Clinical and pathological prognostic factors in colon and rectal cancer

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CLINICAL and PATHOLOGICAL PROGNOSTIC FACTORS in COLON and RECTAL CANCER

L.G.J Leijssen

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Lisa Godelieve Josephine Leijssen

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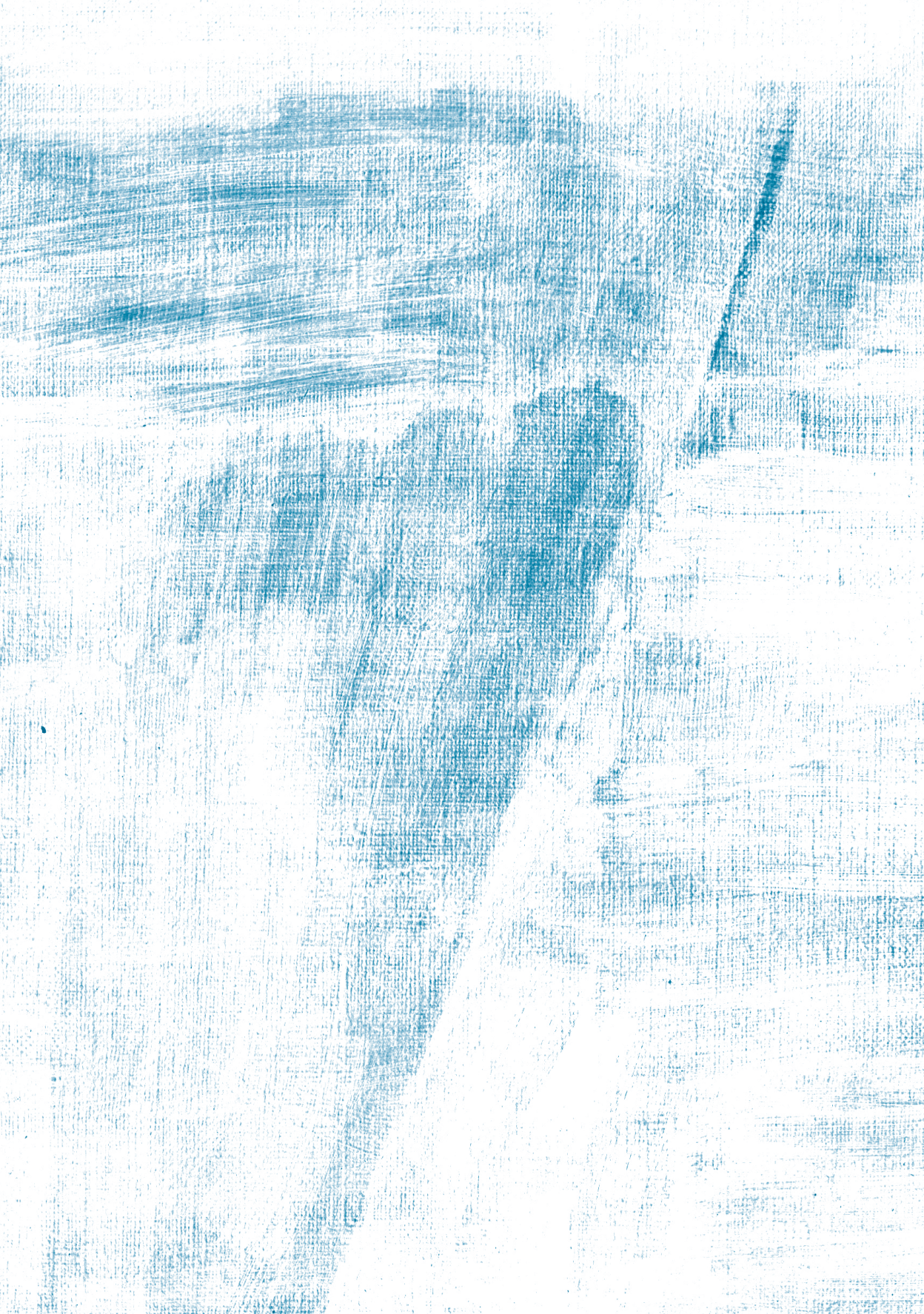


GENERAL INTRODUCTION and OUTLINE of this THESIS

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Colorectal cancer (CRC) has a profound impact on public health. In 2018, over 1.8 million new cases of CRC were diagnosed worldwide with an estimated of almost 862,000 deaths.[1] Its burden is expected to rise 70% to more than 3 million new cases and 1.5 million related deaths by 2040. This increase will be caused by rapidly transitioning countries, whose populace adopt a Western lifestyle and subsequently develop potential consequences including obesity, physical inactivity, high red meat consumption and smoking.[2-3] At the same time, there is a declining trend of CRC incidence and mortality in more developed countries due to the adoption of formalized screening programs, removal of precancerous lesions and improvements in treatment.[4]

The current standard for clinical prediction of survival and recurrence in CRC is principally based on pathological staging per the Tumor-Node-Metastasis (TNM) classification, as defined by the American Joint Committee on Cancer (AJCC).[5] This classification system focuses on depth of invasion of the bowel wall (T), extent of lymph node involvement (N), and presence of distant sites of disease (M). At an early stage, the estimated 5-year survival is 90% or greater but this percentage decreases dramatically with more advanced disease.[6] Consequently, treatment regimens vary by stage. Despite increasing interest in using innovative less invasive procedures for early stage CRC and significant improvements in systemic therapy for patients with metastatic disease, surgical therapy remains the gold standard for all stages in colorectal cancer.[7-10]

In addition to stage of disease, tumor location has an impact on treatment management. Colorectal cancer is often considered one disease, though distinct differences exist between colon and rectal tumors including tumor biology, anatomy and epidemiology.[11-12] Consequently, the recommended therapy for primary colon and rectal cancer differ considerably. This difference is most apparent in stage II (lymph node negative) and stage III (lymph node positive) disease. Specific surgical resection (total mesorectal excision - TME) preceded by radiation or chemotherapy is the current standard of care for locally advanced rectal cancer.[13-14] The role of postoperative treatment in rectal cancer to reduce local recurrence remains controversial if a high-quality TME can be assured and is therefore only advocated in patients with unexpected adverse histopathological outcomes.[15] The treatment algorithm is different in colon cancer. While the efficacy of preoperative treatment is not elucidated yet, the prognostic impact of postoperative chemotherapy is well established in stage III disease and suggested in high-risk cases with node-negative disease.[16-18]

OUTLINE OF THIS THESIS

The scope of this thesis will be to address issues related to the assessment and treatment of patients who have been diagnosed with and surgically treated for colon and rectal cancer. Issues related to differences between colon and rectal cancer (part I), problems encountered perioperatively (part II) and the prognostic impact of histopathological outcomes (part III) will be addressed separately. In the latter two sections, the focus will be solely on colon

cancer, due to aforementioned differences between colon and rectal cancer.

PART I: COLORECTAL CANCER: ONE DISEASE, TWO ENTITIES

A distinction between left and right sided colon cancer was first mentioned by Bufill et al. in the early '90s.[19] Subsequent research elaborated on this topic and demonstrated differences in epidemiology, tumor biology and behavior which consequently have led to modifications in treatment patterns and a more targeted disease management in colon and rectal cancer separately.[7-10]

Part I of this thesis discusses the importance of tumor location, specifically studying the effect of tumor location on different colonoscopy indications and investigating long-term outcomes in early stage as well as metastatic disease.

Chapter 1 starts with the baseline presentation and evaluates the impact on clinical outcomes in patients diagnosed with CRC after different indications for a colonoscopy. Screening for colorectal cancer in general is recommended by the US Preventive Services Task Force (USPSTF), starting at an age of 50 years and continuing until age 75.[20] Although rates of population screening increased over the last decade, about one-third of all eligible adults in the USA have never been screened for CRC.[21-22] In this chapter, patients who underwent primary screening were compared to patients who got diagnosed after developing symptoms as well to patients who underwent surveillance. Additionally, differences in colon and rectal cancer were evaluated.

The overall 5-year survival rate for patients diagnosed with CRC between 2009 and 2015 was 66.2%.[6] This rate is dependent upon many factors, of which stage of disease remains one of the most important in oncological outcomes. In patients with localized disease which accounts for 39% of all cases, the estimated 5-year survival reaches 90% after complete tumor resection. Nonetheless, disease recurrence occurs in 10%.[23-25] A well-known risk factor for disease recurrence in stage I disease is method of resection, particularly in rectal cancer since a local excision has become a more commonly used procedure. Other than that, however, not much is known about prognostic risk factors in stage I colon and rectal cancer. **Chapter 2** attempts to further optimize prognosis by investigating the prognostic value of several pathologic risk factors in stage I colon and rectal cancer separately.

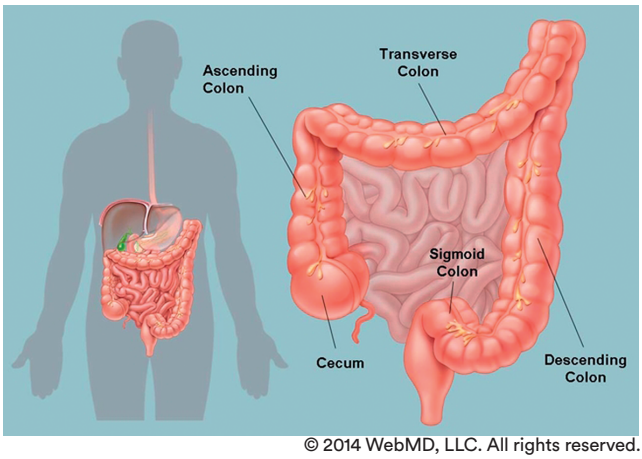
On the opposite side of the spectrum, approximately 22% of all newly diagnosed colon cancer patients and 18% of all rectal cancer patients present with synchronous distant metastasis, with a dismal 5-year survival 14%.[6] In patients with advanced disease, the ultimate intent is prolonging overall survival without sacrificing quality of life. **Chapter 3** focuses on clinicopathological risk factors for worse short-term outcomes and impaired survival. As in the previous chapters, outcomes were determined by tumor location.

PART II: SURGICAL PROCEDURES AND OUTCOMES IN COLON CANCER

Despite improvements in systemic therapy, surgery remains the mainstay for malignant CRC tumors. The second part of this thesis puts the empha-

sis on issues or difficulties occurring during colon cancer surgery.

Aside from dividing CRC into colon and rectal cancer, the colon itself can also be separated into different sections. The proximal colon comprises the ascending (extending upward on the right side) and transverse colon (situated horizontal from right to left), whereas the distal part covers the descending (left side) and sigmoid colon (final part, joining the rectum) [*Figure*]. The optimal surgical approach for cancer in the transverse colon is not standardized and depends on several factors including anatomical factors but to a great extent on surgeons' preference. A clear paucity of literature exists on the outcome of less extensive procedures for tumors in the transverse colon compared to the mostly used extended colectomies. **Chapter 4** compares surgical and oncologic outcomes in patients undergoing a transverse colectomy compared to an extended approach for mid-transverse colon cancer.



After the first report of laparoscopic colectomy in 1991 [26] this minimally invasive approach has developed from a highly complex procedure with uncertainty regarding feasibility and oncologic safety to being incorporated in routine daily practice for abdominal surgery.[27-30] The need to convert an initially intended laparoscopic approach to open surgery is associated with numerous factors, including patient and tumor-related factors (obesity, advanced stage of disease) as well as procedure-related factors (perioperative complication, (anticipated) operative difficulty, and surgeon experience). A higher rate of postoperative morbidity has been associated with conversion [31-33], though previous literature compared the outcomes of converted patients to patients who underwent a successfully completed laparoscopy. **Chapter 5** aims to find a true answer concerning the question whether conversion should be considered a complication rather than a simple change in technique by comparing outcomes between planned open surgery to converted patients.

As complete tumor resection is mandatory to achieve the optimal oncological outcome after surgery, a local multivisceral resection (LMR) is required when tumors invade adjacent organs (classified as pathologic stage T4 tumors).[34-35] Despite increased survival rates after LMR, the vast majority of patients with this stage of disease do not receive an extended surgery.[36] This may be explained by the expected morbidity resulting in reluctance of the surgeon or difficulty to make a true discernment be-

tween oncological invasion and inflammatory adhesions. **Chapter 6** explores the impact of a multivisceral resection on morbidity, disease recurrence, and survival rates and attempts to find an answer of the infrequently performed LMR for locally advanced colon cancer.

PART III: HISTOPATHOLOGICAL FEATURES AND OUTCOMES IN COLON CANCER

Although the TNM classification is considered the most important factor in predicting oncological outcomes in colon cancer, it appears that it is not the optimal staging tool for clinicians.[37] In 2009, the seventh edition of TNM staging was published [5], though this version did not provide greater accuracy in predicting prognosis in patients with colon and rectal cancer. The result of the update is predominantly a more complex classification which allows a physician's own interpretation. The most relevant issue is the possibility of over- and undertreatment when only using TNM staging for treatment allocation.[38-39] In an attempt to further optimize management of colon cancer, several clinical and histopathological outcomes have been identified as high-risk features that might help a clinician in the consideration as to whether or not to administer adjuvant chemotherapy in node-negative disease. TNM staging particularly falls short in this area and the role of adjuvant treatment in an early stage remains debatable. In order to expand on previously suggested risk features, the last part of this thesis focuses on the prognostic importance of additional histopathologic features on surgical outcomes.

Chapter 7 starts by exploring the impact of specific tumor location in colon cancer. While a distinction between colon and rectal cancer is well established, previous studies investigating prognostic disparities between different tumor locations in colon cancer are not consistent. The first chapter of the last section in this thesis focuses on this specific topic.

Vascular invasion, defined as the presence of tumor cells in large vessels within or beyond the muscularis propria, is one of the acknowledged pathologic factors which could play a role in deciding upon adjuvant therapy.[40-41] Unfortunately, this recommendation is mainly based on results from cohorts comprising both colon and rectal cancer patients. Vascular invasion, in particular extramural localized, has been well scrutinized in rectal cancer [42-44] though far less so in tumors of the colon. **Chapter 8** assesses whether the presence of large vessel invasion is a true prognostic factor in colon cancer only.

Similarly, perineural invasion (PNI), defined as the presence of cancer cells inside the perineurium of any nerve, could be another factor considered following current guidelines. However, this recommendation is also based on studies combining both colon and rectal cancer patients [45-46], notwithstanding the fact that it is to be expected that the detection rate of PNI would be higher in rectal cancer due to the anatomy and a more extensive examination of the mesorectal fat. **Chapter 9** evaluates both the prognostic and the predictive value of PNI in colon cancer.

This thesis will be concluded by summarizing our findings and discussing future perspectives.

REFERENCES

1.
Ferlay J, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953.

2.
Arnold M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691.

3.
Center MM, et al. Worldwide variations in colorectal cancer. *CA Cancer J Clin*. 2009;59(6):366-378.

4.
Edwards BK, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. 2010;116(3):544-573.

5.
Edge SB, et al. The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17(6):1471-1474.

6.
Howlader N, et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD,https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.

7.
Benson AB III, et al; National Comprehensive Cancer Network. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;*16*(7):874-901.

8.
Benson AB III, et al; National Comprehensive Cancer Network. NCCN Guidelines Insight: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw*. 2018; 16(4):359-369.

9.
Glynne-Jones R, et al; on behalf of the ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;18(suppl_4):iv22-iv40.

10.
Labianca R, et al; on behalf of the ESMO Guidelines Working Group. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.*2013;24(-suppl_6): vi64-72.

11.
Wei EK, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer.* 2004;108(3):433-442.

12.
Tamas K, et al. Rectal and colon cancer: Not just a different anatomic site. *Cancer Treat Rev.* 2015;41(8):671-679.

13.
Kapiteijn E, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345(9):638-646.

14.
Sauer R, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17): 1731-1740.

15.
Taylor FG, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol.* 2014;32(1):34-43.

16.
Quasar Collaborative Group, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet.* 2007;370 (9604):2020-2029.

17.
Schrag D, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. *J Clin Oncol.* 2002;20(19):3999-4005.

18.
Figueredo A, et al. Adjuvant therapy for completely resected stage II colon cancer. *Cochrane Database of Systematic Reviews.* 2008(3):CD005390.

19.
Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med.* 1990;113(10):779-788.

20.
US Preventive Services Task Force. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315(23):2564-2575.

21.
Shapiro JA, et al. Patterns of colorectal cancer test use, including CT colonography, in the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev*. 2012;21(6):895-904.

22.
Centers for Disease Control and Prevention (CDC). Vital signs: colorectal cancer screening test use: United States, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(44):881-888.

23.
Patel SA, et al. Early-stage rectal cancer: clinical and pathologic prognostic markers of time to local recurrence and overall survival after resection. *Dis Colon Rectum.* 2014;57(4):449-459.

24.
Bouvier AM, et al. Incidence and patterns of late recurrences in colon cancer patients. *Int J Cancer.* 2015;137(9): 2133-2138.

25.
Bertelsen CA, et al; Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol*. 2015;16(2):161-168.

26.
Jacobs M, et al. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc.* 1991;1(3):144-50.

27.
Clinical Outcomes of Surgical Therapy Study Group, Nelson H, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. 2004;350(20):2050-2059.

28.
Guillou PJ, et al; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet.* 2005;365(9472):1718-1726.

29.
Buunen M, et al; Colon cancer Laparoscopic or Open Resection Study Group (COLOR). Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol.* 2009;10(1):44-52.

30.
Allaix ME, et al. Laparoscopic versus open resection for colon cancer: 10-year outcomes of a prospective clinical trial. *Surg Endosc.* 2015;29(4):916-924.

31.
Chan AC, et al. Impact of conversion on the long-term outcome in laparoscopic resection of colorectal cancer. *Surg Endosc.* 2008;22(12):2625-2630.

32.
Li J, et al. The impact of laparoscopic converted to open colectomy on short-term and oncologic outcomes for colon cancer. *J Gastrointest Surg.* 2015;19(2): 335-343.

33.
Masoomi H, et al. Risk factors for conversion of laparoscopic colorectal surgery to open surgery: does conversion worsen outcome? *World J Surg.* 2015; 39(5):1240-1247.

34.
Mohan HM, et al. Multivisceral resection in colorectal cancer: a systematic review. *Ann Surg Oncol.* 2013; 20(9):2929-2936.

35.
Chang GJ, et al. Practice Parameters for the Management of Colon Cancer. *Dis Colon Rectum.* 2012;55(8):831-843.

36.
Govindarajan A, et al. Population based assessment of the surgical management of locally advanced colorectal cancer. *J Natl Cancer Inst.* 2006;98(20):1474-1481.

37.
Nitsche U, et al. Prediction of prognosis is not improved by the seventh and latest edition of the TNM classification for colorectal cancer in a single-center collective. *Ann Surg.* 2011;254(5):793-800.

38.
Reimers MS, et al. Biomarkers in Precision Therapy in Colorectal Cancer. *Gastroenterol Rep (Oxf).* 2013;1(3):166-183.

39.
Davies M, et al. The clinical significance of lymph node

micrometastasis in stage I and stage II colorectal cancer. *Clin Transl Oncol*. 2008;10(3):175-179.

40. Ueno H, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology.* 2004;127(2):385-394.

41. Compton CC, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*. 2000;124(7):979-994.

42. Chand M, et al. EMVI-positive stage II rectal cancer has similar clinical outcomes as stage III disease following pre-operative chemoradiotherapy. *Ann Oncol*. 2014; 25(4): 858–863.

43. Bhangu A, et al. Prognostic significance of extramural vascular invasion in T4 rectal cancer. *Colorectal Dis*. 2013;15(11):e665–671.

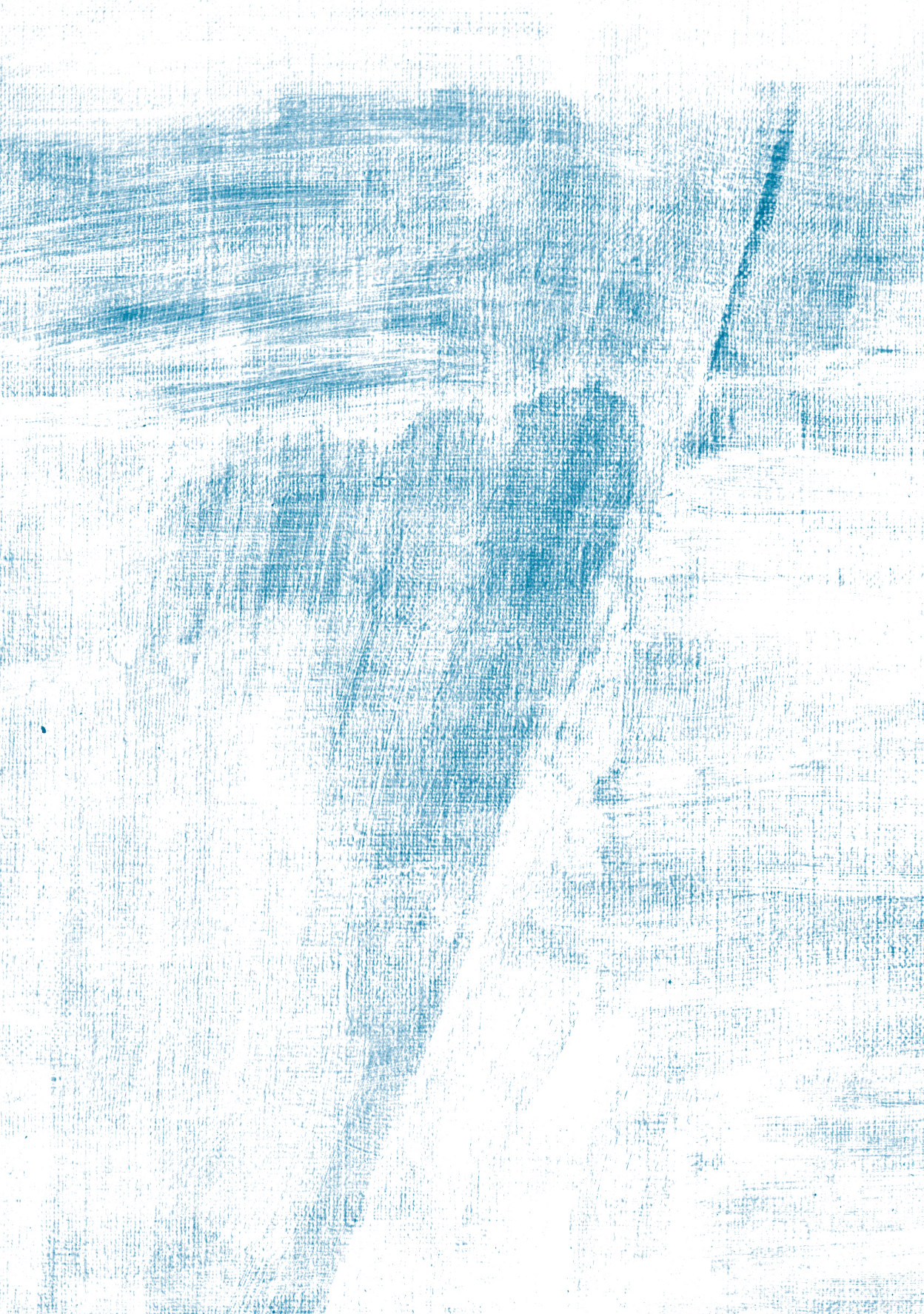
44. Smith NJ, et al. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229–236.

45. Liebig C, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol*. 2009; 27(31):5131-5137.

46. Knijn N, et al. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. *Am J Surg Pathol*. 2016;40(1):103–112.

PART I

COLORECTAL CANCER: one DISEASE, two ENTITIES



CHAPTER 1

DETRIMENTAL IMPACT OF SYMPTOM-DETECTED COLORECTAL CANCER

L.G.J. Leijssen, A.M. Dinaux, H. Kunitake, L.G. Bordeianou, D.L. Berger
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ABSTRACT

BACKGROUND

The incidence and mortality rates of colorectal cancer (CRC) have been steadily decreasing, largely attributable to screening colonoscopies that either remove precancerous lesions or identify CRC earlier. We aimed to assess the prognostic difference between colorectal cancers diagnosed by screening (SC), diagnostic (DC), or surveillance (SU) colonoscopies.

METHODS

All 1809 surgically treated patients with primary CRC diagnosed through colonoscopy at our tertiary center (2004-2015) were extracted from a prospectively maintained database. Oncologic outcomes were compared, including multivariate Cox regression.

RESULTS

DC patients presented with more advanced disease (15.0% vs. 53.2% (SC) and 55.3% (SU) AJCC I, P<0.001), subsequently leading to impaired survival and higher recurrence rates (P<0.001). After adjustment for age, ASA-score and gender, oncologic outcomes remained significantly worse after DC. Hazard ratios (HR) of overall mortality (OS) compared to DC were 0.36 for SC and 0.58 for SU (P<0.001). Adjusted HRs of disease-free survival (DFS) were 0.43 and 0.32, respectively (P<0.001). Worse outcomes in OS withstood adjustment for stage, tumor site and (neo)adjuvant treatment (SC: HR 0.46, P<0.001; SU: HR 0.73, P=0.036). The benefits of SC were particularly seen in colon cancer, stages I-II and female patients. With regards to DFS, outcomes were less profound and mainly true in early stage disease and surveillance patients.

CONCLUSIONS

This study demonstrates the enormous impact of asymptomatic screening in CRC. Patients with CRC diagnosed through screening or surveillance had a significantly better prognosis compared to patients who presented symptomatically. This emphasizes the importance of screening.

