de conclusie getrokken dat het routinematige excisie van de ductus choledochus alleen dient te geschieden indien radicale resectie anders niet mogelijk is.

Nieuwe behandelingen

In deel III werden niet-chirurgische technieken en hun werkzaamheid in BTC verder onderzocht. In **hoofdstuk 11** is een algemeen overzicht van behandelingen, predictie en prognosticatie van ICC gegeven. Sinds enkele jaren worden nieuwe stageringssystemen en modellen ontwikkeld, maar op dit moment is het meest gebruikte stageringssysteem de Amerikaanse Joint Committee on Cancer TNM-staging. De hoeksteen van de behandeling voor ICC blijft een operatie, maar nieuwe technieken worden onderzocht. Deze nieuwe technieken omvatten de chemopomp, transarteriële chemo-embolisatie en Y-90 radio-embolisatie. De conclusie van dit literatuuroverzicht was dat er nog steeds onderzoek nodig is voor gepersonaliseerde behandeling van ICC-patiënten. Toekomstige studies zouden zich moeten richten op voorspellende biomarkers voor de respons op behandeling en prognose na behandeling.

In **hoofdstuk 12** werd het effect van preoperatieve chemotherapie (pCT) bij ICC-patiënten onderzocht. Ondanks het succesvolle gebruik van preoperatieve chemotherapie om tumoren te verkleinen en micrometastasen te behandelen bij andere maligniteiten, is het gebruik van pCT bij patiënten met ICC niet goed onderzocht. In deze retrospectieve analyse werd geen verschil tussen ziektevrije- en algehele overleving waargenomen, ondanks het feit dat pCT-patiënten aanzienlijk slechtere ziektekenmerken hadden. Nadat er gecorrigeerd was voor het verschil tussen patiënten, had de groep die pCT kreeg een overlevingsvoordeel van 17 maanden, hoewel dit verschil niet significant was. Verder prospectief onderzoek is

nodig om de rol van pCT beter te definiëren en de patiënten te identificeren die het meeste baat hebben bij gebruik van pCT.

Zoals eerder genoemd, worden veel patiënten met BTC gediagnosticeerd wanneer curatieve resectie niet meer haalbaar is. In andere gevallen blijkt dat patiënten irresectabele of metastatische ziekte hebben op het moment van operatie. Behandeling zonder operatie wordt meestal aanbevolen bij patiënten met een levensverwachting van minder dan 6 maanden. In **hoofdstuk 13** werden de uitkomsten en effecten van palliatieve resectie voor GBC en PHC in een groot Amerikaanse cohort onderzocht. Mediane overleving onder patiënten die een palliatieve resectie ondergingen en onder patiënten bij wie resectie werd afgebroken, was 8 maanden. Deze overleving was dus niet hoger na palliatieve resectie. Wel kreeg een hoger percentage van patiënten die palliatieve resectie ondergingen een complicatie.

Een veelbelovende nieuwe techniek voor patiënten met een irresectabele kanker, is Y-90 radio-embolisatie (Y-90). Deze techniek is gebaseerd op de toediening van kralen gevuld met een radioactief yttriumisotoop in de leverslagader die het tumorgebied verzorgt. Verschillende kleine studies hebben aangetoond dat Y-90 goede uitkomsten geeft bij patiënten die verder gezond zijn. Y-90 was in deze patiëntengroep geassocieerd met een betere overleving. In **hoofdstuk 14** is een samenvatting gegeven van de ervaring van vijf grote centra die gebruik maken van deze techniek. Een gemiddelde overleving van 10 maanden werd gezien na behandeling met Y-90, met een overleving na diagnose van 29 maanden. Dit is langer dan de overleving van vergelijkbare patiënten die geen Y-90 behandeling ondergaan, maar prospectief onderzoek en klinische trials zijn noodzakelijk om definitieve uitspraken te kunnen doen.

List of Publications

Amini N, Margonis GA, **Buttner S**, Besharati S, Kim Y, Gani F, Sobhani F, Kamel IR, Pawlik TM. Liver regeneration after major liver hepatectomy: Impact of body mass index. Surgery. 2016 Jul;160(1):81-91.

Antoniou E, Andreatos N, Margonis GA, Papalois A, Wang J, Damaskos C, Garmpis N, **Buettner S**, Deshwar A, Pappas V, Weiss MJ, Pawlik TM, Pikoulis E. Systemic treatment and primary tumor location in patients with metastatic colorectal cancer. J Buon. 2017 Nov-Dec;22(6):1447-56.

Bagante F, Tran T, Spolverato G, Ruzzenente A, **Buttner S**, Ethun CG, Groot Koerkamp B, Conci S, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Vitiello G, JN IJ, Maithel SK, Poultsides G, Guglielmi A, Pawlik TM. Perihilar Cholangiocarcinoma: Number of Nodes Examined and Optimal Lymph Node Prognostic Scheme. J Am Coll Surg. 2016 May;222(5):750-9 e2.

Barbon C, Margonis GA, Andreatos N, Rezaee N, Sasaki K, **Buettner S**, Damaskos C, Pawlik TM, He J, Wolfgang CL, Weiss MJ. Colorectal Liver Metastases: Does the Future of Precision Medicine Lie in Genetic Testing? J Gastrointest Surg. 2018 Apr 11.

Beal EW, Lyon E, Kearney J, Wei L, Ethun CG, Black SM, Dillhoff M, Salem A, Weber SM, Tran TB, Poultsides G, Shenoy R, Hatzaras I, Krasnick B, Fields RC, **Buttner S**, Scoggins CR, Martin RCG, Isom CA, Idrees K, Mogal HD, Shen P, Maithel SK, Pawlik TM, Schmidt CR. Evaluating the American College of Surgeons National Surgical Quality Improvement project risk calculator: results from the U.S. Extrahepatic Biliary Malignancy Consortium. HPB (Oxford). 2017 Dec;19(12):1104-11.

Beal EW, Wei L, Ethun CG, Black SM, Dillhoff M, Salem A, Weber SM, Tran T, Poultsides G, Son AY, Hatzaras I, Jin L, Fields RC, **Buettner S**, Pawlik TM, Scoggins C, Martin RC, Isom CA, Idrees K, Mogal HD, Shen P, Maithel SK, Schmidt CR. Elevated NLR in gallbladder cancer and cholangiocarcinoma - making bad cancers even worse: results from the US Extrahepatic Biliary Malignancy Consortium. HPB (Oxford). 2016 Nov;18(11):950-7.

Buettner S, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Weiss M, Fields RC, Krasnick B, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Koerkamp BG, Maithel SK, Pawlik TM. Surgical Site Infection Is Associated with Tumor Recurrence in Patients with Extrahepatic Biliary Malignancies. J Gastrointest Surg. 2017 Nov;21(11):1813-20.

Buettner S, Galjart B, van Vugt JLA, Bagante F, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Gamblin TC, Maithel SK, Pulitano C, Margonis GA, Weiss M, Bauer TW, Shen F, Poultsides GA, Marsh JW, JNM IJ, Groot Koerkamp B, Pawlik TM. Performance of prognostic scores and staging systems in predicting long-term survival outcomes after surgery for intrahepatic cholangiocarcinoma. J Surg Oncol. 2017 Dec;116(8):1085-95.

Buettner S, Gani F, Amini N, Spolverato G, Kim Y, Kilic A, Wagner D, Pawlik TM. The relative effect of hospital and surgeon volume on failure to rescue among patients undergoing liver resection for cancer. Surgery. 2016 Apr;159(4):1004-12.

Buettner S, Koerkamp BG, Ejaz A, Buisman FE, Kim Y, Margonis GA, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Gamblin TC, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Marsh JW, JN IJ, Pawlik TM. The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients-A multi-institutional analysis. J Surg Oncol. 2017 Mar;115(3):312-8.

Buettner S, Margonis GA, Kim Y, Gani F, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Conditional probability of long-term survival after resection of hilar cholangiocarcinoma. HPB (Oxford). 2016 Jun;18(6):510-7.