INTRODUCTION

Strong evidence exists that screening for colorectal cancer (CRC) reduces the incidence and mortality of this disease. [1-2] This benefit is mainly attributed to the identification and removal of precancerous lesions and earlier detection of CRC. When colorectal cancer is identified at an early stage, 5-year survival rates are 90% or greater but this percentage decreases dramatically with more advanced disease. [3] In line with the proven reduction of CRC incidence and mortality with screening, The US Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer starting at age 50 years and continuing until age 75. [4] Moreover, the American Cancer Society (ACS) just changed their guidelines and now recommends regular screening beginning at 45 years. [5] The decision to screen adults older than 75 years should be made individually, taking into account the patient's overall health, life expectancy, patient preference, and prior screening history. A range of test modalities are available as a screening method, including annual fecal occult blood testing (FOBT), a sigmoidoscopy or CT colonography every five years, or a colonoscopy every ten years. Although no randomized controlled trials have quantified the efficacy of colonoscopy, this procedure is nonetheless the preferred screening method [6] and the most common screening method in the United States. [7]

While CRC screening programs in Europe and Australia are based on an organized system-wide approach, screening programs in the United States have been established on an opportunistic basis. Although rates of screening increased over the last decade, about one-third of all eligible adults in the USA have never been screened for colorectal cancer. [8-9] Previous studies demonstrated that people without insurance or a regular care provider were at risk for non-screening. [6] However, among those who had never been screened, more than 75% had health insurance insinuating that actively reaching out to patients is necessary and presumably will increase the number of screened patients. [10]

Despite the widely accepted advantage of screening colonoscopies, only a few studies investigated the impact of indication on the clinical outcomes of endoscopy. Previous studies, including a previous report from our institute [11], often excluded or did not distinguish between patients with an increased risk of CRC, including those presenting with symptoms, a positive FOBT test, a positive family history of CRC, or a personal history of adenomas, CRC, or inflammatory bowel disease (IBD). It is to be expected that symptomatic patients will have less favorable outcomes compared to average-risk asymptomatic screening colonoscopies. However, it is unknown to what extent a colonoscopy is beneficial in high-risk patients and how outcomes in symptomatic patients differ from patients who are undergoing surveillance. Furthermore, data on long-term outcomes are scarce and might help in emphasizing the importance of screening instead of waiting until symptoms develop. Therefore, the aim of our study was to investigate whether oncologic outcomes differed based on indication of colonoscopy, including primary screening, follow-up after positive FOBT results or other symptoms, and surveillance.

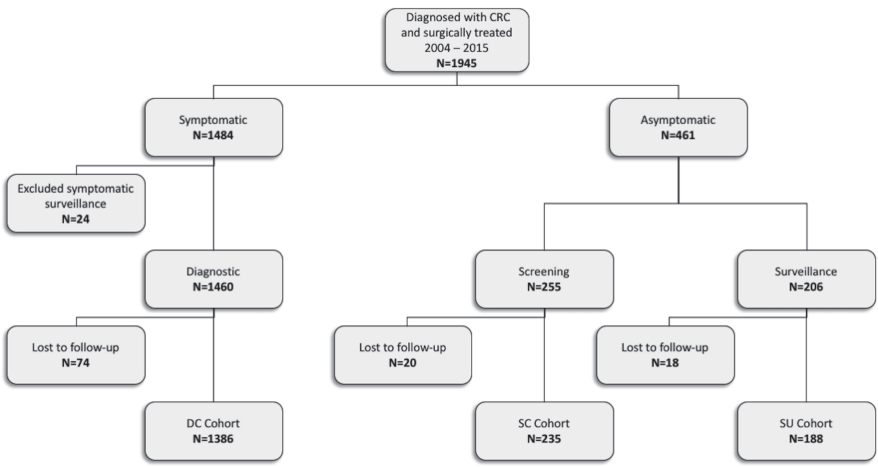
MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

This retrospective cohort includes all patients who underwent surgery for colorectal cancer between January 1, 2004 and December 31, 2015 at Massachusetts General Hospital, a tertiary referral hospital. All patients included in this review were diagnosed with CRC through colonoscopy. The study was approved by the Institutional Review Board.

We subdivided the study cohort into three groups: screening (SC), diagnostic (DC), and surveillance (SU). The indication for colonoscopy were grouped according to the American Society for Gastrointestinal Endoscopy [12] and the European Panel for the Appropriateness of Gastrointestinal Endoscopy [13] guidelines. The first group included all asymptomatic, average-risk patients who never had a prior colonoscopy. Patients in the second cohort also did not have a prior colonoscopy but reported symptoms associated with CRC. Symptoms included: hematochezia (on more than one occasion), occult bleeding (non-visible bleeding detected by fecal occult blood testing (FOBT)), unexplained anemia (absence of hematochezia or positive FOBT), changes in stool habit, lower abdominal pain (without known IBD), unintentional weight loss (>10% of baseline weight), or evaluation of an abnormality seen on barium enema or other imaging. The latter group included all patients with either a personal history of adenomas, IBD or a positive family history. Patients who should undergo surveillance but presented earlier because of symptoms were excluded (n=24). Moreover, to define the impact of colonoscopy indication on oncologic outcomes, all patients who were lost to follow-up were excluded (n=112) (*Figure 1*).

FIGURE 1. Flowchart of patient selection



Patient demographics, pathologic tumor location and stage, and long-term outcomes were prospectively obtained for each patient. Tumor stage was categorized according to the seventh edition of the American Joint Committee on Cancer (AJCC). [14] Patients were followed up from the colo-

noscopy examination until death or study end (April 30, 2018), whichever came first. According to the National Comprehensive Cancer Network (NCCN) guidelines, routine post-operative follow-up was completed for all patients. Regardless of the tumor stage, all patients received a colonoscopy within 1 year after surgery followed by 3-year and later 5-year intervals if the first colonoscopy after surgery was without pathologic findings. In cases an advanced adenoma was detected, colonoscopy within 1 year was recommended. In addition to endoscopic surveillance, all patients with stage II or higher underwent monitoring through a carcinoembryonic antigen (CEA) and computed tomography (CT)-scans. [15-17] Data on long-term outcomes were updated periodically by reviewing patient's records and the Massachusetts General Hospital cancer registry. In case this information was not recently updated, the Social Security Death Index was used for survival data.

STATISTICAL ANALYSIS

Descriptive data are presented as the mean with standard deviation (±SD) or the median and interquartile range (IQR), according to the distribution, and were analyzed using the Kruskal-Wallis test. Categorical variables are presented as the percentages of patients compared by the Chi-square (χ^2) test. While survival rates were analyzed for all patients, disease recurrence was evaluated in AJCC I-III only. Bonferroni correction was applied to correct for multiple testing of the three colonoscopy indications. Post-hoc analyses using a Dunn's test was performed after a Kruskal-Wallis test was rejected. Survival distribution was estimated according to the Kaplan-Meier method, using a log-rank test. A multivariate Cox regression analysis was performed to identify predictive factors for poor overall (OS) and disease-free survival (DFS). The first adjustment was performed with patient characteristics only, including patient's age, gender, and ASA-score. The second analysis included additionally AJCC-substage, tumor site, and (neo)adjuvant treatment. The results are reported as hazard ratios (HR) with a 95% confidence interval (CI). All tests were two-sided and a P-value of 0.05 or less indicated statistical significance. Statistical analyses were carried out using SPSS *(Version 24.0; SPSS Inc, Chicago, IL, USA).*

RESULTS

A total of 1945 patients were surgically treated between 2004 and 2015 for colorectal cancer, after being diagnosed through colonoscopy. Of all surveillance patients, 24 presented with symptoms and were therefore excluded from further analysis. Follow-up was incomplete in 112 patients. Reasons for loss of follow-up were inability to contact the patient (n=67), follow-up elsewhere after first postoperative consult (n=39), and follow-up refusal (n=6). The remaining 1809 patients were included in the study. Table 1 demonstrates the distribution of colonoscopy indication. Of all patients, 235 (13.0%) were diagnosed with CRC through screening, 1386 (76.6%) underwent a diagnostic colonoscopy, and surveillance was done in 188 (7.4%) of the study cohort. Hematochezia was the most common symptom (40.4% of all DC), followed by abdominal pain (22.0%), and unexplained anemia (19.2%). The vast majority of the SU group was referred because of a history of adenomas (79.3%).

TABLE 1. Distribution of indication of colonoscopy

	No. (%) N=1809
Screening	235 (13.0)
Symptoms	1386 (76.6)
Hematochezia	560 (30.6)
Positive FOBT	243 (13.4)
Unexplained anemia	269 (14.9)
Changes in stool habit	245 (13.5)
Abdominal pain	305 (16.9)
Unintended weight loss	29 (1.6)
Suspect barium enema or other imaging	54 (3.0)
Surveillance	188 (10.4)
History of adenoma	149 (8.2)
Positive family history	18 (1.1)
IBD	21 (1.2)

Abbreviations: FOBT: fecal occult blood testing; IBD: inflammatory bowel disease
All values are expressed as number (%)

BASELINE CHARACTERISTICS

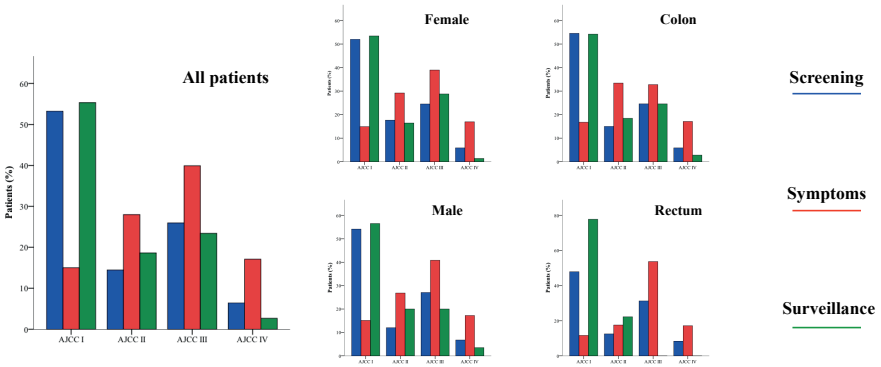
The main characteristics of the study groups are demonstrated in table 2. Age was significantly different between the groups, with the youngest patients in the screening group (median 59.4 years) and the oldest in the surveillance group (median 70.4 years). With regards to gender, female patients presented more often with symptoms (79.5% vs. 74.1%, P=0.018) while more male patients underwent asymptomatic surveillance (8.6% vs. 12.0%, P=0.048). In addition, screening patients had less comorbidities and a higher BMI than symptomatic patients (P<0.001). A difference in colonoscopy indication was also found with regards to tumor site; while screening and surveillance accounted for almost one-third of all colon patients, diagnostic colonoscopy was strongly correlated with rectal cancer (89.2% vs. 71.4%, P<0.001).

Symptomatic patients had significantly less favorable Tumor Node Metastasis (TNM)-staging, including more T3-T4 tumors, nodal disease, and distant metastasis (all P<0.001). No differences were found between SC and SU. Figure 2 demonstrates the distribution of AJCC-staging in the complete study cohort, and for gender and tumor site separately. Overall, SC and SU were associated with stage I disease (P<0.001), whereas DC was associated with stage II or higher. The same pattern was seen when analyzing gender and tumor site separately. However, after Bonferroni correction, no significant difference was seen between DC and SU in stage II rectal cancer and male patients, and stage III colon cancer and female patients. Interestingly, none of the surveillance patients who got diagnosed with rectal cancer had nodal or metastatic disease.

n = 1809	SCREENING 235 (13.0%)	SYMPTOMS 1386 (76.6%)	SURVEILLANCE 188 (10.4%)	P-VALUE
Age	59.4 (52.6-66.0)	65.3 (52.6-77.4)	70.4 (61.1-78.0)	<0.001 α β γ
Gender1				0.016
Female	102 (43.4)	678 (48.9)	73 (38.8)	
Male	133 (56.6)	708 (51.1)	115 (61.2)	
Caucasian	205 (87.2)	1177 (84.9)	170 (90.4)	0.159
ASA-score	2 (2-2)	2 (2-3)	2 (2-3)	<0.001 α β
BMI	28.6 (24.9-32.2)	26.2 (23.1-30.2)	27.1 (24.6-30.7)	<0.001 α γ
Tumor location2				<0.001
Colon	187 (79.6)	913 (65.9)	179 (95.2)	
Rectum	48 (20.4)	473 (34.1)	9 (4.8)	
TNM-staging				
T-stage				<0.001 α γ
T1	106 (45.1)	117 (8.4)	74 (39.4)	
T2	41 (17.4)	152 (11.0)	43 (22.9)	
T3	74 (31.5)	823 (59.4)	53 (28.2)	
T4	14 (6.0)	192 (21.2)	18 (9.6)	
N-stage				<0.001 α γ
N0	162 (68.9)	637 (46.0)	141 (75.0)	
N1	57 (24.3)	487 (35.1)	38 (20.2)	
N2	16 (6.8)	262 (18.9)	9 (4.8)	
M-stage				<0.001 α γ
M0	220 (93.6)	1149 (82.9)	183 (97.3)	
M1	15 (6.4)	237 (17.1)	5 (2.7)	
Tumor size	2.5 (0.0-5.0)	4.5 (2.9-7.5)	2.6 (1.2-4.5)	<0.001 α γ
Neoadjuvant therapy	24 (10.2)	405 (29.2)	3 (1.6)	<0.001 α β γ
Follow-up duration, months	59.7 (34.7-95.5)	40.4 (22.5-68.5)	49.8 (31.1-83.5)	<0.001 α γ
Disease recurrence3	20 (9.1)	205 (17.8)	12 (6.6)	<0.001 α γ
Local	4 (1.8)	52 (4.5)	1 (0.5)	0.008 γ
Locoregional	7 (3.2)	101 (8.8)	8 (4.4)	0.004 α
Distant	18 (8.2)	186 (16.2)	12 (6.6)	<0.001 α γ
Disease-free survival	64.0 (37.0-111.5)	41.9 (21.4-72.3)	51.6 (34.7-86.0)	<0.001 α γ
Deceased	37 (15.7)	544 (39.2)	53 (28.2)	<0.001 α β γ
Colorectal cancer mortality	22 (9.4)	287 (20.7)	14 (7.4)	<0.001 α γ
Overall survival, months	64.7 (38.0-111.3)	45.1 (26.8-72.6)	53.2 (35.2-86.5)	<0.001 α γ
Adjuvant therapy	85 (36.2)	718 (51.8)	47 (25.0)	<0.001 α β γ

1. Percentages tumor location overall / within specific site
2. Percentages gender overall / within gender
3. Disease recurrence analysis: AJCC I-III only
Proportions are presented for categorical data, median with IQR for continuous data.
α Screening versus Symptoms P<0.05 ; β Screening versus Surveillance P<0.05 ; γ Symptoms versus Surveillance P<0.05

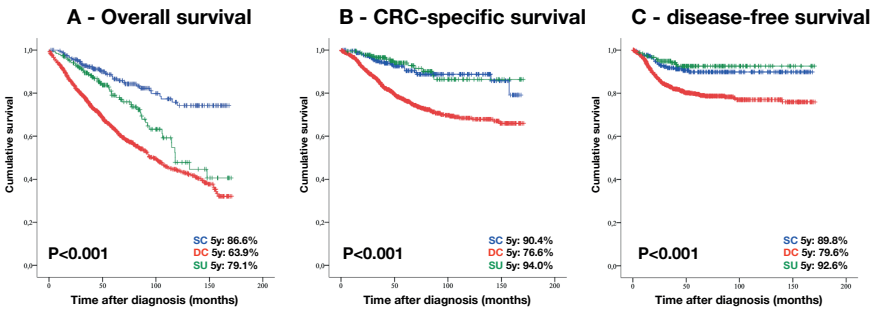
FIGURE 2. The distribution of AJCC-staging in all patients, and for gender and tumor site separately



LONG-TERM OUTCOMES

Median follow-up duration was 44.9 months (IQR 25.6 – 73.2 months), and significantly longer in SC and SU patients (P<0.001). Along with less favorable pathologic outcomes, DC was associated with poor prognostic outcomes. Mortality rates, both overall and colorectal cancer specific, were higher in the DC group compared to both SC and SU (P<0.001). With regards to differences between SC and SU; only overall survival rates were significantly higher in the latter group (SC: 15.7% vs. SU: 28.2%, P=0.006) while colorectal cancer mortality rates were similar (SC: 9.4% vs. SU: 7.4%, P=0.483). To analyze difference in disease recurrence, we included only patients with AJCC I-III stage (n=1552). In line with survival outcomes, disease recurrence occurred significantly more often in symptomatic patients (P<0.001), with no differences between screening and surveillance. Kaplan Meier curves underscored the detrimental impact on long-term outcomes in symptomatic patients (Figure 3), in particular in the first years of follow-up.

FIGURE 3. Kaplan-Meier curves for overall survival (A), colorectal cancer specific survival (B) and disease-free survival (C)



MULTIVARIATE ANALYSIS

To assess the actual impact of colonoscopy indication on long-term outcomes, we conducted multivariate analyses adjusted for various covariables. We included age, gender, and ASA-score in the first model, and additionally tumor site, AJCC-substage, and (neo)adjuvant treatment in the second model. Figure 4 demonstrates the survival curves after adjustment. Worse outcomes in overall, disease-specific, and disease-free

survival after DC remained significant in the first model (all P<0.001). After additional adjustment for stage, tumor site and (neo)adjuvant treatment, screening patients had a 54% overall mortality reduction (P<0.001). Although colorectal cancer specific mortality was reduced by 35%, this was not significant compared to symptomatic patients (P=0.053). Similarly decreased mortality rates were observed in the surveillance group (HR: 0.73, HR: 0.57, respectively). Furthermore, while screening patients had an enhanced overall survival compared to SU (HR: 0.63, *95% CI:* 0.42 – 0.97, P=0.035), rates of colorectal cancer specific survival were similar (HR: 1.13, *95% CI:* 0.58 – 2.22, P=0.713). Disease-free survival was significantly worse after DC in the first model (P<0.001) and remained worse compared to surveillance patients (HR: 0.51, *95% CI:* 0.28 – 0.91 P=0.024), though the impact was less evident compared to SC in the second model (HR: 0.69, *95% CI:* 0.43 – 1.10, P=0.121).

FIGURE 4. Multivariate Cox proportional Hazard model curves

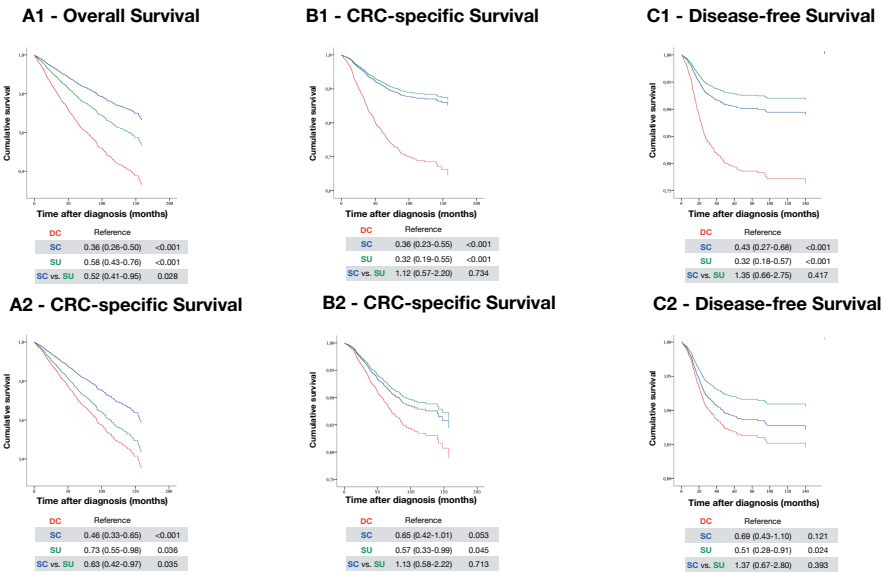


Table 3 demonstrates subgroup specific overall mortality analysis. Reduced overall survival after a screening colonoscopy remained true in all stages but was more profound in early stage disease (AJCC I-II: HR:0.42, *95% CI:* 0.25 – 0.72, P=0.002). Compared to SU, outcomes were only slightly better in the stage-for-stage analysis. Tumor site, on the other hand, was very important. Favorable outcomes after screening colonoscopy were strongly related to colon cancer, compared to both symptomatic patients (HR: 0.46, *95% CI:* 0.32 – 0.68, P<0.001) and surveillance (HR: 0.60, *95% CI:* 0.38 – 0.95, P=0.028). With regards to gender, screening patients had over 50% mortality reduction compared to DC. However, female screening patients did significantly better than female surveillance patients (HR: 0.48, *95% CI:* 0.24 – 0.96, P=0.039), whereas outcomes were comparable in men (HR: 0.74, *95% CI:* 0.43 – 1.26, P=0.261). On the other hand, male surveillance patients did better than symptomatic male patients (HR: 0.64, *95% CI:* 0.45 – 0.93, P=0.019), while outcomes were similar in the female cohort (HR: 0.95, *95% CI:* 0.58 – 1.56, P=0.835).

Table 3 Overall mortality stage I-IV, adjusted

					Hazard Ratio (95% CI)			
			Patients	Events	Adjusted for age, ASA, gender [a]	P-value	Adjusted for multiple covariates b	P-value
All								
		Symptoms	1386	544	Reference		Reference	
		Screening	235	37	0.36 (0.26-0.50)	<0.001	0.46 (0.33-0.65)	<0.001
		Surveillance	188	53	0.58 (0.43-0.76)	<0.001	0.73 (0.55-0.98)	0.036
		Screening vs. Surveillance			0.52 (0.41-0.95)	0.028	0.63 (0.42-0.97)	0.035
Stage	I-II							
		Symptoms	596	172	Reference		Reference	
		Screening	159	15	0.42 (0.25-0.72)	0.002	0.42 (0.25-0.72)	0.002
		Surveillance	139	33	0.82 (0.56-1.19)	0.291	0.82 (0.56-1.19)	0.291
		Screening vs. Surveillance			0.52 (0.28-0.96)	0.035	0.52 (0.28-0.96)	0.035
	III							
		Symptoms	553	195	Reference		Reference	
		Screening	61	11	0.55 (0.30-1.01)	0.054	0.63 (0.34-1.16)	0.138
		Surveillance	44	15	0.72 (0.43-1.23)	0.228	0.83 (0.49-1.40)	0.481
		Screening vs. Surveillance			0.76 (0.35-1.67)	0.494	0.76 (0.35-1.67)	0.494
	IV							
		Symptoms	237	177	Reference		Reference	
		Screening	15	11	0.68 (0.37-1.25)	0.213	0.65 (0.35-1.21)	0.174
		Surveillance	5	5	0.68 (0.28-1.68)	0.409	0.51 (0.20-1.25)	0.141
		Screening vs. Surveillance			0.99 (0.34-2.86)	0.985	1.29 (0.45-3.74)	0.638
Location	Colon							
		Symptoms	913	381	Reference		Reference	
		Screening	187	30	0.35 (0.24-0.50)	<0.001	0.46 (0.32-0.68)	<0.001
		Surveillance	179	52	0.59 (0.44-0.78)	<0.001	0.77 (0.57-1.04)	0.089
		Screening vs. Surveillance			0.59 (0.37-0.93)	0.022	0.60 (0.38-0.95)	0.028
	Rectum							
		Symptoms	473	163	Reference		Reference	
		Screening	48	7	0.39 (0.18-0.84)	0.015	0.48 (0.22-1.05)	0.066
		Surveillance	9	1	0.23 (0.03-1.68)	0.148	0.43 (0.06-3.18)	0.409
		Screening vs. Surveillance			1.67 (0.20-16.66)	0.632	1.11 (0.14-9.20)	0.921

Gender	Men						
	Symptoms	708	275	Reference		Reference	
	Screening	133	23	0.41 (0.27-0.63)	<0.001	0.48 (0.31-0.74)	0.001
	Surveillance	115	35	0.55 (0.38-0.78)	0.001	0.64 (0.45-0.93)	0.019
	Screening vs. Surveillance			0.75 (0.44-1.28)	0.296	0.74 (0.43-1.26)	0.261
	Women						
	Symptoms	678	269	Reference		Reference	
	Screening	102	14	0.30 (0.17-0.51)	<0.001	0.45 (0.26-0.78)	0.005
	Surveillance	73	18	0.61 (0.38-0.99)	0.044	0.95 (0.58-1.56)	0.835
	Screening vs. Surveillance			0.48 (0.24-0.98)	0.042	0.48 (0.24-0.96)	0.039

a Adjusted for Age, ASA, gender, AJCC substage (TNM), tumor site
b Adjusted for Age, ASA, gender, AJCC substage (TNM), tumor site, neoadjuvant chemoradiation and adjuvant treatment

TABLE 4 Disease-free survival stage I-III, adjusted

					Hazard Ratio (95% CI)		
			Patients	Events	Adjusted for age, ASA, gender [a]	P-value	Adjusted for multiple covariates [b]	P-value
All								
		Symptoms	1386	332	Reference		Reference	
		Screening	235	33	0.43 (0.27-0.68)	<0.001	0.69 (0.43-1.10)	0.121
		Surveillance	188	17	0.32 (0.18-0.57)	<0.001	0.51 (0.28-0.91)	0.024
		Screening vs. Surveillance			1.35 (0.66-2.75)	0.417	1.37 (0.67-2.80)	0.393
Stage	I-II							
		Symptoms	596	65	Reference		Reference	
		Screening	159	3	0.14 (0.05-0.45)	0.001	0.26 (0.08-0.84)	0.025
		Surveillance	139	3	0.17 (0.05-0.55)	0.003	0.29 (0.09-0.93)	0.037
		Screening vs. Surveillance			0.82 (0.17-4.07)	0.809	0.90 (0.18-4.45)	0.895
	III							
		Symptoms	553	139	Reference		Reference	
		Screening	61	17	1.00 (0.60-1.66)	0.999	0.88 (0.53-1.47)	0.634
		Surveillance	44	9	0.74 (0.37-1.45)	0.376	0.60 (0.30-1.19)	0.141
		Screening vs. Surveillance			1.36 (0.60-3.08)	0.462	1.48 (0.66-3.33)	0.347
Location	Colon							
		Symptoms	913	213	Reference		Reference	
		Screening	187	24	0.39 (0.23-0.67)	0.001	0.66 (0.39-1.14)	0.135
		Surveillance	179	17	0.32 (0.18-0.58)	<0.001	0.54 (0.30-0.98)	0.041
		Screening vs. Surveillance			1.22 (0.57-2.61)	0.605	1.23 (0.58-2.64)	0.588
	Rectum							
		Symptoms	473	119	Reference		Reference	
		Screening	48	9	0.55 (0.22-1.36)	0.195	0.66 (0.26-1.68)	0.380
		Surveillance	9	0	N/A		N/A	
		Screening vs. Surveillance			N/A		N/A	
Gender	Men							
		Symptoms	708	169	Reference		Reference	
		Screening	133	21	0.52 (0.30-0.90)	0.020	0.84 (0.47-1.48)	0.542
		Surveillance	115	12	0.33 (0.16-0.69)	0.003	0.52 (0.25-1.09)	0.084
		Screening vs. Surveillance			1.55 (0.65-3.69)	0.325	1.60 (0.67-3.82)	0.291

Women						
Symptoms	678	163	Reference		Reference	
Screening	102	12	0.31 (0.13-0.70)	0.005	0.48 (0.21-1.09)	0.080
Surveillance	73	5	0.29 (0.11-0.79)	0.016	0.49 (0.18-1.34)	0.162
Screening vs. Surveillance			1.05 (0.30-3.73)	0.936	0.98 (0.28-3.47)	0.970

[a] Adjusted for Age, ASA, gender, AJCC substage (TNM), tumor site
[b] Adjusted for Age, ASA, gender, AJCC substage (TNM), tumor site, neoadjuvant chemoradiation and adjuvant treatment

With the exception of stage I-II, the impact of colonoscopy indication was less evident in the subgroup disease-free survival analysis (Table 4). In this early stage of colorectal cancer, screening and surveillance patients had a significant reduction compared to symptomatic patients (HR: 0.26, 95% CI: 0.08 – 0.84, P=0.025 ; HR: 0.29, 95% CI: 0.09 – 0.93, P=0.037). No differences were found in stage III disease, nor in the comparison between screening and surveillance. Outcomes were worse after DC in colon cancer, though only significant compared to SU in the second adjustment model (HR: 0.54, 95% CI: 0.30 – 0.98, P=0.041). The reduction in disease-free survival was more prominent in female than men, with a 52% reduction in the female screening cohort and only 16% in the male screening cohort (P=0.080, P=0.542, respectively).