Buettner S, Margonis GA, Kim Y, Gani F, Ethun CG, Poultsides GA, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Changing Odds of Survival Over Time among Patients Undergoing Surgical Resection of Gallbladder Carcinoma. Ann Surg Oncol. 2016 Dec;23(13):4401-9.

Buettner S, van Vugt JL, Gani F, Groot Koerkamp B, Margonis GA, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Guglielmi A, JN IJ, Pawlik TM. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. J Gastrointest Surg. 2016 Oct;20(10):1716-24.

Buettner S, van Vugt JL, JN IJzermans, Groot Koerkamp B. Intrahepatic cholangiocarcinoma: current perspectives. Onco Targets Ther. 2017;10:1131-42.

Buettner S, van Vugt JLA, Gaspersz MP, Coelen RJS, Roos E, Labeur TA, Margonis GA, Ethun CG, Maithel SK, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, JNM IJ, van Gulik TM, Pawlik TM, Groot Koerkamp B. Survival after resection of perihilar cholangiocarcinoma in patients with lymph node metastases. HPB (Oxford). 2017 Aug;19(8):735-40.

Buettner S, Wagner D, Kim Y, Margonis GA, Makary MA, Wilson A, Sasaki K, Amini N, Gani F, Pawlik TM. Inclusion of Sarcopenia Outperforms the Modified Frailty Index in Predicting 1-Year Mortality among 1,326 Patients Undergoing Gastrointestinal Surgery for a Malignant Indication. J Am Coll Surg. 2016 Apr;222(4):397-407 e2.

Buettner S*, Wilson A*, Margonis GA, Gani F, Ethun CG, Poultsides GA, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Assessing Trends in Palliative Surgery for Extrahepatic Biliary Malignancies: A 15-Year Multicenter Study. J Gastrointest Surg. 2016 Aug;20(8):1444-52.

Buttner S*, Lalmahomed ZS*, Coebergh van den Braak RR, Hansen BE, Coene PP, Dekker JW, Zimmerman DD, Tetteroo GW, Vles WJ, Vrijland WW, Fleischeuer RE, van der Wurff AA, Kliffen M, Torenbeek R, Meijers JH, Doukas M, JN IJ. Completeness of pathology reports in stage II colorectal cancer. Acta Chir Belg. 2017 Jun;117(3):181-7.

Buettner S*, Margonis GA*, Andreatos N, Sasaki K, Ijzermans JNM, van Vugt JLA, Pawlik TM, Choti MA, Cameron JL, He J, Wolfgang CL, Weiss MJ. Anatomical Resections Improve Disease-free Survival in Patients With KRAS-mutated Colorectal Liver Metastases. Ann Surg. 2017 Oct;266(4):641-9.

Buettner S*, Margonis GA*, Sasaki K, Kim Y, Ratti F, Russolillo N, Ferrero A, Berger N, Gamblin TC, Poultsides G, Tran T, Postlewait LM, Maithel S, Michaels AD, Bauer TW, Marques H, Barroso E, Aldrighetti L, Pawlik TM. The role of liver-directed surgery in patients with hepatic metastasis from primary breast cancer: a multi-institutional analysis. HPB (Oxford). 2016 Aug;18(8):700-5.

Buettner S*, Margonis GA*, Andreatos N, Sasaki K, Pour MZ, Deshwar A, Wang J, Ghasebeh MA, Damaskos C, Rezaee N, Pawlik TM, Wolfgang CL, Kamel IR, Weiss MJ. Preoperative bevacizumab and volumetric recovery after resection of colorectal liver metastases. J Surg Oncol. 2017 Dec;116(8):1150-8.

Coebergh van den Braak RRJ, Lalmahomed ZS, **Buttner S**, Hansen BE, Ijzermans JNM, Group MS. Nonphysician Clinicians in the Follow-Up of Resected Patients with Colorectal Cancer. Dig Dis. 2018;36(1):17-25.