DISCUSSION

The benefits of screening for colorectal cancer have been clearly established. This is mainly attributed to the detection and subsequent removal of adenomatous polyps and other precancerous lesions, as well as the detection of CRC in an early stage. Accumulative evidence has led to national screening recommendations, which have been established on an opportunistic basis in the United States since 2002. [18] Several options for CRC screening are available, including stool-based tests and visual examination. In the United States, the use of stool-based testing is decreasing while colonoscopy is the predominate method. And although no outcomes of randomized controlled trials are available, large observational cohort studies have proved the efficacy of a colonoscopy. [19-20]

In this large cohort of patients with CRC detected through colonoscopy, patients whose cancer was detected after symptomatic presentation had significantly reduced survival compared to asymptomatic average- and high-risk patients. This difference was partly explained by the less favorable stage distribution in symptomatic patients which was expected and underscores once more the importance of a screening colonoscopy in terms of early detection of CRC. The larger tumor size and likeliness of locally advanced tumors was anticipated in symptomatic patients, subsequently leading to more nodal disease and distant metastasis. However, the extent of stage distribution was strongly significant. Symptomatic patients were more than twice as likely to present with positive lymph-nodes, had an almost 3-fold higher risk of distant metastasis compared to SC and more than 6-fold higher risk of metastatic disease than SU. Despite the fact that symptomatic patients presented far more often with advanced disease, oncologic outcomes remained worse after adjustment for patient characteristics, stage and (neo)adjuvant treatment. This was particularly true in colon cancer and early stage disease (AJCC I-II). A delayed diagnosis in colon cancer might be explained by the late onset of recognized symptoms since colon cancer symptoms are rather nonspecific including fatigue, change in stool habit, and abdominal pain compared to more profound symptoms usually seen in rectal cancer, with rectal bleeding as the most common. The reason why symptomatic stage I-II patients did worse than asymptomatic stage I-II patients in terms of compromised overall survival and disease-free survival is not clearly elucidated in our study. A possible explanation could be the difference in histo-

pathologic risk-factors, with higher rates of extramural vascular invasion, lymphatic invasion, perineural invasion and high-grade tumors (including poorly differentiated adenocarcinomas, mucinous and signet-cell carcinomas) in the symptomatic cohort. However, this was predominantly true compared to the screening group and not significant compared to the surveillance group (*Table S1*).

Our results expand on previous research from various countries with different screening programs. The detrimental outcomes for symptomatic patients are consistent with findings in prior studies. [11, 21-23] However, despite the significant difference in stage of disease, only a few studies addressed the long-term outcomes by stage and (neo)adjuvant treatment. Amri et al reported the prognostic advantage of screen-detection compared to nonscreen-detection in colon cancer, regardless of stage. [11] Moreover, Brenner et al found significant better outcomes in patients who were diagnosed through screening or positive FOBT. [23] To our knowledge, the present study is the only study to date investigated both colon and rectal cancer and additionally distinguishes between screening and surveillance patients. When comparing this high-risk asymptomatic group to the average-risk symptomatic cohort, the impact of symptoms was even more evident. This was underlined by a persisting higher risk reduction of colorectal cancer specific survival in surveillance patients, even higher than the risk reduction in the screening group. Furthermore, disease-free survival was significantly better in the surveillance group with a trend toward better outcomes compared to the screening group. A reasonable explanation could be the better compliance to follow-up colonoscopy, though this could unfortunately not be assessed with our data.

Despite the advantage and the steadily improving compliance to screening, only one-third of eligible adults in the United States have had a CRC screening. Screening rates vary by ethnicity (lower rates among Hispanics), insurance (only 25.1% of uninsured adults report recent CRC screening versus 65.6% of insured adults), education, and age (45.3% of adults age 50-54 versus 71.8% of adults age 65-75). [24] The latter is in particular important now that the recommendations from the ACS are changed and regular screening is advised from 45 years instead of the previous 50 years of age. [5] The lower rate of CRC screening in younger eligible patients underscores the effort that will be needed to reach appropriate adherence in the 45-50 year population. To further decrease both incidence and mortality rates of CRC, optimizing adherence to CRC screening is essential. This will require a multifaceted approach tailored to patient, physician, and policy levels. A recent systematic review demonstrated the tremendous effect of clinical recommendation on screening adherence. [25] In addition, outreach strategies could account for a 10-20% increase in adherence rates. [10,26-27] Our study stresses the importance of screening before symptoms develop. More awareness of the consequences of a delayed diagnosis will hopefully enhance adherence and further reduce the burden associated with colorectal cancer.

Despite the strengths of our study, a number of limitations were present. Our study was performed in a single center, highly specialized institution. Therefore, the number of symptomatic and complicated cases referred might be higher compared to other centers. This may have affected the generalizability of the outcomes and worsened the survival rates of symptomatic or complicated cases by some extent. Because the inci-

dence of 30-day mortality was low in all cohorts (<1.5%), we do not expect that this had had a major effect on long-term outcomes. One of the major strengths of this study was the additional comparison to surveillance patients and the addition of subgroup specific analyses. Unfortunately, the proportion of events was not equally distributed in all subgroups with relatively wide confidence intervals in some areas. This was especially true in the rectal cohort. Therefore, we were not able to adjust for other potential covariables, including histopathologic features.

Patients, physicians and policy makers should be aware of the tremendous impact of asymptomatic screening for colorectal cancer. Regardless of the estimated risk based on personal and family history, symptomatic patients present with significantly less favorable pathologic outcomes leading to impaired survival. The detrimental impact of symptomatic colonoscopy remained true after adjustment for patient characteristics, stage, and (neo)adjuvant treatment. This stresses the importance of screening colonoscopy before symptoms develop. To improve the adherence to screening, certainly after the altered recommended screening age of 45 years, several steps on patient, physician, and policy levels have to be taken. More awareness of the consequences of a delayed diagnosis, along with informative communication between the caregiver and patient, and the expansion of screening coverage is expected to enhance adherence and further reduce the CRC burden.

TABLE S1. Histopathologic features

All patients, n = 1809	SCREENING 235 (13.0%)	SYMPTOMS 1386 (76.6%)	SURVEILLANCE 188 (10.4%)	P-VALUE
T4 tumors	14 (6.0)	294 (21.2)	18 (9.6)	<0.001 α γ
Extramural vascular invasion	37 (15.7)	419 (30.2)	28 (14.9)	<0.001 α γ
Lymphatic invasion	45 (19.1)	482 (34.8)	47 (25.0)	<0.001 α γ
Perineural invasion	22 (9.4)	333 (24.1)	25 (13.4)	<0.001 α γ
High Grade				

Stage I-II, n = 894	SCREENING 159 (17.8%)	SYMPTOMS 596 (66.7%)	SURVEILLANCE 139 (15.5%)	P-VALUE
T4 tumors	3 (1.9)	71 (11.9)	5 (3.6)	<0.001 α γ
Extramural vascular invasion	10 (6.3)	79 (13.3)	4 (2.9)	<0.001 α γ
Lymphatic invasion	12 (7.5)	105 (17.6)	20 (14.4)	0.007 α
Perineural invasion	4 (2.5)	63 (10.6)	8 (5.8)	0.002 α
High Grade	7 (4.5)	80 (13.6)	14 (10.2)	0.006 α

Stage III, n = 658	SCREENING 61 (9.3%)	SYMPTOMS 553 (84.0%)	SURVEILLANCE 44 (6.7%)	P-VALUE
T4 tumors	7 (11.5)	102 (18.4)	12 (27.3)	0.112
Extramural vascular invasion	19 (31.1)	194 (35.1)	21 (47.7)	0.181
Lymphatic invasion	27 (44.3)	237 (42.9)	24 (54.5)	0.322
Perineural invasion	14 (23.3)	158 (28.6)	15 (34.1)	0.481
High Grade	16 (26.2)	110 (20.1)	13 (31.0)	0.163

Stage IV, n = 257	SCREENING 15 (5.8%)	SYMPTOMS 237 (92.2%)	SURVEILLANCE 5 (1.9%)	P-VALUE
T4 tumors	3 (20.0)	101 (42.6)	1 (20.0)	0.404
Extramural vascular invasion	8 (53.3)	146 (61.6)	3 (60.0)	0.815
Lymphatic invasion	6 (40.0)	140 (59.1)	3 (60.0)	0.347
Perineural invasion	4 (26.7)	112 (47.5)	2 (50.0)	0.290
High Grade	4 (26.7)	63 (26.8)	3 (60.0)	0.258

α Screening versus Symptoms P<0.05 ; β Screening versus Surveillance P<0.05 ; γ Symptoms versus Surveillance P<0.05

REFERENCES

1
Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008;149:659–69.

2
Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, Eide TJ, Skovlund E, Schneede J, Tveit KM, Hoff G. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: A randomized clinical trial. *JAMA*. 2014;312(6):606-615.

3
Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

4
US Preventive Services Task Force. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564–2575.

5
Wolf AM, Fontham ET, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, Walter LC, Andrews KS, Brawley OW, Brooks D, Fedewa SA, Manassaram-Baptiste D, Siegel RL, Wender RC, Smith RA. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA: A Cancer Journal for Clinicians.

6
Meissner HI, Breen N, Klabunde CN, Vernon SW. Patterns of colorectal cancer screening uptake among men and women in the United States. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb;15(2):389-394.

7
Klabunde CN, Joseph DA, King JB, White A, Plescia M. Vital Signs: Colorectal Cancer Screening Test Use — United States, 2012. *MMWR Morbidity and Mortality Weekly Report.* 2013;62(44):881-888.

8
Shapiro JA, Klabunde CN, Thompson TD, Nadel MR, Seeff LC, White A. Patterns of colorectal cancer test use, including CT colonography, in the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev*. 2012;21(6):895-904.

9
Centers for Disease Control and Prevention (CDC). Vital signs: colorectal cancer screening test use: United States, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(44):881-888.

10
Gupta S, Halm EA, Rockey DC, Hammons M, Koch M, Carter E, Valdez L, Tong L, Ahn C, Kashner M, Argenbright K, Tiro J, Geng Z, Pruitt S, Skinner CS. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. *JAMA Intern Med*. 2013;173:1725-1732.

11
Amri R, Bordeianou LG, Sylla P, Berger DL. Impact of screening colonoscopy on outcomes in colon cancer surgery. *JAMA surgery.* 2013;148:747-754.

12
ASGE Standards of Practice Committee, Early DS, Ben-Menachem T, Decker GA, Evans JA, Fanelli RD, Fisher DA, Fukami N, Hwang JH, Jain R, Jue TL, Khan KM, Malpas PM, Maple JT, Sharaf RS, Dominitz JA, Cash BD. Appropriate use of GI endoscopy. *Gastrointest Endosc* 2012;75:1127-1131.

13
Vader JP, Froehlich F, Dubois RW, Beglinger C, Wietlisbach V, Pittet V, Ebel N, Gonvers JJ, Burnand B. European panel for the appropriateness of gastrointestinal endoscopy (EPAGE): Conclusion and WWW Site. *Endoscopy* 1999;31:687-694.

14
Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.

15
National Comprehensive Cancer Network. Colon Cancer (Version 2.2017).

16
National Comprehensive Cancer Network. Rectal Cancer (Version 3.2017).

17
Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130(6):1865-1871.

18
U.S. Preventive Services Task Force. Screening for colorectal cancer: recommendation and rationale. *Ann Intern Med* 2002;137:129-131.

19
Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095-1105.

20
Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, Smith N, Whitlock EP. Screening for Colorectal Cancer: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 135. AHRQ Publication No. 14-05203-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2016.

21
Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology* 2014;146:709-717.

22
Friedrich K, Grüter L, Gotthardt D, Eisenback C, Stremmel W, Scholl SG, Rex DK, Sieg A. Survival in patients with colorectal cancer diagnosed by screening colonoscopy. *Gastrointest Endosc* 2015;82:133-137.

23
Brenner H, Jansen L, Ulrich A, Chang-Clause J, Hoffmeister M. Survival of patients with symptom- and screening-detected colorectal cancer. *Oncotarget* 2016;7(28):44695-44704.

24
White A, Thompson TD, White MC, Sabatino SA, de Moor J, Doria-Rose PV, Geiger AN, Richardson LC. Cancer Screening Test Use – United States, 2015. *MMWR Morb Mortal Wkly Rep* 2017;66:201-206.

25
Peterson EB, Ostroff JS, DuHamel KN, D'Agostino TA, Hernandez M, Canzona MR, Bylund CL. Impact of provider-patient communication on cancer screening adherence: a systematic review. *Prev Med*. 2016;93:96-105.

26
Singal AG, Gupta S, Tiro JA, Skinner CS, McCallister K, Sanders JM, Bishop WP, Agrawal D, Mayorga CA, Ahn C, Loewen AC, Santini NO, Halm EA. Outreach invitations for FIT and colonoscopy improve colorectal cancer screening rates: a randomized controlled trial in a safety-net health system. *Cancer* 2016;122:456-463.

27
Denberg TD, Coombes JM, Byers TE, Marcus AC, Feinberg LE, Steiner JF, Ahnen DJ. Effect of a mailed brochure on appointment-keeping for screening colonoscopy: a randomized trial. *Ann Intern Med* 2006;145:895-900.

CHAPTER 2

Do STAGE I COLORECTAL CANCERS with LYMPHATIC INVASION REQUIRE a DIFFERENT POSTOPERATIVE APPROACH?

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ABSTRACT

BACKGROUND

Although stage I colorectal cancer has an excellent prognosis after complete surgical resection, disease recurrence still occurs. This study aimed to assess prognostic risk factors in this early stage of disease.

METHODS

All non-neoadjuvantly treated stage I colon (CC) and rectal (RC) patients who underwent a surgical resection between 2004-2015 were identified. Clinicopathological differences and long-term oncological outcomes were compared.

RESULTS

CC patients (n=433) were older and had more pre-existing comorbidities. RC patients (n=86) were associated with more T2 tumors, venous invasion, and higher rates of 30-day morbidity. In multivariate analysis, lymphatic invasion was found to be an independent predictor for disease recurrence (OR: 4.57, P=0.010) and worse disease-free survival (HR: 4.26, P=0.012). This was particularly true for distant recurrence, with eight-times higher hazard ratios when lymphatic invasion was present (HR: 8.02, P<0.001). T2 tumors were at risk, though no significant association was found (OR: 3.86, P=0.051, HR: 3.61, P=0.065, respectively).

CONCLUSIONS

Lymphatic invasion was strongly associated with worse DFS, in particular distant recurrence. This subgroup of stage I patients might benefit from a more intensive follow-up and maybe should be considered for adjuvant therapy.

INTRODUCTION

Colorectal cancer (CRC) has a profound impact on public health. In 2017, an estimated 135,430 new cases of large bowel cancer were diagnosed in the United States.[1] Due to screening programs, changing patterns in risk factors and improvements in treatment, a declining trend in CRC incidence and mortality is noted over the last decades.[2] Nonetheless, CRC is still the third most commonly diagnosed cancer among men and women and approximately 50,260 patients died from colorectal cancer in 2017. The overall 5-year survival rate for patients diagnosed with CRC between 2006 and 2012 was 65%, slightly higher for rectal cancer (67% vs. 64%).[3] This rate is dependent upon many factors, but stage of disease at diagnosis remains one of the most important in oncological outcomes.

Approximately 39% of all CRC patients present with localized disease, including all cases where the cancer is found to be confined to the primary site. Surgical resection without neoadjuvant or adjuvant chemoradiation is still the gold standard for these patients, notwithstanding the increasing interest and improved techniques for less invasive procedures such as transanal excision in rectal cancer and endoscopic removal of colonic neoplasms over the last decades.[4-5] The estimated 5-year survival rate reaches 90% for this early stage disease, thus the prognosis is excellent. Nonetheless, disease recurrence rates are in the range of 5-17%.[6-8]

An established risk factor for disease recurrence in stage I disease is method of resection, particularly in rectal cancer since a local excision has become a more commonly used procedure. Other than that, however, not much is known about prognostic risk factors in this stage of colorectal cancer. Most of the studies which focus on poor outcomes in early stage CRC include either stage I and II disease [9-10] or investigated predictors for lymph-node metastasis [11-13] and are therefore less applicable to pT1-2N0 tumors. In addition, although colon and rectal cancer have a different tumor biology and require different treatment in more advanced stages, the recommendations for stage I disease is not different between the two. To further optimize prognosis, particularly with the current increase in less invasive procedures, it is essential to increase our knowledge of prognostic factors in early stage disease. Therefore, the objective of this study is to examine risk-stratifying factors in stage I colorectal cancer and to assess differences between colon and rectal cancer patients.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

The study population consisted of all patients who underwent primary surgical treatment for stage I colon or rectal cancer at Massachusetts General Hospital between 2004-2015. All data was extracted from a prospectively maintained, IRB-approved database. Patient who received neoadjuvant treatment for stage II disease and downgraded to pathologic stage I were excluded (n=11) as were patients who underwent a transanal excision (n=19). The remaining 519 cases were included for subsequent analysis. Colon cancer (CC) was defined as a tumor located between the cecum and sigmoid. Rectal cancer (RC) included all tumors within 15 cm

of the anal verge. Baseline characteristics, operative and postoperative details, pathology features and long-term outcomes were reviewed. Surgical procedures were compared, including segmental colectomies, low anterior (LAR), and abdominoperineal resections (APR). Short–term outcomes included length of stay, rate of readmission, complications during and post-admission, and mortality within 30-days of surgery. Long-term outcomes included the rate of recurrence, both local and distant recurrence rates, as well as overall survival (OS), and disease-free survival (DFS). Local recurrence was defined as peri-anastomotic recurrence or regional nodal recurrence, while distant metastasis included other organs such as liver, lung, peritoneum, bone, and brain. Data on long-term outcomes was updated periodically by reviewing patient's records and the Massachusetts General Hospital's cancer registry. All time to events was calculated from date of surgery.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.). Differences in dichotomous variables were assessed using a Chi-squared (χ^2) test, and categorical variables are presented as the percentage of patients. Continuous variables are presented as the mean ± standard deviation (SD) or the median and interquartile range (IQR), according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Differences in continuous variables were analyzed using a Mann-Whitney U test. Survival-analyses were performed with Kaplan-Meier curves, using a log-rank test. Multiple logistic regression models were used to determine the association between disease recurrence, tumor location, and other clinicopathological variables. Significant explanatory univariate variables, as well as clinically important factors were considered as potential covariates and were kept in the model if they improved the goodness of fit, according to Hosmer-Lemeshow purposeful variable selection method.[14] The results are reported as odds ratios (OR) with a 95% confidence interval (CI). Furthermore, we performed Cox proportional hazard models to assess the impact on time to disease recurrence, reported as hazard ratios (HR) with a 95% CI. All reported P-values are two-sided, with P£0.05 denoting statistical significance.

RESULTS

Between 2004 and 2015, 433 CC and 86 RC patients with stage I disease underwent a surgical resection at our institution. Median age was 66.3 years. Rectal cancer patients were significantly younger (67.3 vs. 59.7, P=0.001). CC was associated with a higher ASA-score (P=0.027), and more urgent admissions (5.5% vs. 0.0%, P=0.025). One-third of the CC patients received surgical resection for a T2 tumors, while the majority of surgically treated RC patients had a T2 tumor (58.1%, P<0.001). High grade tumors were rarely seen and only present in CC tumors (6.8%, P=0.014), whereas the prevalence of lymphovascular invasion (LVI), and in particular venous invasion, was significantly higher in RC tumors (11.3% vs. 33.7%, P<0.001). Besides tumor location, LVI was found to be correlated with his-

tological risk factors including pT2 tumors (OR 4.79, P<0.001), poor differentiation (OR 2.86, P=0.010), and perineural invasion (OR 3.34, P=0.046). The prevalence of microsatellite instability was significantly different between tumor location, with more MSI stable and low tumors in the rectal cancer cohort (27.0% vs. 46.5%, P<0.001). Although the number of retrieved lymph nodes was comparable, more CC patients had less than 12 lymph-nodes harvested (18.0% vs. 9.3%, P=0.047). Table 1.

Table 1. Baseline characteristics

	All patients	Colon cancer	Rectal cancer	P-value
n = 519	n = 519	n = 433 (83.4%)	n = 86 (16.6%)	
Age	66.3 (56.2 – 75.8)	67.3 (57.4 – 77.0)	59.7 (51.6 – 72.3)	0.001
Male gender	281 (54.1%)	233 (53.8%)	48 (55.8%)	0.733
BMI	26.9 (23.4 – 31.2)	27.1 (23.7 – 31.6)	26.4 (22.6 – 30.1)	0.085
ASA	2 (2 – 3)	2 (2 – 3)	2 (2 – 2)	0.027
IBD	22 (4.2%)	20 (4.6%)	2 (2.3%)	0.335
Alcohol abuse	35 (6.7%)	30 (6.9%)	5 (5.8%)	0.707
Nicotine dependence	55 (10.6%)	46 (10.6%)	9 (10.5%)	0.965
Urgent admission	24 (4.6%)	24 (5.5%)	0 (0.0%)	0.025
Family history CRC	71 (13.7%)	59 (13.6%)	12 (14.0%)	0.936
History of cancer	67 (12.9%)	53 (12.2%)	14 (16.3%)	0.308
Pathology features				
T2 tumor	209 (40.3%)	159 (36.7%)	50 (58.1%)	<0.001
High Grade	28 (5.6%)	28 (6.8%)	0 (0.0%)	0.014
LVI	78 (15.0%)	49 (11.3%)	29 (33.7%)	<0.001
Lymphatic	53 (10.2%)	41 (9.5%)	12 (14.0%)	0.210
Venous	26 (5.0%)	12 (2.8%)	14 (16.3%)	<0.001
Perineural invasion	11 (2.1%)	8 (1.9%)	3 (3.5%)	0.336
Microsatellite instability				<0.001
MSI stable or low	157 (30.3%)	117 (27.0%)	40 (46.5%)	
MSI high	31 (6.0%)	31 (7.2%)	0 (0.0%)	
Unknown	331 (63.8%)	285 (65.8%)	46 (53.5%)	
LN examined	18 (14 – 24)	18 (13 – 25)	17 (15 – 23)	0.592
LN <12 examined	86 (16.6%)	78 (18.0%)	8 (9.3%)	0.047
Tumor size, *cm*	2.0 (0.0 – 3.5)	2.0 (0.0 – 3.5)	2.1 (0.0 – 15.0)	0.066

Proportions are presented for categorical data, median with IQR for continuous data.
Abbreviations: BMI: Body Mass Index (kg/m^2), ASA: American Society of Anesthesiologists, IBD: Inflammatory Bowel Disease, LVI: lymphovascular invasion

INTRA-AND POSTOPERATIVE OUTCOMES

Table 2 demonstrates perioperative outcomes. The majority of patients underwent open surgery (CC: 51.3% vs. RC: 60.5%) explained by the length of the study. There was a remarkable shift towards laparoscopic surgery over the study period, with an average of 31.8% procedures done laparoscopically in the first half of the study and 65.3% in the latter. The procedures performed in the rectal group were low anterior resections (LAR, 89.0%), and abdominoperineal resections due to sphincter involvement (APR, 11.0%). Surgery for rectal cancer took significantly longer (124

vs. 194 minutes, P<0.001), with no differences in intraoperative complications. RC patients experienced more complications during their initial admission (23.6% vs. 40.7%, P=0.001), and had a higher readmission rate (7.2% vs. 15.1%, P=0.016). The most common reasons for readmission were dehydration (36.4%), ileus (27.3%), and anastomotic leakage (18.2%). While the overall rate of anastomotic leak/intra-abdominal abscesses, surgical site infections, and urinary tract infections were only slightly higher, postoperative ileus occurred significantly more often in RC patients (10.9% vs. 20.9%, P=0.010).