Ethun CG, Postlewait LM, Le N, Pawlik TM, **Buettner S**, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Jin LX, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Kooby DA, Maithel SK. Association of Optimal Time Interval to Re-resection for Incidental Gallbladder Cancer With Overall Survival: A Multi-Institution Analysis From the US Extrahepatic Biliary Malignancy Consortium. JAMA Surg. 2017 Feb 1;152(2):143-9.

Ethun CG, Postlewait LM, Le N, Pawlik TM, **Buettner S**, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Jin LX, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Merchant N, Cardona K, Maithel SK. A Novel Pathology-Based Preoperative Risk Score to Predict Locoregional Residual and Distant Disease and Survival for Incidental Gallbladder Cancer: A 10-Institution Study from the U.S. Extrahepatic Biliary Malignancy Consortium. Ann Surg Oncol. 2017 May;24(5):1343-50.

Gani F, **Buettner S**, Margonis GA, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik

TM. Assessing the impact of common bile duct resection in the surgical management of gallbladder cancer. J Surg Oncol. 2016 Aug;114(2):176-80.

Gani F, **Buettner S**, Margonis GA, Sasaki K, Wagner D, Kim Y, Hundt J, Kamel IR, Pawlik TM. Sarcopenia predicts costs among patients undergoing major abdominal operations. Surgery. 2016 Nov;160(5):1162-71.

Gani F, Cerullo M, Amini N, **Buettner S**, Margonis GA, Sasaki K, Kim Y, Pawlik TM. Frailty as a Risk Predictor of Morbidity and Mortality Following Liver Surgery. J Gastrointest Surg. 2017 May;21(5):822-30.

Gaspersz MP, **Buettner S**, van Vugt JLA, Roos E, Coelen RJS, Vugts J, Belt EJ, de Jonge J, Polak WG, Willemssen F, van Gulik TM, JNM IJ, Groot Koerkamp B. Conditional survival in patients with unresectable perihilar cholangiocarcinoma. HPB (Oxford). 2017 Nov;19(11):966-71.

Kim Y, Amini N, Gani F, Wagner D, Johnson DJ, Scott A, Ejaz A, Margonis GA, Xu L, **Buettner S**, Wasey JO, Goel R, Frank SM, Pawlik TM. Age of Transfused Blood Impacts Perioperative Outcomes Among Patients Who Undergo Major Gastrointestinal Surgery. Ann Surg. 2017 Jan;265(1):103-10.

Kim Y, Gani F, Spolverato G, Ejaz A, Xu L, **Buettner S**, Wagner D, Wasey JO, Frank SM, Pawlik TM. Variation in crystalloid administration: an analysis of 6248 patients undergoing major elective surgery. J Surg Res. 2016 Jun 15;203(2):368-77.

Kim Y, Winner M, Page A, Tisnado DM, Martinez KA, **Buettner S**, Ejaz A, Spolverato G, Morss Dy SE, Pawlik TM. Patient perceptions regarding the likelihood of cure after surgical resection of lung and colorectal cancer. Cancer. 2015 Oct 15;121(20):3564-73.

Klaphake S, **Buettner S**, Ultee KH, van Rijn MJ, Hoeks SE, Verhagen HJ. Combination of endovascular revascularization and supervised exercise therapy for intermittent claudication: a systematic review and meta-analysis. J Cardiovasc Surg (Torino). 2018 Apr;59(2):150-7.

Lafaro K, **Buettner S**, Maqsood H, Wagner D, Bagante F, Spolverato G, Xu L, Kamel I, Pawlik TM. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? J Gastrointest Surg. 2015 Nov;19(11):2079-92.

Margonis GA, Amini N, **Buettner S**, Besharati S, Kim Y, Sobhani F, Kamel IR, Pawlik TM. Impact of early postoperative platelet count on volumetric liver gain and perioperative outcomes after major liver resection. Br J Surg. 2016 Jun;103(7):899-907.

Margonis GA, Amini N, **Buettner S**, Ghasebeh MA, Besharati S, Kim Y, Gani F, Sobhani F, Samaha M, Kamel IR, Pawlik TM. Impact of Perioperative Phosphorus and Glucose Levels on Liver Regeneration and Long-term Outcomes after Major Liver Resection. J Gastrointest Surg. 2016 Jul;20(7):1305-16.

Margonis GA, Amini N, Sasaki K, Kim Y, Merath K, **Buettner S**, Pikoulis E, Andreatos N, Wagner D, Antoniou E, Pawlik TM. Perioperative Hyperglycemia and Postoperative Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. J Gastrointest Surg. 2017 Feb;21(2):228-37.

Margonis GA, **Buettner S**, Andreatos N, Wagner D, Sasaki K, Barbon C, Beer A, Kamphues C, Loes IM, He J, Pawlik TM, Kaczirek K, Poultsides G, Lonning PE, Cameron JL, Mischinger HJ, Aucejo FN, Kreis ME, Wolfgang CL, Weiss MJ. Prognostic Factors Change Over Time After Hepatectomy for Colorectal Liver Metastases: A Multi-institutional, International Analysis of 1099 Patients. Ann Surg. 2018 Jan 18.

Margonis GA, Gani F, **Buettner S**, Amini N, Sasaki K, Andreatos N, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium. HPB (Oxford). 2016 Nov;18(11):872-8.

Margonis GA, Kim Y, Samaha M, **Buettner S**, Sasaki K, Gani F, Amini N, Pawlik TM. Blood loss and outcomes after resection of colorectal liver metastases. J Surg Res. 2016 May 15;202(2):473-80.

Margonis GA, Kim Y, Sasaki K, Samaha M, **Buettner S**, Amini N, Pawlik TM. Activating KRAS mutation is prognostic only among patients who receive preoperative chemotherapy before resection of colorectal liver metastases. J Surg Oncol. 2016 Sep;114(3):361-7.

Margonis GA, Sasaki K, Andreatos N, Kim Y, Merath K, Wagner D, Wilson A, **Buettner S**, Amini N, Antoniou E, Pawlik TM. KRAS Mutation Status Dictates Optimal Surgical Margin Width in Patients Undergoing Resection of Colorectal Liver Metastases. Ann Surg Oncol. 2017 Jan;24(1):264-71.

Margonis GA, Sasaki K, Andreatos N, Nishioka Y, Sugawara T, Amini N, **Buettner S**, Hashimoto M, Shindoh J, Pawlik TM. Prognostic impact of complications after resection of early stage hepatocellular carcinoma. J Surg Oncol. 2017 Jun;115(7):791-804.

Margonis GA, Sasaki K, Andreatos N, Pour MZ, Shao N, Ghasebeh MA, **Buettner S**, Antoniou E, Wolfgang CL, Weiss M, Kamel IR, Pawlik TM. Increased kinetic growth rate during late phase liver regeneration impacts the risk of tumor recurrence after colorectal liver metastases resection. HPB (Oxford). 2017 Sep;19(9):808-17.

Margonis GA, Sasaki K, Gholami S, Kim Y, Andreatos N, Rezaee N, Deshwar A, **Buettner S**, Allen PJ, Kingham TP, Pawlik TM, He J, Cameron JL, Jarnagin WR, Wolfgang CL, D'Angelica MI, Weiss MJ. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. Br J Surg. 2018 Apr 25.

Margonis GA, Sasaki K, Kim Y, Samaha M, **Buettner S**, Amini N, Antoniou E, Pawlik TM. Tumor Biology Rather Than Surgical Technique Dictates Prognosis in Colorectal Cancer Liver Metastases. J Gastrointest Surg. 2016 Nov;20(11):1821-9.

Margonis GA, Sergentanis TN, Ntanasis-Stathopoulos I, Andreatos N, Tzanninis IG, Sasaki K, Psaltopoulou T, Wang J, **Buettner S**, Papalois Alpha E, He J, Wolfgang CL, Pawlik TM, Weiss MJ. Impact of Surgical Margin Width on Recurrence and Overall Survival Following R0 Hepatic Resection of Colorectal Metastases: A Systematic Review and Meta-analysis. Ann Surg. 2017 Nov 16.