Table 2. Intra- and postoperative outcomes

	All patients	Colon cancer	Rectal cancer	P-value
Surgery				
Operation duration, minutes	139 (80 – 190)	124 (74 – 171)	194 (144 – 237)	<0.001
Laparoscopic approach	245 (47.2%)	211 (48.7%)	34 (39.5%)	0.119
Conversion to open surgery	17 (3.3%)	13 (3.0%)	4 (4.7%)	0.433
Admission				
Admission duration, days	4 (3 – 6)	4 (3 – 6)	5 (4 – 7)	0.004
Complication rate during admission	137 (26.4%)	102 (23.6%)	35 (40.7%)	0.001
Complication rate total	172 (33.1%)	127 (29.3%)	45 (52.3%)	<0.001
Ileus	65 (12.5%)	47 (10.9%)	18 (20.9%)	0.010
Abscess/leak	15 (2.9%)	11 (2.5%)	4 (4.7%)	0.286
Surgical site infection	54 (10.4%)	43 (9.9%)	11 (12.8%)	0.428
Sepsis	3 (0.6%)	3 (0.7%)	0 (0.0%)	0.741
Blood transfusion	75 (14.5%)	65 (15.0%)	10 (11.6%)	0.415
ICU transfer	14 (2.7%)	9 (2.1%)	5 (5.8%)	0.051
Pneumonia	12 (2.3%)	10 (2.3%)	2 (2.3%)	0.993
Renal failure/insufficiency	14 (2.7%)	12 (2.8%)	2 (2.3%)	0.816
Urinary tract infection	23 (4.4%)	17 (3.9%)	6 (7.0%)	0.209
Readmission	44 (8.5%)	31 (7.2%)	13 (15.1%)	0.016
Reoperation	16 (3.1%)	13 (3.0%)	3 (3.5%)	0.812
Death	3 (0.6%)	2 (0.5%)	1 (1.2%)	0.434

Proportions are presented for categorical data, median with IQR for all continuous data.

LONG-TERM OUTCOMES

Median follow-up duration at our institution was 51.4 months, which was shorter for RC patients (55.8 vs. 41.5 months, P=0.022). Of all CC patients, 2.3% experienced cancer recurrence versus 4.7% of RC patients (P=0.221). Median time to disease recurrence was one year later in CC (52.3 months vs. 39.8 months, P=0.015). This was mainly explained by local recurrence, which was earlier detected in RC (CC: 55.8 months, RC: 16.2 months, P=0.038). With regards to survival, rates of overall mortality were higher in CC patients (21.5% vs. 11.6%, P=0.036), whereas colorectal cancer mortality rates were scarce and comparable (2.3% vs. 0.0%, P=0.155, respectively). Log-rank testing demonstrated a similar 5-year overall survival (CC: 84.3% vs. RC: 85.5%, P=0.242) as well as 5-year disease-free survival (CC: 97.1% vs. RC: 94.0%, P=0.144).

Table 3. Long-term oncological outcomes

	All patients	Colon cancer	Rectal cancer	P-value
Recurrence	14 (2.7%)	10 (2.3%)	4 (4.7%)	0.221
local	4 (0.8%)	2 (0.5%)	2 (2.3%)	0.071
distant	11 (2.1%)	8 (1.8%)	3 (3.5%)	0.335
Follow-up duration, months	51.4 (285 – 90.1)	55.8 (29.2 – 93.1)	41.5 (22.6 – 76.0)	0.022
Disease-free survival, months	49.4 (27.4 – 86.7)	52.3 (28.2 – 90.4)	39.8 (17.7 – 74.1)	0.015
Deceased	103 (19.8%)	93 (21.5%)	10 (11.6%)	0.036
Colorectal cancer mortality	10 (1.9%)	10 (2.3%)	0 (0.0%)	0.155

Proportions are presented for categorical data, median with IQR for all continuous data.

MULTIVARIATE ANALYSES

Table 4 demonstrates the outcomes of the logistic regression model and the Cox proportional hazard model. In univariate analysis, the odds of developing disease recurrence were remarkably higher after open surgery, tumors ³ 2 cm, T2 tumors, lymphatic invasion, and perineural invasion. Patients with colon cancer had lower odds of disease recurrence (OR: 0.49, P=0.221). After adjustment, while the odds were clinically higher for T2 tumors (OR: 3.86, P=0.051), only lymphatic invasion was found to be an independent predictor for disease recurrence (OR: 4.57, P=0.010). When looking at time to disease recurrence, the same variables were found to have higher hazard ratios. Perineural invasion was contributory in the multivariate Cox model, though only lymphatic invasion was significantly associated with worse disease-free survival (HR 4.26, P=0.012).

DISTANT AND LOCAL RECURRENCE

We analyzed the impact of various variables on time to distant and local recurrence separately. As demonstrated in Figure 1, lymphatic invasion, T-stage, and tumor location were associated with either distant or local recurrence. Lymphatic invasion was strongly related to distant recurrence (HR: 8.02, 95% CI: 2.45 – 26.29, P<0.001), as were T2 tumors (HR: 6.77, 95% CI: 1.46 – 31.35, P=0.005). Although hazard ratios for local recurrence were higher in patients with lymphatic invasion, the difference was not significant (HR: 3.09, 95% CI: 0.32 – 29.68, P=0.304). The only factor associated with local recurrence was rectal cancer (HR: 6.14, 95% CI: 0.86 – 43.70, P=0.038). Variables including surgical approach, tumor size, and other histopathologic features (venous invasion, perineural invasion, MSI, poor differentiation) were not associated with either one of the recurrence patterns.

DISCUSSION

Over the last decades, the incidence and mortality rates of colorectal cancer have decreased in Western countries.[15] The reason for this decline is multifactorial and reflects benefits of early detection through screening programs, awareness of risk factors and therapeutic improvements. As with almost all types of cancer, the earlier the diagnosis, the better the outcomes. However, cure is never guaranteed even in early stage disease. Despite the favorable outcome for patients with stage I colorectal cancer, disease recurrence still occurs. In line with recent SEER cancer statistics

Table 4. Univariate and multivariate analysis, disease recurrence and disease-free survival

			Disease recurrence *			
			Univariate		Multivariate	
	Patients, No	Events, No	OR (95% CI)	P-value	OR (95% CI)	P-value
Colon cancer	433	10	0.49 (0.15 – 1.58)	0.221		
ASA III-IV	165	5	1.63 (0.56 – 4.77)	0.370		
Age ³65 years	278	7	0.86 (0.30 – 2.50)	0.863		
Urgent admission	24	0	--	--		
Male gender	281	7	0.84 (0.29 – 2.44)	0.752		
Alcohol abuse	35	1	1.07 (0.14 – 8.39)	0.952		
Nicotine dependence	55	0	--	--		
Open approach	274	10	2.28 (0.71 – 7.37)	0.157		
Postoperative complication	172	3	0.54 (0.15 – 1.97)	0.345		
Tumor size ³2 cm	235	9	2.18 (0.66 – 7.18)	0.190		
T2 tumor	209	11	5.69 (1.57-20.63)	0.003	3.86 (0.99 – 14.95)	0.051
High Grade	28	0	--	--		
Lymphatic invasion	53	6	7.31 (2.43 – 21.96)	<0.001	4.57 (1.44 – 14.54)	0.010
Venous invasion	25	1	1.48 (0.19 – 11.74)	0.711		
Perineural invasion	11	1	3.80 (0.45 – 31.92)	0.187		
LN ³12	433	11	0.72 (0.20 – 2.64)	0.620		

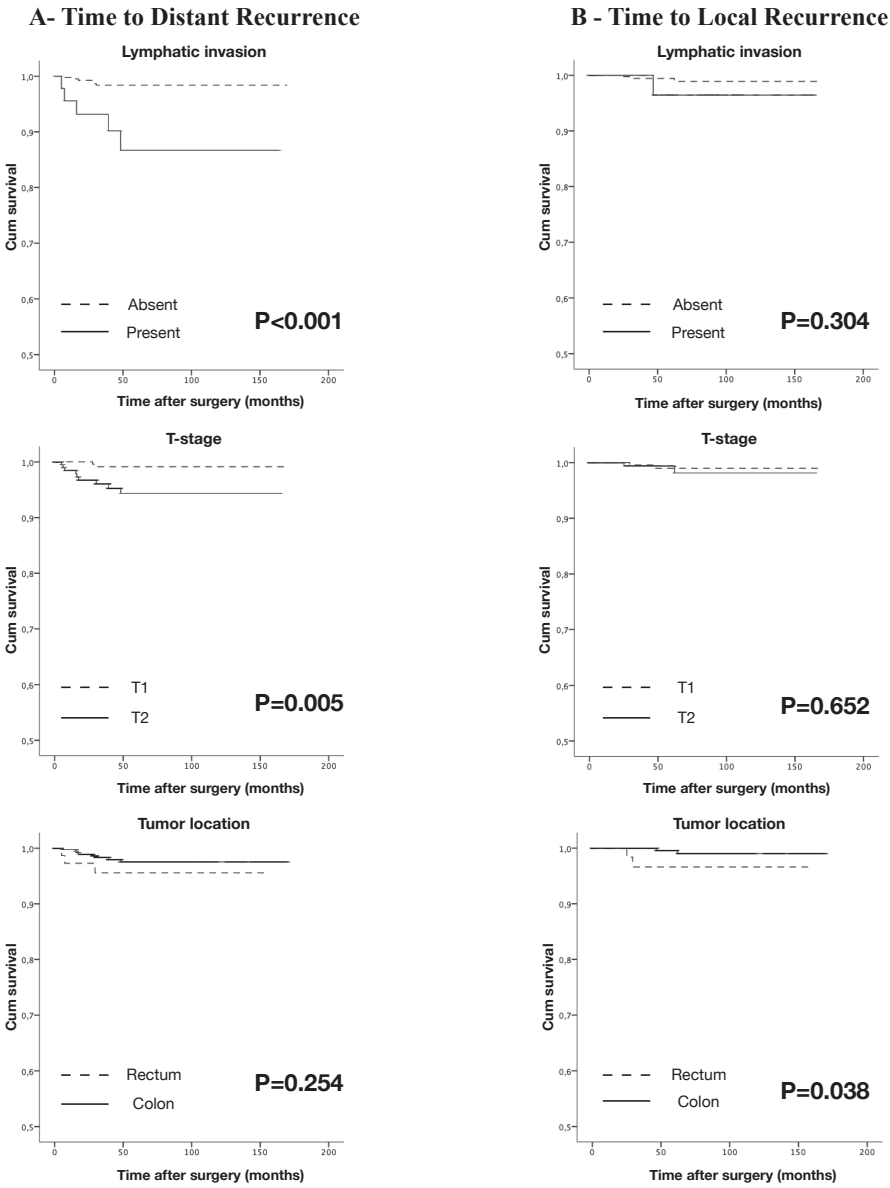
			Disease-free survival **			
			Univariate		Multivariate	
	1Y estimate	5Y estimate	HR (95% CI)	P-value	HR (95% CI)	P-value
Colon cancer	99.7%	97.1%	0.43 (0.14 – 1.38)	0.144		
ASA III-IV	99.3%	94.8%	1.74 (0.60 – 5.01)	0.300		
Age ³65 years	99.6%	96.4%	0.91 (0.32 – 2.60)	0.862		
Male gender	99.2%	97.2%	1.08 (0.64 – 1.82)	0.785		
Alcohol abuse	96.7%	96.7%	0.97 (0.35 – 2.68)	0.952		
Open approach	99.2%	95.9%	1.87 (0.58 – 5.98)	0.285		
Postoperative complication	99.3%	97.7%	0.55 (0.15 – 1.95)	0.344		
Tumor size ³2 cm	99.0%	95.2%	2.29 (0.71 – 7.45)	0.155		
T2 tumor	98.4%	93.8%	5.56 (1.55 – 19.94)	0.003	3.61 (0.92 – 14.09)	0.065
Lymphatic invasion	95.6%	83.6%	7.14 (2.48 – 20.57)	<0.001	4.26 (1.38 – 13.20)	0.012
Venous invasion	95.8%	95.8%	1.83 (0.24 – 14.00)	0.557		
Perineural invasion	100%	90.0%	3.84 (0.50 – 29.41)	0.163	3.60 (0.47 – 27.86)	0.219
LN ³12	99.5%	96.8%	0.75 (0.21 – 2.69)	0.656		

* Variables included in the model: T2 stage, lymphatic invasion
** Variables included in the model: T2 stage, lymphatic invasion, perineural invasion

outcomes, our study underlines the excellent prognosis, with an estimated 5-year overall survival of 84.3% for colon cancer and 85.5% for rectal cancer.[3] Yet, disease recurrence still occurred in 2.3% of all colon cancer patients and in twice as many rectal cancer patients (4.7%). The corresponding 5-year disease-free survival was 97.1% and 94.0%, respectively. After adjustment, lymphatic invasion was found to be an independent predictor for worse disease-free survival. The prognostic impact of T2 tumors was present, with higher hazard ratios, though not significant.

The impact of depth of tumor invasion in lymph-node negative disease is better understood in rectal cancer than colon cancer.[6,16] The increase over the last decade in local excisions for T1-2 rectal cancer and

Figure 1. Kaplan-Meier curves for local and distant recurrence



subsequently the need to stratify risk factors for poor outcomes in early stage rectal cancer have certainly contributed to that. As a result, the current NCCN, ESMO, and Japanese guidelines for stage I rectal cancer are based more on facts than assumptions.[4-5, 17-18] When pathology demonstrates either a T2 tumor or other high-risk features including deep submucosal invasion (>1 mm), positive margins, poorly differentiated tumors, and lymphovascular invasion, a transabdominal resection or adjuvant chemoradiation is required after a transanal excision. Considering colon cancer, one could presume that the risk factors applicable to stage I rectal cancer are valid for colon cancer as well, but definitive knowledge is lacking. Little is written about pT1-2N0 colon cancers, since previous studies included either all

node-negative patients (pT1-pT4) [9-10] or investigated predictors for lymph-node metastasis.[11-13] Additionally, the need to subdivide high- and low-risk stage I colon cancer patients has been less mandatory considering surgery as the gold standard associated with an excellent overall prognosis. The incremental benefit of postoperative treatment in lymph-node negative colorectal cancer in general is small, and most likely even smaller for T1-T2 tumors. Considering the risk of overtreatment and the associated morbidity of postoperative chemotherapy, indiscriminate use of postoperative treatment in localized CRC is definitely not recommended. However, assessing high-risk features in early stage CRC might help to determine which patients would benefit from adjuvant therapy. Unfortunately, other than requirements after a local excision, recommendations for pT2 tumors with poor histology after a complete surgical resection remain unclear and data concerning stage I colon cancer in general is deficient.

For stage I colorectal cancer, the cause of disease recurrence is either undetectable local residual of the tumor or the presence of micrometastasis. Okabe et al demonstrated already a decade ago the association between LVI and micrometastasis in patients with N0 disease in colorectal cancer.[19] Moreover, multiple studies reported histologic predictors for lymph-node metastasis, including lymphovascular invasion.[20-21] In addition to that, a recent prospective multicenter trial concluded that LVI, along with high tumor grade, was correlated with occult nodal metastases in patients with colon cancer extended to the muscularis propria or beyond.[22] Along with T2 tumors, LVI is one of the histologic risk factors for which a local excision is contraindicated according to current guidelines. However, recommendations for LVI positive T1 or T2 tumors after surgical resection remain unclear and do not differ from LVI negative tumors as only surveillance is required in both groups, starting one year after surgery. In addition to previous studies, our study underlined the impact of lymphovascular invasion in surgically treated lymph-node negative T1 and T2 tumors as the presence of LVI was even stronger related to disease recurrence than pathologic T-stage. Moreover, an important difference between lymphatic and vascular invasion was demonstrated since only the first was found to be associated with worse outcomes. Tumors with lymphatic invasion carried over fourfold higher hazard ratios of disease-free survival (HR: 4.26, P=0.012), and lymphatic invasion was even stronger associated with time to distant recurrence (HR: 8.02, P<0.001). Moreover, LVI in general was associated with other high-risk features in stage I disease, including pT2 tumors, high-grade tumors, and perineural invasion. Of all patients whom developed distant recurrence, 45.5% had LVI positive tumors. This number was even more remarkable in rectal cancer (66.7%), and especially true for liver metastasis since all rectal cancer patients who were diagnosed with liver metastasis during their follow-up were LVI positive.

Besides the pathological risk factors found in our study, a number of differences between colon and rectal cancer were assessed. Previous studies elaborated on this distinction [23-25] which have led to modifications in treatment patterns and a more targeted disease management.[4-5] Considering stage I CRC, guidelines are not different and additional treatment in general after surgery is not given. Our study demonstrated a significant difference in the distribution of histopathologic factors, including more T2 tumors, LVI, MSI stable or low tumors in rectal cancer patients. Nevertheless, tumor location was only associated with local recurrence. The

fact that the incidence of venous invasion and not lymphatic invasion was higher, might be a reasonable explanation for the comparable disease-free survival. Furthermore, we included only patients who underwent a surgical resection, which have led to a relatively higher number of T2 tumors in the rectal cohorts, since most T1 tumors were approached by a local excision. Incorporating those findings, we might conclude that guidelines for colon and rectal cancers do not need to be different in this early stage of disease.

Despite the existing controversy as to whether endoscopic removal of malignant colorectal polyps is feasible and as safe as the standard surgical approach [26-28] it is clear that endoscopic removal for early stage colonic neoplasms has gained a lot of interest over the last years. As colonoscopic devices and techniques continue to improve, an increase in non-surgical treatment is expected, both in colon as well as rectal cancer. Additionally, an increase in early stage colorectal cancer is estimated due to colorectal screening. All of this increases the need to identify high-risk patients in this stage of disease. To our knowledge, this is one of the first studies that included only patients with stage I colon and rectal cancer and found a significant impact of lymphatic invasion in both tumor locations. Nevertheless, this study has several limitations. Although our database was prospectively maintained, potential biases inherent to our retrospective design apply to our study. Despite the noteworthy number of patients whom were referred to our hospital, possibly because of a relatively high comorbidity rate or difficulty of the surgical approach, the recurrence rate was lower compared to previous studies. The fact that we excluded all local excisions might have contributed to this relatively low recurrence rate. With regards to the low incidence of disease recurrence, we could only adjust for strongly associated univariate variables to minimize potential bias. Moreover, rates of disease-specific survival were too low to perform Cox proportional hazard models to assess independent factors associated with colorectal cancer mortality. Nonetheless, the main strength of the current study is the comparison between only stage I colon and rectal cancer patients, who underwent surgery in one single center during the same time frame.

In conclusion, although disease recurrence is uncommon in stage I colorectal cancer, it occurs. Lymphatic invasion is an independent predictor for worse disease-free survival and in particular, strongly associated with distant recurrence. Therefore, we should be aware of potential worse outcomes in patients with lymphatic invasion in T1-T2 lymph-node negative colorectal tumors. The question now remains as to whether T2 and even T1 patients who have lymphatic invasion should receive routine oncologic follow-up or even adjuvant chemotherapy considering the risks of overtreatment and the marginal benefit in lymph-node negative colorectal cancer in general.[29]

REFERENCES

1
Siegel RL, Miller KD, Stacey A. Colorectal Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:177-193

2
Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544-573

3
Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975- 2013. Bethesda, MD: National Cancer Institute; 2016

4
National Comprehensive Cancer Network. Colon Cancer (Version 2.2016).

5
National Comprehensive Cancer Network. Rectal Cancer (Version 2.2016).

6
Patel SA, Chen YH, Hornick JL, Catalano P, Nowak JA, Zukerberg LR, Bleday R, Shellito PC, Hong TS, Mamon HJ. Early-stage rectal cancer: clinical and pathologic prognostic markers of time to local recurrence and overall survival after resection. Dis Colon Rectum 2014;57:449-459

7
Bouvier AM, Launoy G, Bouvier V, Rollot F, Manfredi S, Faivre J, Cottet V, Jooste V. Incidence and patterns of late recurrences in colon cancer patients. Int J Cancer 2015;137:2133–2138

8
Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Iversen ER, Kristensen B, Gögenur I; Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. The Lancet Oncology 2015;16:161-168

9
Mroczkowski P, Schmidt U, Sahm M, Gastinger I, Lippert H, Kube R. Prognostic factors assessed for 15,096 patients with colon cancer in stages I and II. World J Surg 2010;36:1693-1698

10
Young PE, Womeldorph CM, Johnson EK, Maykel JA, Brucher B, Stojadinovic A, Avital I, Nissen A, Steele SR. Early detection of colorectal cancer recurrence in patients undergoing surgery with curative intent: current status and challenges. J Cancer 2014;5:262-271

11
Kawachi H, Eishi Y, Ueno H, Nemoto T, Fujimori T, Iwashita A, Ajioka Y, Ochiai A, Ishiguro S, Shimoda T, Mochizuki H, Kato Y, Watanabe H, Koike M, Sugihara K. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol 2015;28:872–879

12
Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal IDI. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827-834

13
Huh JW, Kim HR, Kim YJ. Lymphovascular or perineural invasion may predict lymph node metastasis in patients with T1 and T2 colorectal cancer. J Gastrointest Surg 2010;14:1074-1080

14
Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106

15
Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA Cancer J Clin 2009;59:366-378

16
Veereman G, Vlayen J, Robays J, Fairon N, Stordeur S, Rolfo C, Bielen D, Bols A, Demetter P, D'hoore A, Haustermans K, Hendlisz A, Lemmers A, Leonard D, Penninckx F, Van Cutsem E, Peeters M. Systematic review and meta-analysis of local resection or transanal endoscopic microsurgery versus radical resection in stage I rectal cancer: A real standard? Crit Rev Oncol Hematol 2017;114:43-52

17
Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, Arnold D; ESMO Guidelines Working Group. Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi64–vi72

18
Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 2018;23:1-34

19
Okabe S, Shia J, Nash G, Wong WD, Guillem JG, Weiser MR, Temple L, Sugihara K, Paty PB. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. J Gastrointest Surg, 2004;8:1032-1039

20
Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200-206

21
Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patients with pT1 and pT2 colorectal cancer. World J Surg 2007;31:1485-1490

22
Wasif N, Faries MB, Saha S, Turner RR, Wiese D, McCarter MD, Shen P, Stojadinovic A, Bilchik AJ. Predictors of occult nodal metastasis in colon cancer: results from a prospective multicenter trial. Surgery 2010;147:352-357

23
Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–442

24
van der Sijp MP, Bastiaannet E, Mesker WE, van der Geest LG, Breugom AJ, Steup WH, Marinelli AW, Tseng LN, Tollenaar RA, van de Velde CJ, Dekker JW. Differences between colon and rectal cancer in complications, short-term survival and recurrences. Int J Colorectal Dis 2016;31:1683-1691

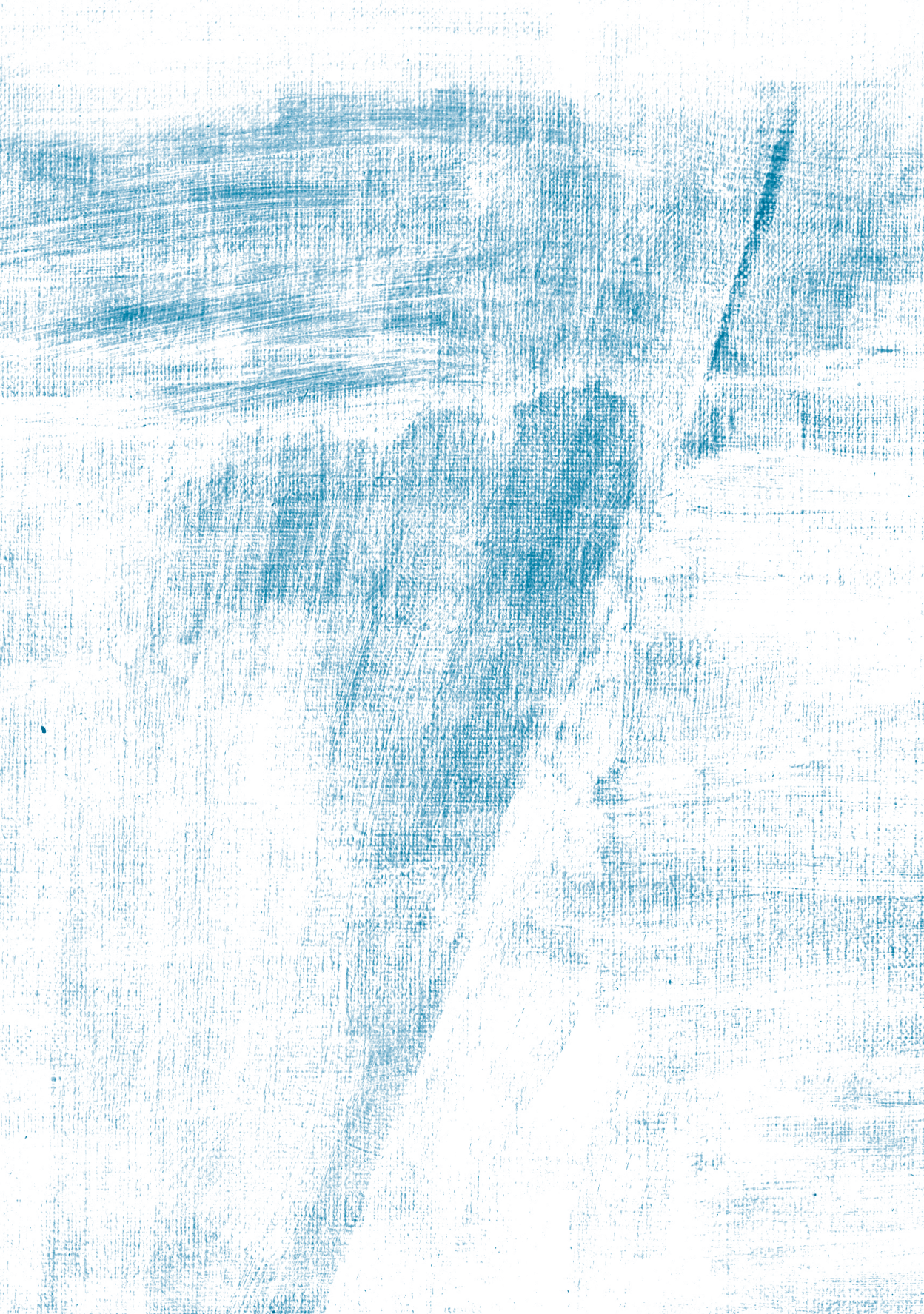
25
Tamas K, Walenkamp AME, de Vries EG, van Vugt MA, Beets-Tan RG, van Etten B, de Groot DJ, Hospers GA. Rectal and colon cancer: Not just a different anatomic site. Cancer Treat Rev 2015;41:671–679

26
Backes Y, de Vos Tot Nederveen Cappel WH, van Bergeijk J, Ter Borg F, Schwartz MP, Spanier BWM, Geesing JMJ, Kessels K, Kerkhof M, Groen JN, Wolfhagen FHJ, Seerden TCJ, van Lelyveld N, Offerhaus GJA, Siersema PD, Lacle MM, Moons LMG. Risk for incomplete resection after macroscopic radical endoscopic resection of T1 colorectal cancer: a multicenter cohort study. Am J Gastroenterol. 2017;112:785-796

27
Seitz U, Bohnacker S, Seewald S, Thonke F, Brand B, Braiutigam T, Soehendra N. Is endoscopic polypectomy an adequate therapy for malignant colorectal polyps? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789-1797

28
Yoshii S, Nojima M, Nosho K, Omori S, Kusumi T, Okuda H, Tsukagoshi H, Fujita M, Yamamoto H, Hosokawa M. Factors Associated With Risk for Colorectal Cancer Recurrence After Endoscopic Resection of T1 Tumors. Clin Gastroenterol Hepatol 2014;12:292-302

29.
Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020-2029



CHAPTER 3

The IMPACT of POSTOPERATIVE MORBIDITY ON SURVIVAL in PATIENTS with METASTATIC COLON and RECTAL CANCER

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ABSTRACT

INTRODUCTION

Avoiding postoperative morbidity is essential in patients with advanced cancer. To further improve treatment in stage IV colorectal cancer, knowledge about risk factors which effect short- and long-term outcomes is important.

METHODS

All stage IV colon and rectal cancer who underwent elective surgery between 2004-2015 were included (n=345). We compared resectable colon (RCC) and rectal (RRC) patients, and unresectable colon (UCC) and rectal cancer patients (URC).

RESULTS

Median follow-up duration was 22.2 (unresectable) and 56.7 months (resectable) with no difference in tumor location. Colon cancer patients were more often considered unresectable (P<0.001). Rectal procedures were correlated with a higher morbidity rate and a longer surgical duration (P<0.001). In the resectable cohort, obese patients, open procedures and a prolonged surgery were independently associated with postoperative complications. Considering the palliative group, neoadjuvant treatment and age were correlated with worse outcomes. Morbidity was not associated with long-term outcomes in the resectable cohort. However, unresectable patients who developed respiratory (HR 7.53) or cardiac (HR 3.75) complications and patients with an ASA-score III-IV (HR 1.51) had an impaired survival.

CONCLUSION

Our results emphasize the need for an adequate pre-operative assessment to identify patients at risk for postoperative complications and impaired survival.

INTRODUCTION

Despite improvements in diagnosis and treatment, colorectal cancer remains a major cause of morbidity and mortality worldwide. Each year, more than one million people are diagnosed with colon or rectal cancer with an estimated annual mortality rate of more than 600,000. [1] Of all newly diagnosed cases in the United States, approximately 22% of colon cancer patients and 18% of all rectal cancer patients have synchronous distant metastasis at the time of diagnosis, with a dismal 5-year survival of 13.6% and 14.6%, respectively.[2] Treatment options include systemic therapy and tumor resection. In patients with resectable metastases, the benefit of metastatectomy is well established. However, 75-90% of all patients with distant metastasis (American Joint Committee on Cancer (AJCC) stage IV disease) present with unresectable metastases and the role of surgical intervention for this group remains controversial.[3-5]

The current National Comprehensive Cancer Network (NCCN) guidelines recommend surgery only in symptomatic patients, including those with bowel obstruction, perforation or excessive bleeding, as these situations may preclude a patient's ability to receive adjuvant therapy.[6-7] Nonetheless, a portion of asymptomatic non-curative patients undergo surgical resection.[8] A few retrospective studies advocate primary tumor resection in asymptomatic patients to prevent local tumor complications and subsequent emergency surgery.[9-15] Furthermore, despite advantages in palliative systemic therapy, recent meta-analyses demonstrated a survival benefit of 5-8 months when surgery was performed when compared to systemic therapy alone.[3,5,15] However, most studies are limited by potential selection bias, since younger or healthier patients with less comorbidity are more likely to undergo surgery.

Avoiding prolonged hospital stay or high morbidity rates is essential in patients with advanced cancer and a limited life expectancy. To further improve both curative and palliative treatment in stage IV colorectal cancer, knowledge about risk factors for worse short- and long-term outcomes is essential. Therefore, the purpose of this study was to identify predictors for postoperative morbidity and assess whether poor short-term outcomes effect oncologic long-term outcomes. These determinants might help clinicians in the decision as to whether or not to perform a resection of the primary tumor in advanced colon and rectal cancer. Additionally, due to distinct differences between colon and rectal cancer in terms of tumor biology, treatment patterns and a suggested different metastatic pattern [16], we evaluated the differences between stage IV colon and rectal cancer and the impact of postoperative outcomes.

MATERIALS & METHODS

STUDY DESIGN AND POPULATION

All consecutive patients who underwent surgical resection for primary colorectal cancer at Massachusetts General Hospital between January 1st 2004 and December 31st 2015 were entered into a prospectively maintained database, approved by the Institutional Review Board. During the study period, 345 patients presented with stage IV disease, of whom 80 (23.2%) underwent emergent surgery. In order to standardize the groups,

emergent cases (complete bowel obstruction, perforation or excessive bleeding) were excluded as were patients who underwent non-resective surgery (diagnostic laparotomy, enteric bypass, stoma). The majority of all elective surgically treated patients were colon cancer patients (64.5%). Colon cancer included all tumors between the cecum and sigmoid, whereas all tumors within 15 cm of the anal verge were defined as rectal cancer. We divided the groups into patients with resectable (N=119) and unresectable metastases (N=146). Clinically resectable metastases included metastases confined to the liver, lung, or resectable metastasis in the reproductive organs. Liver metastases were deemed unresectable when major hepatic vessels were involved, less than two contiguous liver segments could be preserved or in cases when future liver remnant would not be adequate. Furthermore, unresectable cases included all extrahepatic disease other than resectable lung or ovarian metastases [17,18] as well as patients with a poor general health status. Baseline metastasis included all metastasis diagnosed before surgery, while long-term metastasis comprised all metastatic diagnosis after this period. In order to assess differences between tumor location, we divided the groups into resectable colon (RCC) and rectal cancer (RRC), and unresectable colon (UCC) and rectal cancer (URC).

DATA COLLECTION

The following data was prospectively collected for all patients: baseline characteristics (site of primary lesion, age, gender, ASA-score, BMI), carcinoembryonic antigen, metastatic pattern, extent of metastatic spread, surgical characteristics (approach, duration, multivisceral resection), pathological features (depth of local tumor invasion (pT), lymph node metastases (pN), grade of tumor differentiation (poor versus well/moderate), extramural vascular invasion (EMVI), lymphovascular invasion (LVI), perineural invasion, number of harvested lymph nodes, tumor size, R0 resection), and the admission of neoadjuvant and adjuvant treatment. Baseline metastasis included all metastasis diagnosed before surgery, while long-term metastasis comprised all metastatic diagnosis after this period. Short-term outcomes (length of stay, readmission, surgical and medical complications), and survival status were also reported. Data on long-term outcomes were updated periodically by reviewing patient's records and the Massachusetts General Hospital cancer registry. Patients alive at the closure of the study (April 30, 2018) or lost to follow-up were censored using the appropriate statistic methods. All time to events was calculated from date of diagnosis.

MORBIDITY

Postoperative morbidity was defined as any surgical or medical (systemic) complication that occurred within 30 days of surgery. Surgical complications included postoperative ileus, anastomotic leak, surgical site infection, fascial dehiscence, sepsis, and gastrointestinal bleeding. All other complications were defined as medical problems, excluding the requirement for blood transfusion, the need to transfer a patient to the ICU or death. Anastomotic leakage was defined as any intra-abdominal abscess and/or dehiscence or leakage at the anastomotic site. Cardiovascular complications included cardiac arrest, arrhythmias, and acute coronary syndrome, excluding pre-existing atrial fibrillation. Respiratory events im-

plicated pneumonia, acute respiratory distress syndrome, pleural effusion, atelectasis, and pulmonary embolism. Renal complications included both renal failure as well as renal insufficiency. Urinary complications included confirmed urinary tract infections, retention, and urinary incontinence.

STATISTICAL ANALYSES

Categorical variables are presented as the percentage of patients, and differences were assessed using a Chi-squared (χ^2) test. Continuous variables are presented as the median and interquartile range (IQR) or the mean ± standard deviation (SD), according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Differences in continuous variables were analyzed using a Mann-Whitney U test. Survival-analyses were performed with Kaplan-Meier curves, using a log-rank test. To identify predictors for surgical and medical complications, logistic regression analysis was performed. Explanatory variables with univariate P-values ≤ 0.05 as well as important clinical variables and confounders formed the provisional model. The Hosmer-Lemeshow test was used to assess the goodness-of-fit of the predictive models.[19] The results in postoperative morbidity are reported as odds ratio (OR) with a 95% confidence interval (CI). Multivariate Cox regression analyses were conducted to identify independent predictors for overall survival. All significant pre- and perioperative univariate variables were included in the model, as well as variables who changed the model by 10% or more. Survival results are reported as hazard ratios (HR) with a 95% confidence interval (CI). Throughout all statistical analyses a two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.).

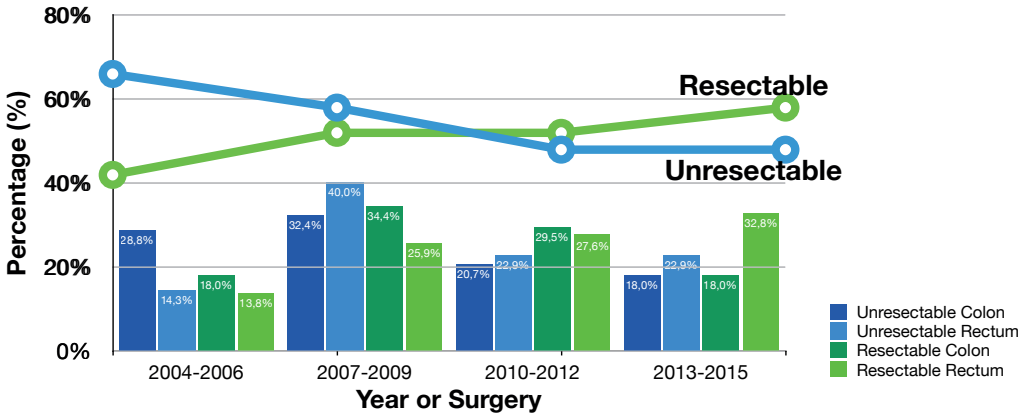
RESULTS

BASELINE CHARACTERISTICS

Of the 345 patients who presented with metastatic colorectal cancer during our study period, 119 (34.5%) patients underwent an elective procedure that was deemed resectable. The prevalence of unresectable disease was higher in colon cancer than rectal cancer (64.3% versus 38.3%, P<0.001). As demonstrated in Figure 1, there was a trend toward fewer primary tumor resections in unresectable cases over time. This was particularly true for rectal cancer.

Table 1 demonstrates differences between tumor location in stage IV disease. Unresectable patients were significantly older (mean 60.5 ±14.5 versus 56.6 ±12.6, P=0.034. Nonetheless, other demographics including comorbidity (mean ASA unresectable: 2.4 ±0.59 versus resectable: 2.3 ±0.52, P=0.072), gender (male: 47.3% versus 52.9%, P=0.358), referred patients (58.2% versus 64.7%, P=0.289) and overall rate of post-operative complications (42.5% versus 33.6%, P=0.141) were comparable. Colon cancer cases were more often considered unresectable (64.3% versus 38.3%, P<0.001) and presented with metastases in more than one organ (32.7% versus 18.1%, P0.011). Moreover, colon cancer patients were older with a significant difference in the resectable cohort (mean 59.2 versus 54.0 years, P=0.028) and had a lower Carcinoembryonic Antigen (CEA) level

Figure 1. Trend PTR



at diagnosis in resectable cases (median 12.8 versus 34.0 mg/L, P=0.006). Pre-operative laboratory results demonstrated anemia and leukocytosis in colon cancer patients (P=0.003, P=0.033, respectively), though this was not significant in subgroup analysis. Regardless of the curability of the disease, rectal cancer patients were more often referred from an outside hospital (52.0% versus 78.7%, P<0.001), and in line with current guidelines, RC patients received more neoadjuvant treatment (27.5% vs. 91.5%, P<0.001).

Histopathologically, colon cancers were associated with worse features including slightly more T4 tumors (unresectable: 61.8% versus 58.3%, P=0.001; and lymph-node positive disease (resectable: 7.7% versus 55.2%, P=0.006). RRC was, on the other hand, associated with a larger tumor size (4.1 cm versus 5.4 cm, P=0.029). Other poor factors were equally distributed. Local tumor clearance was achieved in more than 95% of all resectable cases, without any difference in tumor location. However, rates of R0-resection were slightly lower in the UCC group compared to URC (71.8% vs. 86.1%, P=0.084). As shown in figure 2, the metastatic pattern was different between the groups. The vast majority of the curative patients had liver metastasis (colon: 91.8%, rectal: 89.7%). Considering unresectable patients, RC was significantly correlated with lung metastasis (P=0.002), whereas non-curative CC patients had more peritoneal carcinomatosis (UCC: 39.6% versus URC: 20.0%, P=0.034).

PERIOPERATIVE AND POSTOPERATIVE OUTCOMES

Table 2 demonstrates differences in intra-operative and postoperative outcomes. Open surgery was the chosen approach in the majority of all cases. Surgical duration was significantly longer for rectal procedures in both groups (unresectable 142 versus 187 min, P=0.002; resectable 170 versus 261 min, P=0.001). Metastectomy was performed in 16.4% of all unresectable cases, and in 80.7% of all resectable cases. Surgical removal of metastasis was more often performed before primary tumor resection in resectable rectum cancer patients (9.8% versus 27.6%), whereas resectable colon cancer patients underwent more two-stage procedures (21.3% versus 10.3%).

Patients who underwent a rectal procedure developed more complications, regardless of the treatment intent. Both medical and surgical morbidity rates were higher, with a slight difference between unresectable and resectable cases. The URC group had higher rates of postoperative ileus (OR: 3.46, 95% CI: 1.38 – 8.66, P=0.006), surgical site infections (OR: 11.28, 95% CI: 2.16 – 58.8, P=0.001), and urinary problems (OR: 4.62, 95% CI: 1.92 – 11.12, P=0.001) compared to UCC. Short-term outcomes were also worse for the resectable rectal group compared to the resectable colon group, with a significant odds ratio for urinary problems (OR: 10.29, 95% CI: 2.24 – 47.38, P<0.001). The higher morbidity rate in the rectal cohort translated to a one day longer length of stay in both groups. Non-elective readmission rates were nevertheless comparable. Postoperative chemotherapy was given to the majority of all patients (80.0%). Since most resectable rectal cancer patients finished additional therapy before primary tumor resection, the rates of postoperative treatment in this group was less (70.7%, versus 91.8% RCC, P=0.003).

SURVIVAL

Median follow-up duration was 22.2 months in the palliative cohort, and 56.7 months in the resectable group with no difference in tumor location. Metastatic progression occurred more often during surveillance in the unresectable colon cohort (76.4% versus 55.6%, P=0.017). Figure 3 demonstrates the metastatic pattern during follow-up, with A: new metastasis and B: baseline and long-term metastasis combined. The only site that was significantly related to primary tumor location were bone metastasis, which were more often found as a new metastasis in unresectable rectal cancer (OR: 3.07, 95% ci: 0.96 – 9.86, P=0.050). When considering the total metastatic pattern (Figure 3B), lung metastasis remained associated with unresectable rectal cancer (OR: 2.67, 95% CI: 1.23 – 5.80, P=0.012), and peritoneal carcinomatosis with unresectable colon cancer (OR: 2.37, 95% CI: 1.26 – 4.47, P=0.005).

Rates of overall and disease-specific survival were comparable, as were the log-rank analyses. The estimated 5-year survival in unresectable patients was 4.9% for CC and 3.8% for RC (P=0.921), with an expected higher rate for resectable cases (64.3% versus 57.1%, P=0.446). When analyzing the effect of morbidity on long-term outcomes, we found sig-

Figure 2. Metastatic pattern: baseline

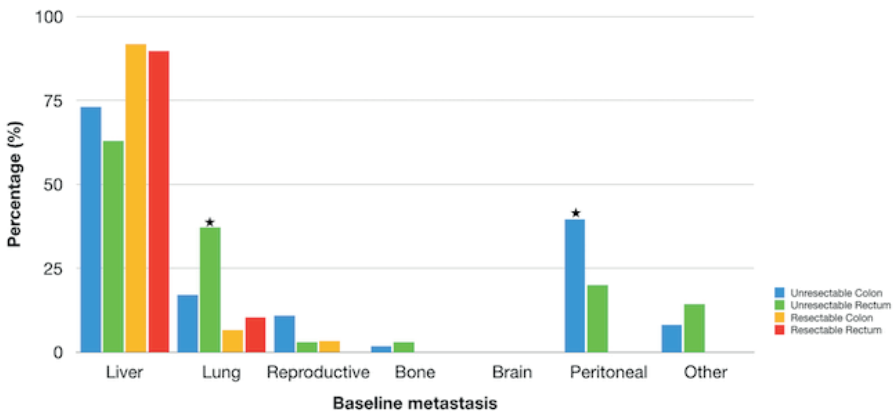


Table 1. Clinical and pathological features of the study population

	Study cohort (N=265)				Unresectable cases (N=146)			Resectable cases (N=119)		
	Total	Colon 171 (64.5%)	Rectum 94 (35.5%)	P	Colon 110 (75.3%)	Rectum 36 (24.7%)	P	Colon 61 (51.3%)	Rectum 58 (48.7%)	P
Baseline										
Age	58.6 ±13.8	59.7 ±14.0	54.3 ±13.3	0.109	60.1 ±14.5	61.8 ±14.5	0.500	59.2 ±13.0	54.0 ±11.7	0.028
Gender, *female*	133 (50.2%)	91 (53.2%)	42 (44.7%)	0.184	60 (54.5%)	17 (47.2%)	0.445	31 (50.8%)	25 (43.1%)	0.399
ASA-score	2.4 ±0.6	2.4 ±0.6	2.4 ±0.6	0.857	2.4 ±0.6	2.5 ±0.7	0.277	2.3 ±0.6	2.3 ±0.5	0.899
CEA (µg/L)	25.0 (9.0 – 87.3)	22.2 (5.0 – 84.9)	35.0 (18.8 – 106.4)	0.016	26.4 (6.4 – 125.1)	39.0 (19.5 – 204.5)	0.223	12.8 (4.5 – 45.2)	34.0 (18.5 – 82.0)	0.006
Pre-op anemia	116 (48.7%)	86 (55.8%)	30 (35.7%)	0.003	60 (61.2%)	14 (46.9%)	0.154	26 (46.4%)	15 (28.8%)	0.060
Pre-op leukocytosis	42 (17.6%)	33 (21.6%)	9 (10.6%)	0.033	23 (23.2%)	5 (15.6%)	0.361	10 (18.5%)	4 (7.5%)	0.092
Unresectable mets	146 (55.1%)	110 (64.3%)	36 (38.3%)	<0.001	100%	100%		0%	0%	
Distant metastasis				0.011			0.558			0.438
Single organ	192 (72.5%)	115 (67.3%)	77 (81.9%)		58 (52.7%)	21 (58.3%)		57 (93.4%)	56 (96.6%)	
Multiple organs	73 (27.5%)	56 (32.7%)	17 (18.1%)		52 (47.3%)	15 (41.7%)		4 (6.6%)	2 (4.3%)	
Neoadjuvant therapy	133 (50.2%)	47 (27.5%)	86 (91.5%)	<0.001	20 (18.2%)	31 (86.1%)	<0.001	27 (44.3%)	55 (94.8%)	<0.001
Referred patient	160 (61.1%)	88 (51.8%)	72 (78.3%)	<0.001	59 (53.6%)	26 (72.2%)	0.050	29 (48.3%)	46 (82.1%)	<0.001
Pathology										
Extent of invasion				<0.001			0.005			0.010
T1	10 (3.8%)	5 (2.9%)	5 (5.3%)		2 (1.8%)	1 (2.8%)		3 (4.9%)	4 (6.8%)	
T2	12 (4.5%)	1 (0.6%)	11 (11.7%)		1 (0.9%)	3 (8.3%)		0 (0.0%)	8 (13.8%)	
T3	144 (54.3%)	82 (48.0%)	62 (66.0%)		39 (35.5%)	21 (58.3%)		43 (70.5%)	41 (70.7%)	
T4	99 (37.4%)	83 (48.5%)	16 (17.0%)	<0.001	68 (61.8%)	11 (30.6%)	0.001	15 (24.6%)	5 (8.6%)	0.020
Lymph node metastasis				0.002			0.396			0.023
N0	64 (24.2%)	31 (18.1%)	33 (35.1%)		18 (16.4%)	7 (19.4%)		13 (21.3%)	26 (44.8%)	
N1	97 (36.6%)	62 (36.3%)	35 (37.2%)		32 (29.1%)	14 (38.9%)		30 (49.2%)	21 (36.2%)	
N2	104 (39.2%)	78 (45.6%)	26 (27.7%)		60 (54.5%)	15 (41.7%)		18 (29.5%)	11 (19.0%)	
Tumor size, *cm*	4.9 (3.0 – 8.3)	4.8 (3.1 – 7.0)	5.1 (2.5 – 25.0)	0.211	6.0 (3.6 – 7.6)	4.5 (2.5 – 25.0)	0.994	4.1 (2.4 – 5.3)	5.4 (2.0 – 25.8)	0.029
Lymph-node harvested	19 (15 – 26)	19 (15 – 27)	19 (15 – 24)	0.269	19 (14 – 27)	17 (14 – 21)	0.082	19 (15 – 28)	21 (15 – 26)	0.831
LN ≥12	232 (87.5%)	152 (88.9%)	80 (85.1%)	0.372	95 (86.4%)	29 (80.6%)	0.398	57 (93.4%)	51 (87.9%)	0.299
Poorly differentiated	75 (28.5%)	60 (35.5%)	15 (16.0%)	0.001	48 (43.6%)	10 (27.8%)	0.091	12 (20.3%)	5 (8.6%)	0.072

EMVI	128 (48.3%)	87 (50.9%)	41 (43.6%)	0.258	64 (58.2%)	21 (58.3%)	0.987	23 (37.7%)	20 (34.5%)	0.715
LVI	186 (70.2%)	128 (74.9%)	58 (61.7%)	0.025	90 (81.8%)	27 (75.0%)	0.373	38 (62.3%)	31 (53.4%)	0.328
Perineural invasion	118 (44.9%)	83 (49.1%)	35 (37.2%)	0.063	62 (56.9%)	18 (50.0%)	0.472	21 (35.0%)	17 (29.3%)	0.508
Final diagnosis				0.043			0.336			0.189
Adenocarcinoma	241 (90.9%)	151 (88.3%)	90 (95.7%)		94 (85.5%)	33 (91.7%)		57 (93.4%)	57 (98.3%)	
Mucinous	24 (9.1%)	20 (11.7%)	4 (4.3%)		16 (14.5%)	3 (8.3%)		4 (6.6%)	1 (1.7%)	
R0-resection	226 (85.3%)	139 (81.3%)	87 (92.6%)	0.013	79 (71.8%)	31 (86.1%)	0.084	60 (98.4%)	56 (96.6%)	0.529

Proportions are presented for categorical data, means with SD for ASA-score and age. Median with IQR for all other continuous data.
Abbreviations: ASA: American Society of Anesthesiologists, CEA: Carcinoembryonic Antigen; EMVI: extramural vascular invasion; LVI: lymphovascular invasion

Table 2. Intra- and postoperative differences between colon or rectum cancer in resectable and unresectable cases.