Postlewait LM, Ethun CG, Le N, Pawlik TM, **Buettner S**, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RCG, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Vitiello G, Cardona K, Maithel SK. Proposal for a new T-stage classification system for distal cholangiocarcinoma: a 10-institution study from the U.S. Extrahepatic Biliary Malignancy Consortium. HPB (Oxford). 2016 Oct;18(10):793-9.

Sasaki K, Margonis GA, Andreatos N, Zhang XF, **Buettner S**, Wang J, Deshwar A, He J, Wolfgang CL, Weiss M, Pawlik TM. The prognostic utility of the "Tumor Burden Score" based on preoperative radiographic features of colorectal liver metastases. J Surg Oncol. 2017 Sep;116(4):515-23.

Sasaki K, Margonis GA, Wilson A, Kim Y, **Buettner S**, Andreatos N, Gani F, Amini N, Spolverato G, Pawlik TM. Prognostic Implication of KRAS Status after Hepatectomy for Colorectal Liver Metastases Varies According to Primary Colorectal Tumor Location. Ann Surg Oncol. 2016 Oct;23(11):3736-43.

Spolverato G, Bagante F, Wagner D, **Buettner S**, Gupta R, Kim Y, Maqsood H, Pawlik TM. Quality of life after treatment of neuroendocrine liver metastasis. J Surg Res. 2015 Sep;198(1):155-64.

Tran TB, Norton JA, Ethun CG, Pawlik TM, **Buettner S**, Schmidt C, Beal EW, Hawkins WG, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Idrees K, Isom CA, Hatzaras I, Shenoy R, Maithel SK, Poultsides GA. Gallbladder Cancer Presenting with Jaundice: Uniformly Fatal or Still Potentially Curable? J Gastrointest Surg. 2017 Aug;21(8):1245-53.

van Vugt JLA, Alferink LJM, **Buettner S**, Gaspersz MP, Bot D, Darwish Murad S, Feshtali S, van Ooijen PMA, Polak WG, Porte RJ, van Hoek B, van den Berg AP, Metselaar HJ, JNM IJ. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. J Hepatol. 2017 Dec 6.

van Vugt JLA, Alferink LJM, **Buettner S**, Metselaar HJ, JNM IJ. Reply to: "May sarcopenia and/or hepatic encephalopathy improve the predictivity of model for end-stage liver disease?" and "Has the time come for using MELD-Sarcopenia score?". J Hepatol. 2018 Apr 3.

van Vugt JLA, **Buettner S**, Alferink LJM, Bossche N, de Bruin RWF, Darwish Murad S, Polak WG, Metselaar HJ, JNM IJ. Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation-a retrospective study. Transpl Int. 2018 Feb;31(2):165-74.

van Vugt JLA, **Buettner S**, Levolger S, Coebergh van den Braak RRJ, Suker M, Gaspersz MP, de Bruin RWF, Verhoef C, van Eijck CHC, Bossche N, Groot Koerkamp B, JNM IJ. Low skeletal muscle mass is associated with increased hospital expenditure in patients undergoing cancer surgery of the alimentary tract. PLoS One. 2017;12(10):e0186547.

van Vugt JLA, Gaspersz MP, Vugts J, **Buettner S**, Levolger S, de Bruin RWF, Polak WG, de Jonge J, Willemssen F, Groot Koerkamp B, JNM IJ. Low Skeletal Muscle Density Is Associated with Early Death in Patients with Perihilar Cholangiocarcinoma Regardless of Subsequent Treatment. Dig Surg. 2018 Feb 16.

Wagner D, **Buttner S**, Kim Y, Gani F, Xu L, Margonis GA, Amini N, Kamel IR, Pawlik TM. Clinical and morphometric parameters of frailty for prediction of mortality following hepatopancreaticobiliary surgery in the elderly. Br J Surg. 2016 Jan;103(2):e83-92.

Wagner D, DeMarco MM, Amini N, **Buttner S**, Segev D, Gani F, Pawlik TM. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg. 2016 Jan 27;8(1):27-40.