	Study cohort (N=265)				Unresectable cases (N=146)			Resectable cases (N=119)		
	Total	Colon 171 (64.5%)	Rectum 94 (35.5%)	Total	Colon 171 (64.5%)	Rectum 94 (35.5%)	Total	Colon 171 (64.5%)	Rectum 94 (35.5%)	Total
Surgery										
Operation 2010-2015	123 (46.4%)	71 (41.5%)	52 (55.3%)	0.031	42 (38.2%)	17 (47.2%)	0.337	29 (47.5%)	35 (60.3%)	0.161
Operating time, *min*	173 (102–255)	148 (90–205)	226 (162–298)	<0.001	142 (95 – 195)	187 (137 – 286)	0.002	170 (83 – 262)	261 (190 – 304)	0.001
Open approach	209 (78.9%)	132 (77.2%)	77 (81.9%)	0.368	91 (82.7%)	31 (86.1%)	0.634	41 (67.2%)	46 (79.3%)	0.137
Metastatectomy	120 (45.3%)	66 (38.6%)	54 (57.4%)	0.003	20 (18.2%)	4 (11.1%)	0.320	46 (75.4%)	50 (86.2%)	0.136
Timing of metastatectomy				0.001			0.163			0.056
Before CRC resection	25 (9.4%)	7 (4.1%)	18 (19.1%)		1 (0.9%)	2 (5.6%)		6 (9.8%)	16 (27.6%)	
During CRC resection	29 (10.9%)	18 (10.5%)	11 (11.7%)		8 (7.3%)	0 (0.0%)		10 (16.4%)	11 (19.0%)	
After CRC resection	45 (17.0%)	26 (15.2%)	19 (20.2%)		9 (8.2%)	2 (5.6%)		17 (27.9%)	17 (29.3%)	
Two-stage resection	21 (7.9%)	15 (8.8%)	6 (6.4%)		2 (1.8%)	0 (0.0%)		13 (21.3%)	6 (10.3%)	
Admission										
Admission duration	5 (4 – 8)	5 (4 – 8)	6 (4 – 8)	0.235	5 (4 – 8)	6 (4 – 10)	0.711	4 (3 – 6)	5 (4 – 7)	0.016
Complication rate	102 (38.5%)	52 (30.4%)	50 (53.2%)	<0.001	39 (35.5%)	23 (63.9%)	0.003	13 (21.3%)	27 (46.6%)	0.004
Surgical complications	64 (24.2%)	30 (17.5%)	34 (36.2%)	0.001	22 (20.0%)	16 (44.4%)	0.004	8 (13.1%)	18 (31.0%)	0.018
Ileus	37 (14.0%)	17 (9.9%)	20 (21.3%)	0.011	13 (11.7%)	11 (31.4%)	0.006	4 (6.6%)	9 (15.5%)	0.117
Intra-abdominal leak/abscess	17 (6.4%)	8 (4.7%)	9 (9.6%)	0.120	7 (6.3%)	4 (11.4%)	0.317	1 (1.6%)	5 (8.6%)	0.082
Surgical site infection	20 (7.5%)	7 (4.1%)	13 (13.8%)	0.004	2 (1.8%)	6 (16.7%)	0.001	5 (8.2%)	7 (12.1%)	0.483
Sepsis	6 (2.3%)	3 (1.8%)	3 (3.2%)	0.452	3 (2.7%)	1 (2.8%)	0.987	0 (0.0%)	2 (3.4%)	0.144
Medical complications	61 (23.0%)	28 (16.4%)	33 (35.1%)	0.001	24 (21.8%)	15 (41.7%)	0.019	4 (6.6%)	18 (31.0%)	0.001
Respiratory	8 (3.0%)	6 (3.5%)	2 (2.1%)	0.530	5 (4.5%)	1 (2.8%)	0.643	1 (1.6%)	1 (1.7%)	0.971
Pneumonia	6 (2.3%)	5 (2.9%)	1 (1.1%)	0.330	4 (3.6%)	0 (0.0%)	0.246	1 (1.6%)	1 (1.7%)	0.971
Cardiac	7 (2.6%)	5 (2.9%)	2 (2.1%)	0.699	4 (3.6%)	0 (0.0%)	0.246	1 (1.6%)	2 (3.4%)	0.529
Urinary	45 (17.0%)	16 (9.4%)	29 (30.9%)	<0.001	14 (12.7%)	14 (38.9%)	0.001	2 (3.3%)	15 (25.9%)	<0.001
UTI	15 (5.7%)	3 (1.8%)	12 (12.8%)	<0.001	2 (1.8%)	6 (16.7%)	0.001	1 (1.6%)	6 (10.3%)	0.044
Renal	5 (1.9%)	1 (0.6%)	4 (4.3%)	0.036	1 (0.9%)	2 (5.6%)	0.088	0 (0.0%)	2 (3.4%)	0.144
Blood transfusion	48 (18.1%)	35 (20.5%)	13 (13.8%)	0.179	26 (23.6%)	6 (16.7%)	0.380	9 (14.8%)	7 (12.1%)	0.668
ICU Transfer	11 (4.2%)	6 (3.5%)	6 (6.4%)	0.282	6 (5.4%)	2 (5.7%)	0.944	0 (0.0%)	4 (6.9%)	0.037
Non-elective readmission	23 (8.7%)	11 (6.4%)	12 (12.8%)	0.080	7 (6.4%)	6 (16.7%)	0.060	4 (6.6%)	6 (10.3%)	0.457

Death	4 (1.5%)	4 (2.3%)	0 (0.0%)	0.135	4 (3.6%)	0 (0.0%)	0.246	--	--	--
Long-term										
Adjuvant therapy	212 (80.0%)	145 (84.8%)	67 (71.3%)	0.008	89 (80.9%)	26 (72.2%)	0.269	56 (91.8%)	41 (70.7%)	0.003
Metastatic progression	182 (68.7%)	121 (70.8%)	61 (64.9%)	0.325	84 (76.4%)	20 (55.6%)	0.017	37 (60.7%)	41 (70.7%)	0.250
Deceased	195 (73.6%)	133 (77.8%)	62 (66.0%)	0.037	102 (92.7%)	33 (91.7%)	0.834	31 (50.8%)	29 (50.0%)	0.929
CRC mortality	173 (65.3%)	123 (71.9%)	50 (53.2%)	0.002	98 (89.1%)	28 (77.8%)	0.087	25 (41.0%)	22 (37.9%)	0.733
Follow-up, months	37.3 (20.3-56.6)	34.6 (18.4-52.8)	44.1 (26.2-61.8)	0.020	22.2 (13.4-34.7)	22.1 (13.3-35.6)	0.995	59.4 (47.6-79.8)	53.6 (43.6-70.7)	0.179
Median survival	40.6 (34.9-46.4)	36.2 (29.2-43.2)	47.0 (40.0-54.0)	0.028*	22.5 (19.8-25.3)	21.7 (15.7-27.6)	0.921*	77.6 (61.9-93.4)	62.4 (52.4-72.3)	0.446*
Estimate 1-year survival		87.7%	92.6%		80.9%	80.6%		100%	100%	
Estimate 3-year survival		50.3%	66.9%		25.8%	30.3%		93.4%	91.4%	
Estimate 5-year survival		26.6%	37.5%		4.9%	3.8%		64.3%	57.1%	

Proportions are presented for categorical data, median with IQR for all other continuous data.
Abbreviations: CRC: colorectal cancer, UTI: urinary tract infection.
* Log-rank test

nificant better survival rates in unresectable patients who did not develop postoperative complications. The one-year estimated survival was 66.0% in patients with ≥ 1 complication(s) versus 81.0% in patients who had an uncomplicated treatment. The three- and five-year estimated survival was respectively 10.9% versus 26.6% and 0.0% versus 4.0%. P=0.042 (Figure 4).

INDEPENDENT PREDICTORS FOR POSTOPERATIVE MORBIDITY AND OVERALL SURVIVAL

Patient characteristics including ASA-score, and age were contributory in the multivariate logistic regression model of unresectable cases, though not in resectable cases and therefore excluded in the latter model (Table 3). Moreover, metastatic spread, baseline metastatic site, and pathologic features (TN-stage, vascular invasion, poor differentiation, etc.) were not correlated with postoperative morbidity in both models and thus excluded from the multivariate analysis. After adjustment, left-sided unresectable tumors did significantly better when compared to rectal tumors (OR: 0.30, 95% CI: 0.10 – 0.95, P=0.041). Postoperative morbidity was comparable between rectal tumors and right-sided tumors (OR: 0.75, 95% CI: 0.25 – 2.22, P=0.601) and transverse colon cancer (OR: 1.58, 95% CI: 0.33 – 7.62, P=0.569). Compared to right-sided tumors, left-sided tumors did slightly better (OR: 0.40, 95% CI: 0.16 – 1.05, P=0.063). Other independent predictors for postoperative complications in the unresectable cohort were age older than 60 years (OR: 2.18, 95% CI: 1.05 – 4.52, P=0.038) and administration of neoadjuvant treatment (OR: 2.84, 95% CI: 1.12 – 7.17, P=0.028).

With regards to the resectable group, tumor location did not withstand multivariate analysis. After adjustment, odds of developing postoperative complications were significantly higher in obese patients (OR: 2.88, 95% CI: 1.14 – 7.27, P=0.025), a long surgical duration (OR: 2.53, 95% CI: 1.02 – 6.23, P=0.044), and lower when a laparoscopic approach was completed (OR: 0.33, 95% CI: 0.12 – 0.93, P=0.035).

Table 4 demonstrates the independent predictors for overall survival in both unresectable and resectable patients. Features contributory in the unresectable model were ASA-score, age, leukocytosis pre-operative, respiratory and cardiac complications, as well as adjuvant chemotherapy. Other factors including tumor location, surgical complications, metastatic pattern and spread, TN-stage and other histopathologic high-risk features were not correlated to overall survival in the unresectable cohort and therefore not included in the Cox proportional hazard model. All included factors, with the exception of age (above 65 years) and adjuvant chemotherapy, remained significant and thus independently correlated to overall survival. Respiratory complications, in particular, demonstrated a strong correlation to a shorter survival time (HR: 7.53, 95% CI: 2.79 – 20.32, P<0.001).

Pathologic risk-factors, including lymph-node positive disease, EMVI and PNI were significant in the univariate analysis when considering resectable patients. In addition to those features, obesity and sepsis postoperative were included in the multivariate analysis. After adjustment, BMI ≥ 30 kg/m^2 (HR: 2.34, 95% CI: 1.30 – 4.22, P=0.005) along with N+ disease (HR: 3.04, 95% CI: 1.50 – 6.15, P=0.002) demonstrated to be independent predictors for overall survival.

Table 3. Multivariate analysis of factors associated with postoperative morbidity in unresectable and resectable stage IV colorectal cancer

	Unresectable cases				
		Univariate analysis		Multivariate analysis	
	Patient - Event (N)	OR (95% CI)	P-value	OR (95% CI)	P-value
Tumor location, colon					
Rectum	35 – 22	1.00		1.00	
Left-sided	42 – 9	0.16 (0.06 – 0.44)	<0.001	0.30 (0.10 – 0.95)	0.041
Transverse	11 – 6	0.71 (0.18 – 2.79)	0.623	1.58 (0.33 – 7.62)	0.569
Right-sided	54 - 22	0.41 (0.17 – 0.97)	0.044	0.75 (0.25 – 2.22)	0.601
ASA-score III-IV	63 – 33	2.05 (1.05 – 4.00)	0.035	1.60 (0.75 – 3.42)	0.228
Age ≥ 60 years	69 – 36	2.14 (1.10 – 4.17)	0.025	2.18 (1.05 – 4.52)	0.038
Surgical duration ≥ 180 min	53 – 28	1.91 (0.98 – 3.86)	0.056	1.83 (0.84 – 3.96)	0.126
Neoadjuvant therapy	51 – 30	2.81 (1.40 – 5.67)	0.003	2.84 (1.12 – 7.17)	0.028

	Resectable cases				
		Univariate analysis		Multivariate analysis	
	Patient - Event (N)	OR (95% CI)	P-value	OR (95% CI)	P-value
Tumor location, colon					
Rectum	57 - 26	1.00		1.00	
Left-sided	35 - 8	0.35 (0.14 – 0.91)	0.031	0.47 (0.17 – 1.32)	0.153
Transverse	2 - 1	1.19 (0.07 – 20.01)	0.903	1.13 (0.07 – 19.69)	0.934
Right-sided	23 - 5	0.33 (0.11 – 1.02)	0.053	0.46 (0.14 – 1.53)	0.205
BMI ≥ 30	28 - 15	3.05 (1.27 – 7.30)	0.011	2.88 (1.14 – 7.27)	0.025
Surgical duration ≥ 180 min	74 – 31	2.88 (1.22 – 6.84)	0.014	2.53 (1.03-6.23)	0.044
Laparoscopic approach	32 – 6	0.36 (0.13-0.97)	0.037	0.33 (0.12-0.93)	0.035

Table 4. Multivariate analysis of factors associated with overall survival in unresectable and resectable stage IV colorectal cancer

	Unresectable cases				
		Univariate analysis		Multivariate analysis	
	Median OS (months)	HR (95% CI)	P-value	HR (95% CI)	P-value
ASA-score III-IV	18.2 (vs. 25.4)	1.49 (1.06 – 2.10)	0.020	1.51 (1.05 – 2.18)	0.026
Age ≥ 65 years	18.6 (vs. 25.0)	1.44 (1.01 – 2.06)	0.043	1.44 (0.98 – 2.12)	0.066
Leukocytosis pre-op	15.1 (vs. 24.6)	1.74 (1.11 – 2.72)	0.014	1.77 (1.10 – 2.83)	0.018
Respiratory complications	3.94 (vs. 23.0)	9.86 (4.06 – 23.90)	<0.001	7.53 (2.79 – 20.32)	<0.001
Cardiac complications	2.50 (vs. 22.7)	5.15 (1.86 – 14.23)	<0.001	3.75 (1.26 – 11.20)	0.018
Adjuvant chemotherapy	24.4 (vs. 9.6)	0.58 (0.39 – 0.88)	0.008	0.76 (0.47 – 1.23)	0.266

	Resectable cases				
		Univariate analysis		Multivariate analysis	
	Median OS (months)	HR (95% CI)	P-value	HR (95% CI)	P-value
BMI ≥ 30	53.7 (vs. 77.6)	1.88 (1.05 – 3.36)	0.030	2.34 (1.30 – 4.22)	0.005
Sepsis post-operative	35.3 (vs. 71.2)	4.29 (1.03 – 17.87)	0.029	1.12 (0.22 – 5.71)	0.892
N+ disease	64.5 (vs. 153.9)	2.99 (1.51 – 5.91)	0.001	3.04 (1.50 – 6.15)	0.002
EMVI	62.0 (vs. 115.2)	2.03 (1.21 – 3.43)	0.006	1.67 (0.98 – 2.84)	0.061
PNI	64.5 (vs. 79.7)	1.73 (1.03 – 2.92)	0.037	1.42 (0.77 – 2.63)	0.263

Figure 3. Metastatic pattern: long-term and total

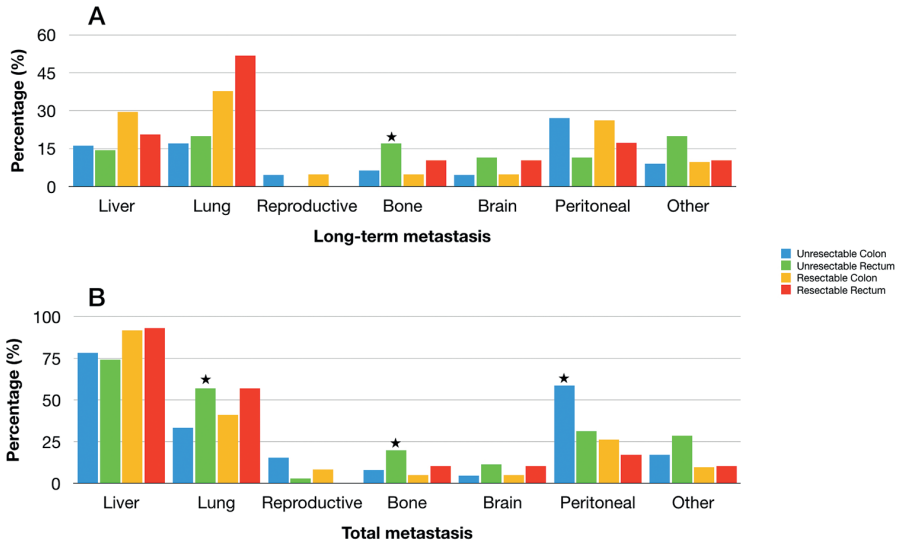
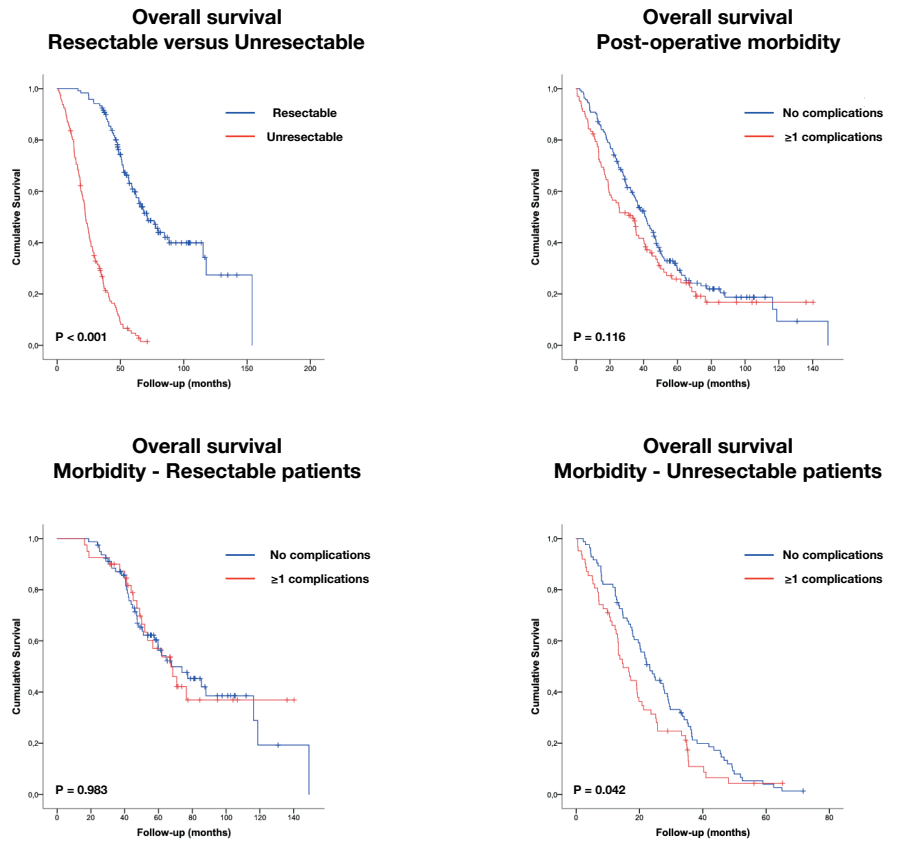


Figure 4. Kaplan Meier survival curves



DISCUSSION

In patients with advanced disease, the ultimate intent is prolonging overall survival with a high quality of life. This goal is a lot easier to achieve in patients with resectable metastasis, because of the established survival benefit of primary tumor resection in this group. Unfortunately, most patients with stage IV colon and rectal cancer require a palliative approach and surgery in these patients remains controversial. The NCCN guidelines recommend surgery only in symptomatic patients, but non-curative resection in asymptomatic patients has been advocated by different authors to prevent emergency procedures and some studies suggest a survival benefit when surgery is performed. On the other hand, colorectal surgery in general is associated with high morbidity rates which are even higher in patients with metastatic colorectal cancer.[20-21] Postoperative complications may result in delayed adjuvant therapy or even precluding postoperative chemotherapy or radiation altogether, as noted by Hendren et al.[22] It is to be expected that with the improvements in chemotherapeutic agents, the number of surgical interventions should decline. Nonetheless, the majority of stage IV colorectal cancer patients still undergo surgery. [8] Therefore, the purpose of this study was to identify independent predictors for postoperative morbidity and overall survival.

The postoperative morbidity rate was 38.5%, which is in line with previous studies.[23,24] Both surgical and medical complication rates were higher in the unresectable cohort and also after rectal procedures. In contrast to what has been reported in previous research, tumor location was not independently associated with postoperative morbidity.[25] It is reasonable to suggest that rectal procedures are correlated with higher morbidity due anatomic differences. Rectal procedures are often considered more difficult, which is also demonstrated by the high rate of referred rectal patients. However, our results imply that it is not tumor location per se but rather surgical which is more important in predicting postoperative complications. This feature is often not considered, and probably related to the aforementioned surgical difficulties.

THE IMPACT ON POSTOPERATIVE MORBIDITY AND MORTALITY

In the curative setting, obesity, long surgical duration, and open surgery were independent predictors for worse short-term outcomes, whereas morbidity was not significantly different between various primary tumor locations. Considering unresectable patients, age over 60 years and patients who received neo-adjuvant treatment did significantly worse. The actual question is, however, not only whether morbidity impacts quality of life but also survival duration. Irrespective of the curability of the disease, the risk of postoperative morbidity and the possible impact thereof should always be weighed against the potential long-term benefit of primary tumor removal. This decision is obviously easier in patients with resectable metastasis, because of the known advantage of resection on survival. According to our findings, the impact of postoperative morbidity on long-term outcomes is less profound in resectable cases than unresectable cases. While respiratory and cardiac complications after surgery were independent predictors for overall survival in the palliative group, factors including obesity and lymph-node positive disease were determinative in a curative setting. Medical and surgical complications were not con-

tributory in the latter model. This underscores the feasibility of primary tumor resection when metastasis appeared to be resectable, whereas the decision to perform PTR in unresectable cases requires a certain caution, in particular in patients with a poor performance status and respiratory or cardiac comorbidities, according to our results. In addition to an adequate pre-operative assessment, a more intense follow-up schedule could be considered in patients with those comorbidities. Additionally, pathologic outcomes were found to be of a significant impact on survival in resectable patients, though not in the palliative group. This may be explained by the high incidence of poor histopathological outcomes in the unresectable group which makes it less distinctive. The majority of unresectable patients had a T4N2 tumor (51.3%) and at least one other risk factor (vascular invasion, perineural invasion, poor differentiation). Considering all aforementioned results, the impact on survival in unresectable patients is most likely a combination of a poor pre-operative status (a higher ASA-score including respiratory and/or cardiac problems) as well as a delay in post-operative treatment.

CURRENT PERSPECTIVES

Chemotherapeutic agents have improved significantly in the last two decades and subsequently there is an increasing trend in nonoperative management in advanced colorectal cancer. [8] Hu et al. conducted a population-based study including data from January 1988 to December 2010 and found a notable reduction in PTR in 2001. This is most likely explained by the change in chemotherapeutic regimens. After 2000, FOLFOX and FOLFIRI became the recommended first-line chemotherapy after the results of several phase-III trails.[26-28] In the following years, several other agents have received FDA approval for the treatment of advanced colorectal cancer demonstrating a significant survival benefit.[29-33] However, despite all improvements in non-surgical treatment, more than 50% of all stage IV patients still received surgery in 2010. Our results, starting in 2004 when the new agents were already being used, also demonstrated a trend toward less resections. Though surgery still plays a significant role in asymptomatic stage IV colorectal patients. The importance of surgery was stressed by our results, demonstrating a median survival of 22.2 months in the unresectable cohort. Compared to recent studies, which found a median survival in between 16 and 23 months after surgery in asymptomatic unresectable stage IV colorectal patients, our results are at the high end and emphasize the benefit of PTR.[3,5,34-37] Although significant selection bias exists in the studies, and patients are more likely to undergo surgery when they have a good performance status and metastatic disease is limited, PTR remained significantly associated with better outcomes after conducting multivariate analysis. Moreover, several meta-analyses found no association between surgery and patient characteristics (age or ASA-grade), which suggests selection bias may be confined to metastatic burden. Median age and comorbidity rate were comparable between our unresectable cohort and the patient population in previous literature. Therefore, we conclude that surgical resection of the primary tumor in unresectable stage IV patients is associated with improved survival, though, randomized controlled trials are needed to confirm this statement. Currently, all randomized controlled trials have failed to recruit enough patients and did not reach the required power. Yet a number of trials evaluating this topic are ongoing.[38-40]

CONCLUSION

Primary tumor resection in advanced colorectal cancer is debatable. Although our results underline the previously reported improved survival after resection, a high morbidity rate remains associated with surgery. The key-question in patients with an impaired life expectancy is not only whether management of the primary tumor effects survival but also to what extent postoperative complications might impact further treatment and quality of life. Our results indicate characteristics in which we may have to be more cautious in suggesting surgery for specific patients diagnosed with advanced colorectal cancer, because of the associated morbidity. Moreover, the results question whether we should perform surgery on patients with unresectable colorectal cancer and a poor performance status or respiratory or cardiac comorbidities because of the associated mortality. Nonetheless, to truly evaluate the impact of primary tumor resection in advanced colon and rectal cancer randomized controlled trials are required.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.

2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

3. Ahmed S, Shahid RK, Leis A, et al. Should noncurative resection of primary tumor be performed in patients with stage IV colorectal cancer? A systematic review and meta-analysis. *Curr Oncol* 2013;20:e420-441.

4. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. *J Clin Oncol* 2012;30:3223-3228.

5. Clancy C, Burke JP, Barry M, et al. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Ann Surg Oncol* 2014;21:3900-3908.

6. National Comprehensive Cancer Network. Colon Cancer (Version 2.2018).

7. National Comprehensive Cancer Network. Rectal Cancer (Version 2.2018).

8. Hu CY, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. *JAMA Surg* 2015;150:245-251.

9. Joffe J, Gordon PH. Palliative resection for colorectal carcinoma. *Dis Colon Rectum* 1981;24:355–360.

10. Longo WE, Ballantyne GH, Bilchik AJ, Modlin IM. Advanced rectal cancer. What is the best palliation? *Dis Colon Rectum* 1988;31:842–847.

11. Nash GM, Saltz LB, Kemeny NE, et al. Radical resection of rectal cancer primary tumor provides effective local therapy in patients with stage IV disease. *Ann Surg Oncol* 2002;9:954– 960.

12. Rosen SA, Buell JF, Yoshida A, et al. Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg* 2000;135:530–534.

13. Ruo L, Gougoutas C, Paty PB, et al. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. *J Am Coll Surg* 2003;196:722–728

14. Tebbutt NC, Norman AR, Cunningham D, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut* 2003;52:568–573.

15. Stillwell AP, Buettner PG, Ho YH. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. *World J Surg* 2010;34:797–807.

16. Qiu M, Hu J, Yang D, et al. Pattern of distant metastases in colorectal cancer: a SEER based study. *Oncotarget* 2015;6:38658-38666.

17. Saito Y, Omiya H, Kohno K, et al. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: a prognostic assessment. *J Thorac Cardiovasc Surg* 2002;124:1007–1013.

18. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008;247:125-135.

19. Hosmer, David W, Lemeshow, Stanley, John Wiley & Sons and Wiley InterScience (Online Service) *Applied logistic regression* (2nd ed). Wiley, New York, 2000.

20. Nitsche U, Stöß C, Stecher L, et al. Meta- analysis of outcomes following resection of the primary tumour in patients presenting with metastatic colorectal cancer. *Br J Surg* 2018;105:784-796.

21. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. *J Am Coll Surg* 2009;208:1009–1016.

22. Hendren S, Birkmeyer JD, Yin H, et al. Surgical complications are associated with omission of chemotherapy for stage III colorectal cancer. *Dis Colon Rectum* 2010;53:1587-1593.

23. Law WL, Chu KW. Outcomes of resection of stage IV rectal cancer with mesorectal excision. *J Surg Oncol* 2006;93:523–528.

24. Kleespies A, Füessl KE, Seeliger H, et al. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. *Int J Colorectcal Dis* 2009;24:1097-1109.

25. Kirchhoff P, Dincler S, Buchmann P. Multivariate Analysis of Potential Risk Factors for Intra- and Postoperative Complications in 1316 Elective Laparoscopic Colorectal Procedures. *Ann Surg* 2008;248:259-265.

26. Cunningham D, Pyrhönen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413-1418.

27. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. *Lancet* 2000;355:1041-1047.

28. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer: Irinotecan Study Group. *N Engl J Med* 2000;343:905-914.

29. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–1417.

30. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.

31. Rinaldi F, George E, Adler AI. NICE guidance on cetuximab, bevacizumab, and panitumumab for treatment of metastatic colorectal cancer after first-line chemotherapy. *Lancet Oncol* 2012;13:233–234.

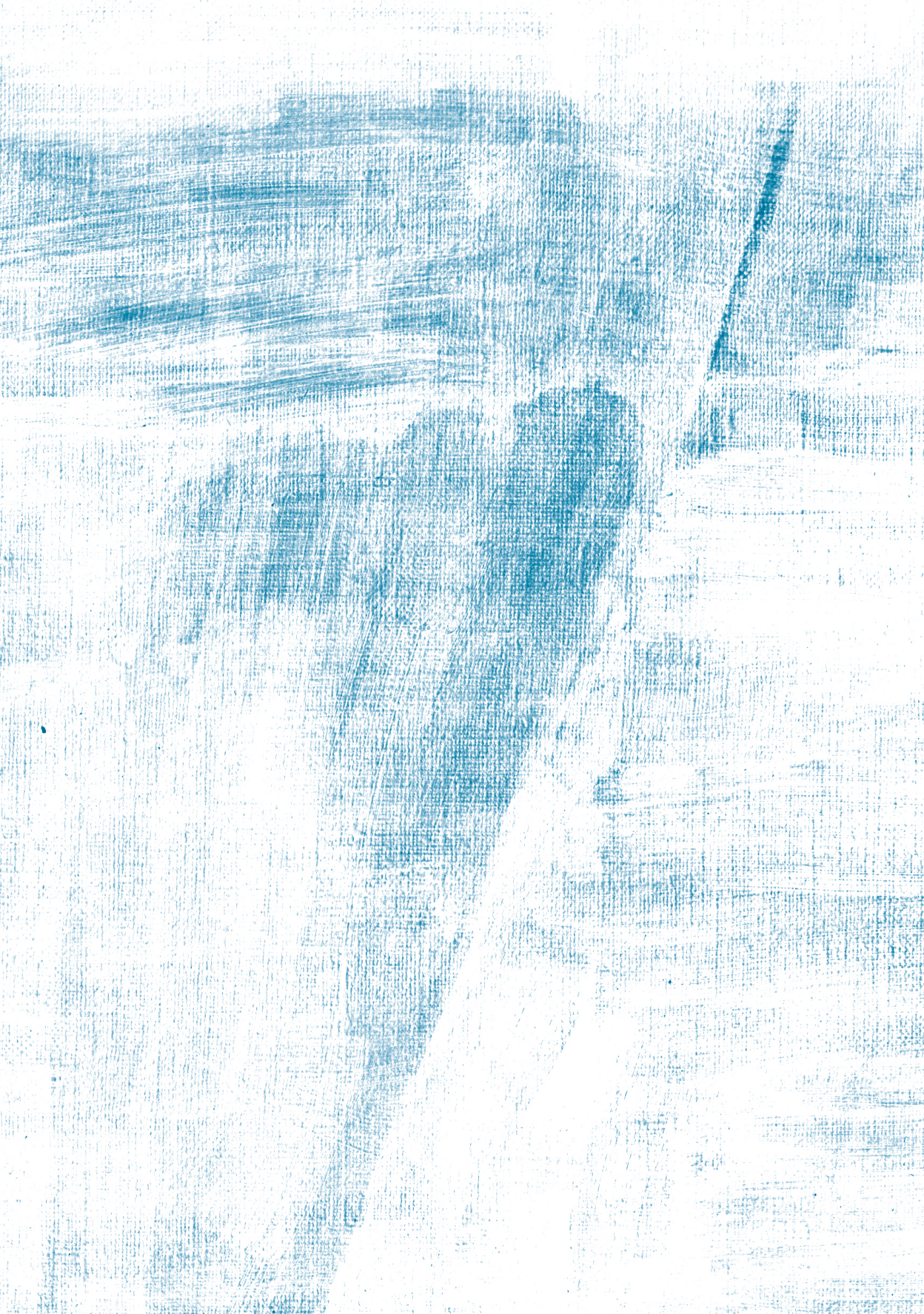
32. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol* 2001;19:2282–2292.

33. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;30:3499-3506.

34.
Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann Surg Oncol* 2011;18:3252-3260.
35.
Gresham G, Renouf DJ, Chan M, et al. Association between palliative resection of the primary tumor and overall survival in a population-based cohort of metastatic colorectal cancer patients. *Ann Surg Oncol* 2014;21:3917-3923.
36.
Tarantino I, Warschkow R, Worni M, et al. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients. *Ann Surg* 2015;262:112-120.
37.
't Lam-Boer J, Van der Geest LG, Verhoef C, et al. Palliative resection of the primary tumor is associated with improved overall survival in incurable-stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands. *Int J Cancer* 2016;139:2082-2094.
38.
't Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer—a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014;14:741.
39.
Biondo S, Frago R, Kreisler, et al. Impact of resection versus no resection of the primary tumor on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4). *Int J Colorectal Dis* 2017;32:1085-1090.
40.
Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS—a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012;12:142.

PART II

SURGICAL PROCEDURES and OUTCOMES in COLON CANCER



CHAPTER 4

A TRANSVERSE COLECTOMY is AS SAFE AS an EXTENDED RIGHT or LEFT COLECTOMY for MID-TRANSVERSE COLON CANCER

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ABSTRACT

BACKGROUND

Although extended colectomy is often chosen for patients with transverse colon cancer, the optimal surgical approach for mid-transverse colon cancer has not been established.

METHODS

We identified patients who underwent a transverse (TC) or an extended colectomy (EC) for mid-transverse colon cancer between 2004-2014. To adjust for potential selection bias between the groups, a propensity score matching analysis was performed.

RESULTS

A total of 103 patients were included, of whom 63% underwent EC (right 47%, left 17%) and 37% TC. EC patients tend to have worse short-term outcomes. Although fewer lymph nodes were harvested after TC, five-year overall (OS) ad disease-free survival (DFS) was comparable between the groups. When comparing long-term outcomes stage-by-stage, worse OS and DFS were seen in stage-II. All stage-II patients died of a non-cancer related cause and recurrence occurred in pT4 TC patients who did not receive adjuvant therapy. The propensity-matched cohort demonstrated similar postoperative morbidity, but more laparoscopic procedures in EC. Additionally, TC tumors were correlated with poorer histopathological features and disease recurrence was only seen after TC.

CONCLUSION

Our study underlines the oncological safety of a transverse colectomy for mid-transverse colon cancer. Although TC tumors were associated with poorer histopathological features, survival rates were comparable.

INTRODUCTION

The transverse colon is an intraperitoneal structure and entirely encased in peritoneum and therefore the least fixed part of the colon. The proximal two-thirds of the transverse colon derives from the midgut and is perfused by the middle colic artery. The latter third rises out the hindgut and is therefore supplied by the left colic artery. Because of this embryological junction, this "watershed" area is sensitive to ischemia. In addition, the transverse colon is attached to the greater omentum and is in close proximity to the upper abdominal organs, such as the liver, spleen and stomach. These factors contribute to the belief that a transverse colectomy is a technically challenging procedure compared to either a right- or left-colectomy. Consequently, transverse colectomies are often excluded from large prospective randomized controlled trials.[1-4]

Although some studies have compared different surgical approaches for transverse colon cancer, the optimal surgical approach remains unclear. Previous research demonstrated the safety and feasibility of less extensive procedures.[5-7] However, these studies focused on tumors located between the distal transverse and proximal descending colon and not specifically on tumors in the transverse colon only. Consequently, they compared extended right with left colectomy or segmental versus extensive segmental resections rather than a comparison with transverse colectomy. van Rongen et al. compared transverse colectomies to extended procedures, though these results dated from two decades ago.[8] Since knowledge is lacking about the optimal surgical approach, the decision whether to perform an extended colectomy or a transverse colectomy is based on a surgeon's preference. Therefore, the aim of this study was to assess short-term technical outcomes, as well as long-term oncologic outcomes in patients undergoing transverse colectomy for a mid-transverse colon cancer.

PATIENTS & METHODS

STUDY DESIGN AND POPULATION

This is a retrospective analysis of a prospectively maintained Institutional Review Board-approved database, including all patients who underwent surgery for colon cancer between 2004 and 2014 at Massachusetts General Hospital (n=1502). Data gathered in this database were collected from internal data repositories as well as the Massachusetts General Hospital cancer registry and the Social Security Death Index for survival data. Data on long-term outcomes is updated periodically by reviewing patient's charts and the social security death index. Records from all consecutive patients undergoing either transverse colectomy or an extended resection for mid-transverse colon cancer were reviewed (n=103), including patient characteristics, clinicopathological results, and both short- and long-term outcomes. Patients with distant metastasis, metachronous or synchronous colon cancer, as well as patients operated on in an emergency setting were excluded.

MEASURED OUTCOMES AND DEFINITION

The primary outcome measures were 5-year overall (OS) and disease-free survival (DFS), defined stage-by-stage. Secondary outcomes were histopathological differences and postoperative morbidity. Mid-transverse colon cancer was defined as a tumor located in between the hepatic and splenic flexure. Tumors located at one of either flexures were excluded. The location was based on both operative and pathology reports. The decision whether to use a laparoscopic or open approach was made by the surgeon only, based on preoperative examination and patient's history. Short-term outcomes were defined as any complications within 30 days of surgery. The overall complication rate included all postoperative events, incorporating the need for blood transfusion as well. Major complications included anastomotic leakage, sepsis, cardiac arrest, respiratory failure and mortality within 30 days of surgery. Long-term oncologic outcomes included local and distant recurrence, DFS, and OS. Survival was calculated as time from surgery to date of death or last date of follow-up. Data on long-term outcomes were periodically updated by reviewing medical records and the social security death index. The latest review of survival status was on October 30, 2017.

PROPENSITY SCORE MATCHING

To minimize the impact of treatment selection bias and potential confounding in this retrospective study, we performed propensity score matching (PSM). The propensity score was calculated based on a logistic regression model, including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, depth of tumor invasion, and nodal status. Moreover, year of surgery was included into the model in order to control for historical bias, which might be expected for studies with a long study period. After estimation of the propensity score, we matched the groups using 1:1 "nearest neighbor" matching of the logit of the propensity score with a caliper width of 0.20 of the standard deviation of the score.[9]

STATISTICAL ANALYSIS

Categorical data were presented as frequencies or percentages and compared using a Chi-square test. Continuous data were presented as the mean with a standard deviation (SD) or the median with an interquartile range (IQR) according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Differences in continuous data were assessed using Mann-Whitney *U* test. Survival analysis was determined using the Kaplan-Meier method and compared by log-rank testing. All analyses were conducted using SPSS *(IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.)*. The threshold for statistical significance was set at a two-sided P-value of < 0.05.

RESULTS

BASELINE CHARACTERISTICS AND CLINICOPATHOLOGICAL OUTCOMES

Between 2004 and 2014, a total of 103 patients underwent elective and curative surgery for mid-transverse colon cancer. Baseline characteristics for the complete study cohort are demonstrated in table 1. Median follow-up duration was 48.6 months (range 19.5-73.5). TC was performed in 38 (36.9%) patients and 65 (63.1%) patients underwent EC resection. The majority of the latter group had an extended right colectomy (n=48, 73.8%). Figure 1 displays that despite a stable incidence of mid-transverse colon cancer, the number of transverse colectomies decreased over the study period. In the first half of our study, 60.5% of all mid-transverse resections were transverse colectomies, while this was 39.5% in the second half.

Table 1. Demographics for all patients with primary mid-transverse colon cancer (n=103)

	N (%)
Age, *years*	68.62 (±14.19)
ASA-score	2.36 (±0.52)
Gender	
Female	50 (48.5%)
Male	53 (51.5%)
Surgical characteristics	
Approach	
Open	66 (64.1%)
Laparoscopic	37 (35.9%)
Procedure	
Transverse colectomy	38 (36.9%)
Extended right	48 (46.6%)
Extended left	17 (16.5%)
Pathological characteristics	
AJCC-stage	
I	32 (31.1%)
II	50 (48.5%)
III	21 (20.4%)
Tumor grade	
Poor	14 (13.6%)
Well/moderate	81 (78.6%)
Not tested	8 (7.8%)
Follow-up duration, *months*	48.6 (19.5-73.5)

Proportions are presented for categorical data, median with IQR for follow-up duration, means with SD for all other continuous data.
Abbreviations: ASA, American Society of Anesthesiologists classification; AJCC, American Joint Committee on Cancer

Clinicopathological differences between the groups are demonstrated in table 2. There were no differences with regards to baseline demographics, only a tendency toward older patients in the TC group (75.4 vs. 68.6 years). Although tumor size was not different between the two approaches, colonic resection length was significantly longer in the EC group (median 25 vs. 34 cm, P0.001). In addition, the number of harvested lymph

nodes was also greater after EC (median 17 vs. 25, P<0.001). Tumor staging was equally distributed between the surgical approaches, with the exception of slightly more T4 tumors in the EC group. Overall, the majority were staged as lymph-node negative T3-disease (AJCC IIa: N=32, 31.0%). R0-resection was achieved in comparable numbers (TC: 94.7% vs. EC 96.9%, P0.287). The presence of microsatellite instability was found to be different (P0.047), with more high microsatellite instability (MSI-H) in EC tumors (2.6% vs. 15.4%) and more stable MSI in TC tumors (21.1% vs. 9.2%). Other poor histological outcomes, such as tumor grade, extramural vascular invasion, lymphovascular invasion and perineural invasion were similar between the groups.

PERIOPERATIVE OUTCOMES

Differences in operative and short-term outcomes are demonstrated in table 3. Laparoscopic surgery was performed in one-third of our study cohort. However, the use of laparoscopic surgery increased over the study period and 73% of all laparoscopic procedures were performed in the last five years of the study. Moreover, while the use of minimally invasive surgery increased in both groups the difference between the first and second half of the study was even greater in the EC group (15% to 51% in the last five years; TC 26% to 46%). Concerning perioperative differences between the groups, EC patients were admitted two days longer (5 vs. 7 days) and tended to have a higher complication rate (39.5% vs. 49.1%). This was mainly explained by a tendency toward more postoperative ileus (10.5% vs. 16.9%, P0.375) and a higher requirement for blood transfusion after EC (18.4% vs. 29.2%, P0.223). The occurrence of a major complication was rare and not different between both groups (5.3% vs. 6.2%, P0.852). Also, the rate of minor complications such as wound infection as well as readmission rates (5.3% vs. 7.7%, P0.636) were low and comparable.

Figure 1. Distribution of surgery for mid-transverse colon cancer

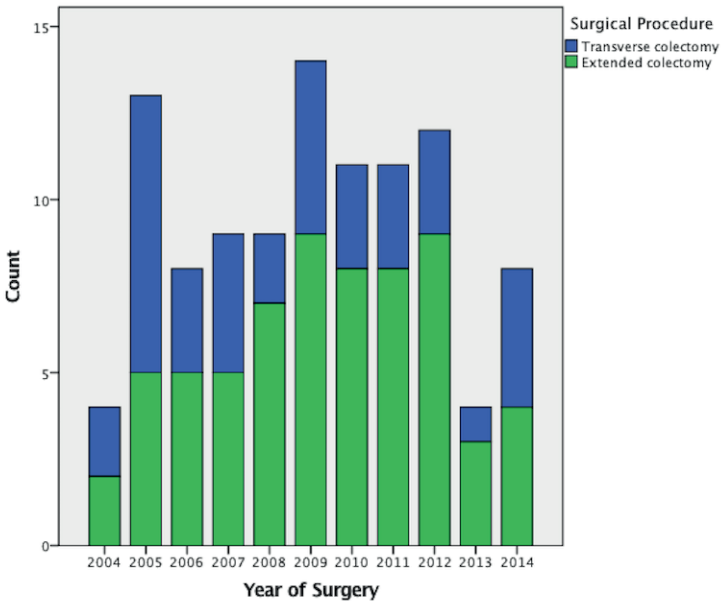


Table 2. Clinicopathological differences between transverse colectomy and extended colectomy, before (n=103) and after (n=64) propensity score matching

	Before PSM			After PSM		
	Transverse colectomy	Extended colectomy	P-value	Transverse colectomy	Extended colectomy	P-value
	N = 38 (36.9%)	N = 65 (63.1%)		N = 32 (50%)	N = 32 (50%)	
Age	75.4 (61.6-82.2)	68.6 (57.7-81.1)	0.795	78.2 (67.3-82.3)	67.5 (63.2-80.9)	0.615
Male gender	47.4	53.8	0.526	50.0	62.5	0.313
ASA	2.32 ±0.56	2.44 ±0.50	0.197	2.43 ±0.51	2.29 ±0.46	0.428
BMI, *kg/m²*	26.6 (24.0-32.1)	27.2 (23.8-29.6)	0.337	26.6 (24.6-31.9)	28.2 (24.0-31.9)	0.314
Ethnicity			0.533			0.864
Caucasian	84.2	90.8		81.3	87.5	
African American	10.5	3.1		12.5	6.3	
Others	5.2	6.1		6.2	6.2	
Prior abdominal surgery	44.7	52.3	0.458	50.0	53.1	0.802
Symptoms	55.3	63.1	0.434	50.0	59.4	0.451
Alcohol abuse	7.9	10.8	0.634	6.3	15.6	0.230
Smoking	5.3	10.8	0.340	3.1	6.3	0.554
AJCC-stage			0.573			0.715
I	26.3	33.8		31.3	34.4	
II	55.3	44.6		53.1	43.8	
III	18.4	21.5		15.6	21.9	
Depth of invasion			0.608			0.823
T1	18.4	21.5		21.9	25.0	
T2	10.5	15.4		12.5	15.6	
T3	50.0	35.4		46.9	37.5	
T4	21.1	27.7		18.8	21.9	
Nodal status			0.976			0.653
N0	81.6	80.0		84.4	81.3	
N1	13.2	13.8		9.4	15.6	
N2	5.3	6.2		6.3	3.1	
Tumor grade			0.313			0.021
Poor	15.8	12.3		15.6	0.0	
Well/moderate	81.6	76.9		81.3	84.4	
Unknown	2.6	10.8		3.1	15.6	
Tumor histology			0.266			0.375
Adenocarcinoma NOS	89.5	73.8		90.6	78.1	
Signet-ring cell	0.0	3.1		--	--	
Mucinous	5.3	12.3		3.1	9.4	
No residual	5.3	10.8		6.2	12.5	
EMVI	21.1	20.0	0.898	18.8	18.8	1
LVI	34.2	33.8	0.970	25.0	28.1	0.777
Perineural invasion	10.5	10.8	0.969	9.4	0.0	0.076
MSI			0.047			0.181
High	2.6	15.4		3.3	6.3	
Stable	21.1	9.2		21.9	6.3	
Unknown	76.3	75.4		75.0	87.5	
Tumor size	3.6 (2.6-7.1)	4.7 (2.5-7.0)	0.525	3.6 (2.6-7.1)	4.9 (2.3-6.8)	0.364
Resection length	25.0 (14.5-30.5)	34.0 (25.0-44.3)	0.001	24.0 (14.5-31.5)	37.5 (24.8-48.8)	0.005
No LN harvested	17 (12-24)	25 (20-33)	<0.001	17 (12-24)	22 (14-32)	0.060
LN >12	84.2	92.3	0.199	84.4	84.4	1
R0-resection	94.7	98.5	0.278	93.8	96.9	0.554

Abbreviations: ASA: American Society of Anesthesiologists, BMI: Body Mass Index (kg/m2), AJCC: American Joint Committee on Cancer, EMVI: extramural vascular invasion, LVI: lymphovascular invasion, MSI: microsatellite instability

Table 3. Perioperative differences between transverse colectomy and extended colectomy, before (n=103) and after (n=64) propensity score matching

	After PSM			Before PSM		
	Transverse colectomy	Extended colectomy	P-value	Transverse colectomy	Extended colectomy	P-value
Surgical duration	137 (86-179)	148 (69-208)	0.959	135 (85-179)	156 (64-224)	0.904
Laparoscopic approach	34.2	36.9	0.782	34.4	43.8	0.442
Conversion	5.3	4.6	0.883	6.3	6.3	1
Multivisceral resection	15.8	13.8	0.787	12.5	9.4	0.689
Admission duration	5 (4-8)	7 (4-10)	0.348	5 (4-8)	6 (4-10)	0.903
Complication rate, *total*	39.5	49.2	0.337	43.8	43.8	1
In-hospital morbidity rate	36.8	46.2	0.357	40.6	43.8	0.800
Major complication	5.3	6.2	0.852	6.3	6.3	1
Ileus	10.5	16.9	0.375	12.5	12.5	1
Wound infection	0.0	4.6	0.179	--	--	--
Anastomotic leakage/abscess	2.6	3.1		3.1	3.1	1
ICU transfer	5.3	1.5	0.278	6.3	3.1	0.554
Blood transfusion	18.4	29.2	0.223	21.9	31.3	0.396
Cardiac	10.5	7.7	0.623	12.5	6.3	0.391
Pneumonia	2.6	1.5	0.698	3.1	3.1	1
Renal	2.6	0.0	0.189	3.1	0.0	0.313
UTI	2.6	3.1	0.897	3.1	6.3	0.554
Readmission	5.3	7.7	0.636	6.3	9.4	0.641
Reoperation	2.6	3.1	0.897	3.1	0.0	0.313
Death	2.6	0.0	0.189	3.1	0.0	0.313
Follow-up duration	65.6 (44.1-86.7)	48.9 (16.6-79.4)	0.240	68.2 (46.1-86.9)	63.9 (28.0-94.6)	0.737
Recurrent disease	10.5	9.2	0.830	12.5	0.0	0.039
Local	0.0	3.1	0.275	--	--	--
Distant	10.5	6.2	0.424	12.5	0.0	0.039
Adjuvant chemotherapy	15.8	26.2	0.223	12.5	28.1	0.120
Diseased, all	23.7	21.5	0.801	18.2	12.1	0.492
Diseased, colon cancer	5.3	6.2	0.852	6.1	3.0	0.555

Proportions are presented for categorical data, median with IQR for all continuous data.

LONG-TERM ONCOLOGICAL OUTCOMES

Median follow-up duration was 48.6 months. Long-term oncological outcomes, including disease recurrence, administration of adjuvant chemotherapy and survival status were similar after TC and EC (Table 3). Figure 2 demonstrates the Kaplan-Meier survival curves. The estimated overall survival rate 5-years after surgery was 78.8% for the TC group, and 73.5% for the EC group (P0.992); the 5-year DFS rate was 87.0% versus 90.1%, respectively (P0.924). When comparing long-term outcomes stage-by-stage, TC patients with stage-II disease tended to have a poorer overall (76.4% vs. 87.4%, P0.284) and disease-free survival (88.4% vs. 100%, P0.122). Baseline characteristics for stage-II patients were similar between the two groups compared to the overall cohort (median age: TC 68.6 vs. EC 68.6 years; ASA-score: TC 2.3 vs. EC 2.3), but differences in postoperative treatment were more clarifying. Despite the small numbers in our cohort, there was a trend toward less adjuvant chemotherapy in pT4 stage-II TC patients (33.3% vs. 72.7%). The worse OS in the stage-II TC group was explained by differences in pre-existing comorbidity. In addition, two stage-I patients were diagnosed with recurrent disease in their follow-up. Both patients underwent an extended colectomy, but a R0 resection was not achieved.

PROPENSITY SCORE MATCHING

After propensity score matching, we repeated the bivariate analysis. A total of 64 patients were included, with comparable baseline and clinical demographics. Although T- and N-stage was equally distributed, TC tumors tend to have poorer histological outcomes, including perineural invasion, poor differentiation, and stable microsatellite instability. The difference in specimen length and harvested lymph nodes remained greater for extended procedures after matching. However, the number of cases where ≥ 12 lymph nodes were retrieved was comparable. Regarding perioperative outcomes, a laparoscopic approach was used more often for EC procedures (34.4% vs. 43.8%, P0.442). The disparity in surgical approach became larger over the study period. In the second half of the study 73.3% of all EC were laparoscopic procedures compared to 42.9% TC (P0.096). Short-term outcomes, including length of stay (P0.903), complication rate (P1.000) and rate of readmission (P0.641) and mortality (P0.313) were comparable.