Wang J, Margonis GA, Amini N, Andreatos N, Yuan C, Damaskos C, Antoniou E, Garmpis N, **Buettner S**, Barbon C, Deshwar A, He J, Burkhart R, Pawlik TM, Wolfgang CL, Weiss MJ. The Prognostic Value of Varying Definitions of Positive Resection Margin in Patients with Colorectal Cancer Liver Metastases. J Gastrointest Surg. 2018 Apr 9.

Zhang XF, Beal EW, Chakedis J, Chen Q, Lv Y, Ethun CG, Salem A, Weber SM, Tran T, Poultsides G, Son AY, Hatzaras I, Jin L, Fields RC, **Buettner S**, Scoggins C, Martin RCG, Isom CA, Idrees K, Mogal HD, Shen P, Maithel SK, Schmidt CR, Pawlik TM. Defining Early Recurrence of Hilar Cholangiocarcinoma After Curative-intent Surgery: A Multi-institutional Study from the US Extrahepatic Biliary Malignancy Consortium. World J Surg. 2018 Feb 5.

Zheng J, Chou JF, Gonen M, Vachharajani N, Chapman WC, Majella Doyle MB, Turcotte S, Vandenbroucke-Menu F, Lapointe R, **Buettner S**, Groot Koerkamp B, Ijzermans JNM, Chan CY, Goh BKP, Teo JY, Kam JH, Jeyaraj PR, Cheow PC, Chung AYF, Chow PKH, Ooi L, Balachandran VP, Kingham TP, Allen PJ, D'Angelica MI, DeMatteo RP, Jarnagin WR, Lee SY. Prediction of Hepatocellular Carcinoma Recurrence Beyond Milan Criteria After Resection: Validation of a Clinical Risk Score in an International Cohort. Ann Surg. 2017 Oct;266(4):693-701.

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PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: S. Büttner	Promotor: prof.dr. J.N.M. IJzermans, prof.dr. T.M. Pawlik
Erasmus MC Department: Surgery	Supervisors: dr. B. Groot Koerkamp
PhD period: 2015-2018	Date of thesis defence: 20-06-2018

PhD training

	Year	Workload (ECTS)
Courses		
- BROK (Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers)	2017	0.9
- Research integrity	2017	0.3
Presentations	**Year**	**Workload (ECTS)**
- American College of Surgeons Annual Meeting, Chicago, IL, United States	2015	1.0
- ASCO GI, San Francisco, CA, United States	2016	1.0
- SSO, Boston, MA, United States	2016	1.0
- IHPBA, Sao Paulo, Brazil	2016	4.0
- Nederlandse Vereniging voor de Gastroenterologie Najaarsdag	2016	2.0
- 9th International Conference on Cachexia, Sarcopenia and Muscle Wasting, Berlin, Germany	2016	1.0
- Americas Hepato-Pancreato-Biliary Association (AHPBA) Annual Meeting, Miami, USA	2017	2.0
- 52nd Congress of the European Society for Surgical Research (ESSR), Amsterdam, the Netherlands	2017	2.0
Conferences		
- National conferences	2015-2017	6.0
- International conferences	2015-2017	5.0
Other	**Year**	**Workload (ECTS)**
- Supervising students	2016-2017	1.5
- Reviewer for scientific journals (Acta Chirurgica Belgica, HPB, Medicine)	2015-2017	5.0

Curriculum Vitae

Stefan Büttner werd op 22 november 1992 geboren te Zwijndrecht. Na het behalen van zijn diploma aan het Johan de Witt-gymnasium te Dordrecht en het volgen van Junior Med School aan de Erasmus Universiteit te Rotterdam, begon hij september 2011 eveneens in Rotterdam aan zijn studie Geneeskunde. In het kader van zijn Clinical Research Master verrichtte hij gedurende 2015 onderzoek aan de Johns Hopkins Universiteit te Baltimore, met als onderwerp prognostische modellen voor cholangiocarcinoom. Dit onderzoek mondde uit in een aantal peer-reviewed publicaties over dit onderwerp, waarop hij het aanbod kreeg het onderzoek voort te zetten aan de Erasmus Universiteit. Dit alles heeft geleid tot het boek dat nu voor u ligt. Stefan zal zich de komende twee jaar richten op zijn coschappen.