Median follow-up duration was longer than five years in both groups (TC: 68.2, EC 63.9 months). TC tumors were associated with disease recurrence. While no local recurrence was found in the PSM cohort, distant recurrence occurred only after TC (12.5%). In addition, despite similarity in staging, administration of adjuvant chemotherapy was more common after EC (12.5% vs 28.1%). Kaplan Meier curves displayed an estimated 5-year OS of 78.5% after TC versus 81.3% after EC (P0.418). However, worse DFS was emphasized after log-rank testing (TC: 84.9% vs. EC: 100%, P0.050) (Figure 2). When comparing stage-by-stage, OS and DFS tend to be worse for stage-II and stage-III TC patients. Two patients with node-negative disease, but poor histology including LVI and stable MSI, developed distant recurrence. These two patients did not receive adjuvant chemotherapy in contrast with the other two patients who developed distant metastasis. They both had node-positive disease, with either EMVI

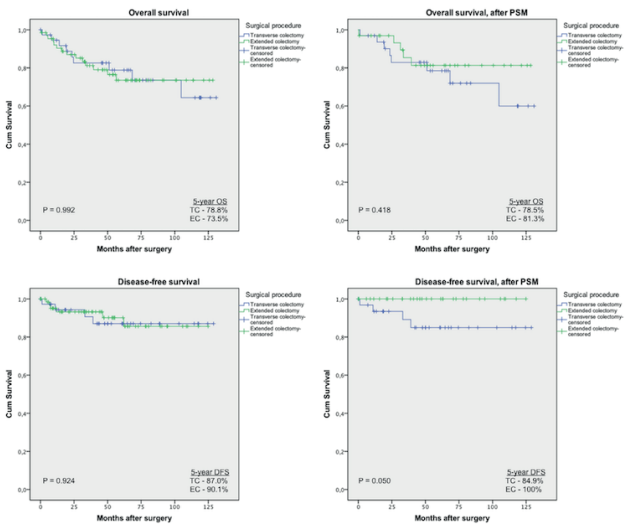
and LVI or stable MSI. Three of the four procedures were laparoscopic procedures. Regarding overall survival, TC patients did worse because of a higher pre-existing comorbidity.

DISCUSSION

Transverse colon cancer is a relatively uncommon occurrence, accounting for approximately 10% of all colon cancers.[10] The surgical approach for this tumor location is frequently based on a surgeon's preference. Due to potential vascular insufficiency, the extent of lymphadenectomy around the middle colic artery, mobilization of both flexures and proximity to upper abdominal organs, a transverse colectomy is often considered a technically challenging procedure. This contributed to the belief that a transverse colectomy is possibly not as safe as an extended right or left colectomy. Furthermore, transverse colon cancer is often excluded from previous large trials due to its low incidence and the even lower proportion of transverse colectomies. Therefore, the optimal surgical procedure for a tumor in this location is not established.

The present study assessed several key outcomes in the comparison of transverse colectomy and extended resection in stage I-III mid-transverse colon cancer. Although the incidence of mid-transverse colon cancer remained stable over the study period, we found a decreasing trend in the proportion of transverse colectomies. A transverse colectomy was mainly used in stage-II disease, while stage-I and stage-III patients were more often surgically treated with EC resection. The higher number of harvested lymph nodes in the EC group, which was previously correlated with better long-term outcomes [11], might be an obvious explanation for the preference of EC in advanced disease. Previous studies demonstrated that a greater specimen length is correlated with lymph node yield. However, resection length per se is not correlated with better outcomes.[12] In addi-

Figure 2 Cumulative overall survival and disease-free survival between transverse colectomy and extended colectomy for mid-transverse colon cancer, before and after propensity score matching



tion, Stracci et al concluded that lengths of less than 20 cm are associated with a high risk of inadequate lymph node harvest and might lead to over-treatment.[13] Although specimen length and the number of retrieved lymph nodes were remarkable smaller after TC, the outcomes were higher than the minimum required length. While the optimal number of lymph nodes required for adequate staging is argued, the reliance on guidelines which recommend a minimum of 12 is maintained and the numbers in our study are in line with this recommendation.

Laparoscopic surgery was performed in about one third of the study population, in both TC and EC procedures. However, there was a noticeable increase in the number of minimally invasive procedures over time in our study. While the rates of laparoscopic surgery increased in both TC and EC, the difference was even greater in the EC group with an average laparoscopy rate of 15% in the first half of the study period to 51% in the latter. Nonetheless, short-term outcomes were comparable between the two groups, with only a tendency toward a longer length of stay, more postoperative ileus and a higher need for blood transfusion. The higher number of laparoscopic procedures in the EC group might be a reasonable explanation for the comparable short-term outcomes, since minimally invasive surgery is associated with lower morbidity rates.[1,3] One would assume that when transverse laparoscopic surgery becomes more acceptable in the treatment of transverse colon cancer, morbidity rates will decrease for TC. Several studies demonstrated the safety and feasibility of minimally invasive surgery for transverse colon cancer [14-16], yet the use of laparoscopic surgery for TC remains relatively low.

Regarding histopathological outcomes after propensity-score matching, we found more perineural invasion, poor differentiation, and stable microsatellite-instability in the TC group. All these factors have been found to be poor prognostic factors in colon cancer. [17-19] However, despite the presence of these three poor prognostic factors in TC patients, we did not find a remarkable difference in long-term outcomes. Previous studies described 5-year overall survival rates for patients with transverse colon cancer ranging between 87.7% and 93.7% in stage-II disease and 64.2% to 89.7% in stage-III.[20-23] Disease free survival rates were slightly worse with a range of 85.5% to 94.4% in stage-II disease and 53.3% to 79.0% in stage-III disease. Rates of DFS were in line with our study, but this study had a lower overall survival rate. This might be explained by the higher average age in our study cohort. Furthermore, this study included only mid-transverse colon cancers, which are associated with poorer outcomes.[24]

To our knowledge, only one study has compared long-term outcomes between transverse colectomy and extended colectomy.[25] Chong et al found a comparable 5-year DFS estimate (TC 89.8%, EC 85.0%), but a slightly better OS in comparison to this study (TC 84.3%, EC 86.6%). However, the study by Chong did not clarify what was defined as a transverse colon cancer. One would presume that due to the low incidence of transverse colon cancer, they included both hepatic flexure and splenic flexure in the cohort. Higher overall survival could be explained by the inclusion of hepatic flexure tumors, as well as the younger median age in their cohort (60.5 vs. 68.6 years in present study).

Our study has several limitations. Despite prospectively collecting our data, a chance of bias is inherent to the retrospective design. Confounding was minimized by conducting propensity-score matching analysis. How-

ever, the decision whether to perform a TC or a more extensive procedure was solely based on a surgeon decision. Since all our surgeons are highly trained in colorectal procedures, we assume that this factor is not as confounding as the known prognostic clinicopathological features. Finally, interpretation of our results should be interpreted with care due to the low incidence of mid-transverse colon cancer and thus the relatively small numbers of patients in this study. However, to our knowledge, our study presents one of the few analyses of both short- and long-term outcomes between different surgical procedures for mid-transverse colon cancers.

CONCLUSION

Our study underlines the oncological safety of a transverse colectomy for stage I-III mid-transverse colon cancer. Despite a higher rate of open surgery in TC, postoperative morbidity was comparable. An increase in minimally invasive surgery is expected to lead to better short-outcomes and therefore may lead to more use of a transverse colectomy.

REFERENCES

1. Clinical Outcomes of Surgical Therapy Study Group (2004) A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. N Engl J Med 350:2050–2059

2. Hazebroek EJ, Color Study Group (2002) COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer. Surg Endosc 16:949–953

3. Guillou Pj, Quirke P, Thorpe H, et al (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): Multicentre, randomised controlled trial. Lancet 365:1718–1726

4. Buunen M, Veldkamp R, Hop WC, et al (2009) Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 10:44–52

5. Gravante G, Elshaer M, Parker R, et al (2016) Extended right hemicolectomy and left hemicolectomy for colorectal cancers between the distal transverse and proximal descending colon. Ann R Coll Surg Engl 98:303-307

6. Secco GB, Ravera G, Gasparo A, et al (2007) Segmental resection, lymph nodes dissection, and survival in patients with left colon cancer. Hepatogastroenterology 54:422-426

7. Beisani M, Vallribera F, García A, et al (2017) Subtotal colectomy versus left hemicolectomy for the elective treatment of splenic flexure colonic neoplasia. Am J Surg [Epub ahead of print].

8. van Rongen I, Damhuis RA, van der Hoeven JA, et al (2013) Comparison of extended hemicolectomy versus transverse colectomy in patients with cancer of the transverse colon. Acta Chir Belg 113:107–111

9. Austin PC (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceut. Statist 10:150–161

10. Wray CM, Ziogas A, Hinojosa MW, et al (2009) Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum 52:1359–1366

11. Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al (2007) Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst. 99:433–41

12. Amri R, Klos, CL, Bordeianou LG, et al (2016) The prognostic value of lymph node ratio in colon cancer is independent of resection length. Am J Surg 212:251-257.

13. Stracci F, Bianconi F, Leite S, et al (2016) Linking surgical specimen length and examined lymph nodes in colorectal cancer patients. Eur J Surg Oncol. 42:260-265

14. Yamamoto M, Okuda J, Tanaka K, et al (2012) Clinical outcomes of laparoscopic surgery for advanced transverse and descending colon cancer: a single-center experience. Surg Endosc 26:1566-1572

15. Lee YS, Lee IK, Kang WK, et al (2008) Surgical and pathological outcomes of laparoscopic surgery for transverse colon cancer. Int J Colorectal Dis 23:669-673

16. Fernández-Cebrián JM, Gil Yonte P, Jimenez-Toscano M, et al (2013) Laparoscopic colectomy for transverse colon carcinoma: a surgical challenge but oncologically feasible. Colorectal Dis 15: e79–e83

17. Le DT, Uram JN, Wang H, et al (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520

18. Knijn N, Mogk SC, Teerenstra S, et al (2016) Perineural Invasion is a Strong Prognostic Factor in Colorectal Cancer: A Systematic Review. Am J Surg Pathol 40:103-112

19. Ueno H, Kajiwara Y, Shimazaki H, et al (2012) New criteria for histologic grading of colorectal cancer. Am J Surg Pathol 36:193-201

20. Zhao L, Wang Y, Liu H, et al (2014) Long-Term Outcomes of Laparoscopic Surgery for Advanced Transverse Colon Cancer. J Gastrointest Surg 18:1003-1009

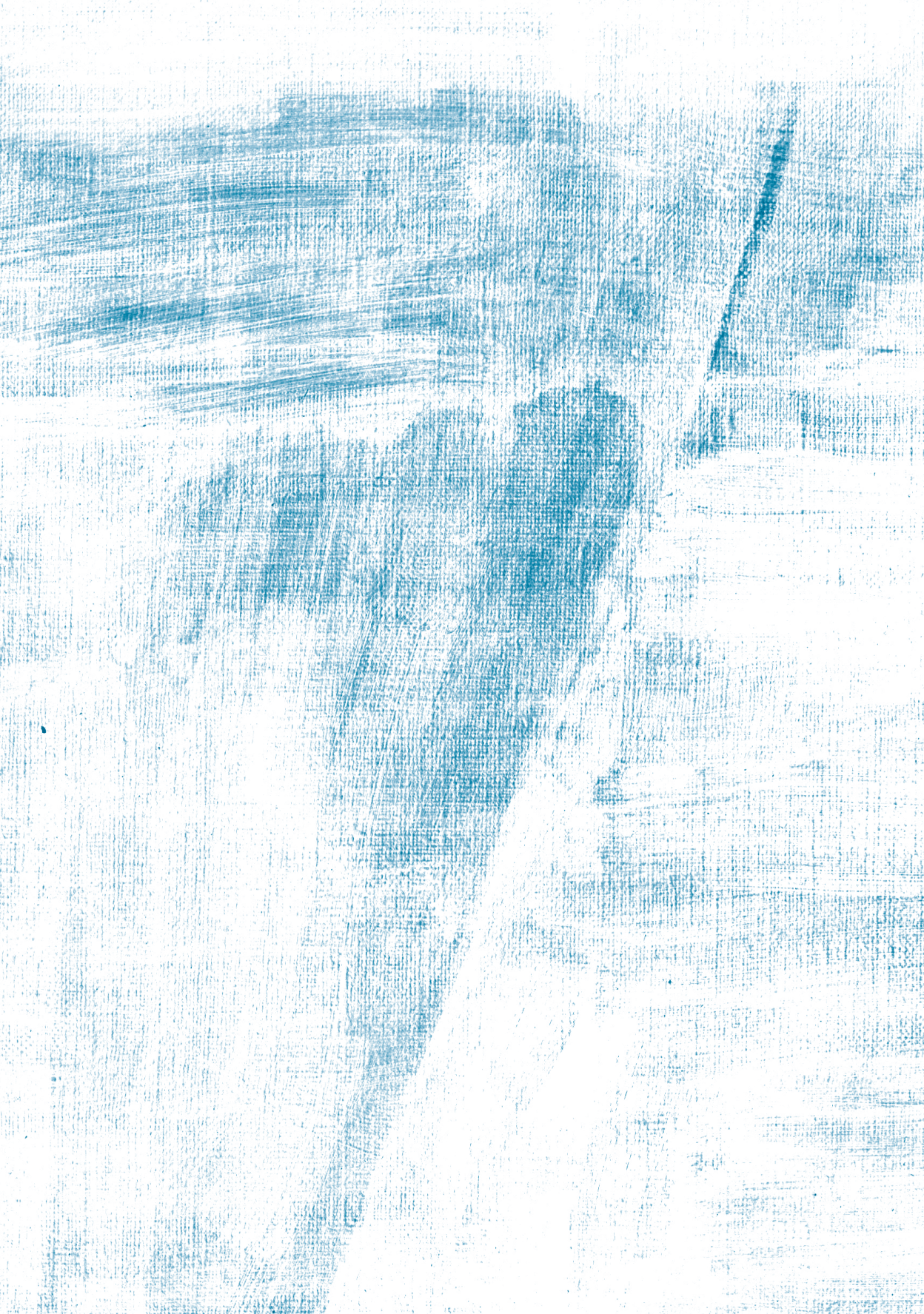
21. Yamamoto M, Okuda J, Tanaka K, et al (2012) Clinical outcomes of laparoscopic surgery for advanced transverse and descending colon cancer: A single-center experience. Surg Endosc 26:1566–1572

22. Kim MK, Won DY, Lee JK, et al (2015) Laparoscopic Surgery for Transverse Colon Cancer: Short- and Long-Term Outcomes in Comparison with Conventional Open Surgery. J Laparoendosc Adv Surg Tech A 25:982-989

23. Hirasaki Y, Fukunaga M, Sugano M, et al (2014) Short- and long-term results of laparoscopic surgery for transverse colon cancer. Surg Today 44:1266–1272

24. SJO OH, Lunde OC, Nygaard K, et al (2008) Tumour location is a prognostic factor for survival in colonic cancer patients. Colorectal Dis 10:33-40

25. Chong SC, Huh JW, Oh BY, et al (2016) Operative Method for Transverse Colon Carcinoma: Transverse Colectomy Versus Extended Colectomy. Dis Colon Rectum *59:630-9*



CHAPTER 5

Is there a DRAWBACK of CONVERTING a LAPAROSCOPIC COLECTOMY in COLON CANCER?

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ABSTRACT

BACKGROUND

Laparoscopic resection is well-established in the treatment of colon cancer. However, conversion rates remain high and the impact of conversion is disputed.

MATERIAL AND METHODS

We retrospectively identified 1347 patients who underwent surgery for colon cancer between 2004-2014 at our tertiary center. Morbidity and oncological outcomes were compared between patients who underwent successfully completed laparoscopic surgery (LS), planned open surgery (OS), and conversion to open surgery (CS). Long-term analysis included patients with stage I-III disease. In addition, we performed propensity score matching (PSM) to adjust for the heterogeneity and selection bias between the treatment groups.

RESULTS

Of all patients, 505 underwent LS, 789 OS, and 53 CS, which corresponded to a conversion rate of 9.5%. Conversion was associated with male gender, left-sided tumors, and stage-III disease. Length of stay, morbidity and readmission rates were lower for LS patients. Kaplan-Meier curves demonstrated worse overall, disease-specific, and disease-free survival in CS than LS, with similar outcomes to OS. However, after PSM, CS was only associated with admission duration and the requirement of blood transfusion while survival outcomes were comparable between all groups.

CONCLUSIONS

CS is associated with adverse short- and long-term outcomes compared to LS. However, when accounting for differences in baseline and pathologic features, CS remained only associated with a longer length of stay and more blood transfusions. Since outcomes were comparable between CS and OS, regardless of stage and other risk factors, our data supports a surgeon's attempt to perform LS in patients with colon cancer.

INTRODUCTION

Laparoscopic surgery is frequently used in the treatment of colon cancer. Large multicenter randomized controlled trials have demonstrated the safety and feasibility of a minimally invasive approach in colon cancer, with less postoperative morbidity, shorter length of stay, reduced costs [1–5], and comparable long-term oncological outcomes in comparison to open surgery.[4–9] Although laparoscopic surgery is often performed when technically feasible, many cases require conversion to open surgery due to tumor size, inability to dissect off of adjacent organs or intraoperative complications. Numerous factors associated with increased odds of conversion have been described, including patient and tumor-related factors such as age, obesity, and advanced stage of disease, as well as procedure-related factors including transverse colectomy, emergency procedures [10-12], and surgeon experience.[13-14] Despite significant improvements in laparoscopic surgery, a high rate of conversion to open surgery still exists, with an estimate of 9-17% in more recent studies.[8,12,15-17]

The impact of conversion to open surgery is disputed. Previous studies suggested a higher rate of postoperative morbidity associated with conversion in comparison to laparoscopic surgery [2,16-18], whereas others demonstrated comparable outcomes. [15,19-20] To truly identify the effect of conversion, a more relevant comparison would be between planned open surgery and converted procedures. However, only a few studies addressed this topic since most placed converted patients in the laparoscopic group, on an "intention-to-treat" basis. Some studies suggested worse outcomes in terms of postoperative morbidity [2,21], while others found comparable 30-day morbidity [17,22-23], or even improved short-term outcomes.[12,24] In addition, only a few studies focused on long-term outcomes and results suggested that conversion is associated with adverse long-term oncological outcomes.[20,25]

The purpose of this study was to evaluate the impact of conversion to open surgery on both short- and long-term outcomes in comparison to patients who underwent a successfully completed laparoscopic or planned open surgery for colon cancer in a tertiary center with highly experienced laparoscopic colorectal surgeons.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

Data for this study was extracted from a prospectively maintained, Institutional Review Board-approved database that includes a consecutive cohort of all surgically treated patients for colon cancer at Massachusetts General Hospital from 2004 through 2014. Informed consent was waived by the IRB as the research involves no more than minimal risk. All emergent cases were excluded (n=152). The remaining 1347 cases were included for subsequent analysis and categorized into three groups: patients who had successfully completed laparoscopic surgery (LS), required conversion to open surgery (CS), or underwent planned open surgery (OS).

Patient characteristics, perioperative details, pathology features and both short- and long-term outcomes were reviewed. Short–term outcomes included length of stay, rate of readmission, complications during and

post-admission, and mortality within 30-days of surgery. Long-term outcomes included local and distant recurrence rates, overall survival (OvS), disease-free survival (DFS), and disease-specific survival (DSS). Data on long-term outcomes were updated periodically by reviewing patient's records and the Massachusetts General Hospital cancer registry. The long-term analysis included only patients with AJCC stage I-III disease.

Minimally invasive surgery was introduced in our institution in the early '90s, and therefore commonly used throughout our study period. All procedures were performed by high-volume surgeons, who were very experienced in performing minimally invasive surgery in colorectal cancer. The decision as to whether to use an open or laparoscopic approach was purely surgeon's preference. Laparoscopic surgery was defined as any resection performed laparoscopically that did not require conversion to open surgery, excluding robotic assisted procedures. Anastomoses could be performed either extra- or intra-corporeally. Open surgery was classified as such when the procedure was planned and performed in an open fashion. Conversion was defined as a procedure that began laparoscopically but required proceeding to an open approach, for numerous reasons. Surgical procedures were classified into right-sided (including cecum, ascending and hepatic flexure), transverse, left-sided (including splenic flexure and descending colon), and sigmoid resections.

To adjust for the heterogeneity and selection bias between the treatment groups, propensity-matched cohort was created. The propensity score was calculated based on a logistic regression model, including age, gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), American Joint Committee on Cancer (AJCC) stage, and tumor size. In addition, we included year of surgery to control for historical bias. We assessed the three possible contrasts (LS vs. CS; CS vs. OS; LS vs. OS) separately and estimated a propensity score for each comparison group. Matching was done in a 1:1 nearest neighbor matter with a caliper width of 0.02 on the propensity score scale.[26-27]

STATISTICAL ANALYSIS

Continuous variables are presented as the mean with standard deviation (±SD) or the median and interquartile range (IQR) and were analyzed using the Mann-Whitney *U* test. Categorical variables are presented as the percentages of patients compared by the Chi-square (χ^2) test. Survival-analyses were performed with Kaplan-Meier curves, using a log-rank test, and included only patients with AJCC stage I-III disease. A multivariate Cox regression analysis was performed to identify predictive factors for poor overall (OvS) and disease-free survival (DFS). Explanatory variables with univariate P-values ≤ 0.200 were included in the multivariate analysis. The results are reported as hazard ratios (HR) with a 95% confidence interval (CI). In addition, we assessed morbidity and mortality rates in the propensity weighed cohort and performed multivariate analysis for this group separately. The threshold for statistical significance was set at a two-sided P-value of 0.05 or less. All statistical analyses were performed using SPSS *(Version 24.0; SPSS Inc, Chicago, IL, USA).*

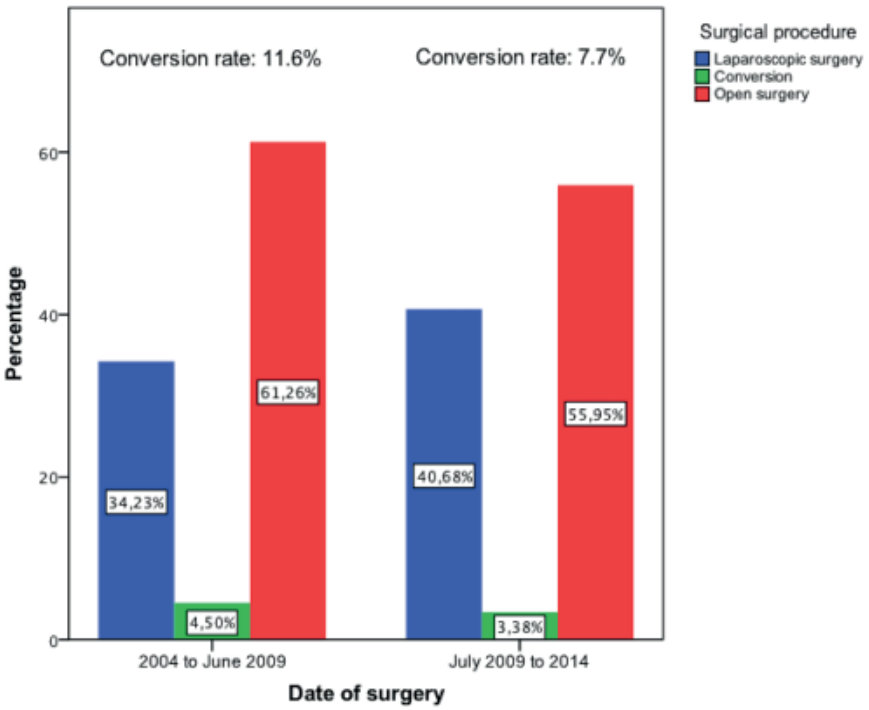
RESULTS

A total of 1347 patients underwent elective surgical treatment for colon cancer between 2004 and 2014, of whom 505 (37.5%) underwent laparoscopic surgery, 789 (58.6%) open surgery, and 53 (3.9%) required conversion to open surgery. This corresponds to a conversion rate of 9.5%. The number of patients undergoing LS increased slightly over time, from 38.7% in the first half of the study to 44.1% in the latter. The conversion rate was higher in the earlier years of the study, with an average of 11.6% in the first half to 7.7% in the latter (Figure 1). The main reasons for conversion were adhesions (24.5%), tumor size (13.2%), tumor adherence (13.2%), poor visualization (7.5%), access or location of tumor (7.5%), bleeding (5.7%).

BASELINE AND PATHOLOGIC CHARACTERISTICS

Conversion was significantly associated with male-gender, higher ASA-score, alcohol abuse or smoking compared to LS. Other than gender, we found no differences in baseline characteristics between CS and OS patients (Table 1). In addition, left-sided tumors required significantly more conversions (P0.032), and there was a trend toward more conversion for transverse tumors (13.2% vs. 7.3%, P0.132). The majority of the CS patients had advanced disease, with significantly more lymph-node positivity compared to LS tumors (P0.026). Extramural vascular invasion (EMVI), lymphovascular invasion (LVI), and perineural invasion were also correlated to CS tumors compared to LS. Pathologic features were comparable with OS tumors, with the exception of more stage-III and less stage-I tumors in CS patients. As indicated before, size of tumor was associated with

Figure 1. Incidence of conversion over the study period



requirement for conversion (median 3.9 vs. 4.5 cm, P0.030). Although a longer colonic specimen length was retrieved after conversion than LS (median 22 vs. 27 cm, P0.020), fewer lymph-nodes were harvested (21 vs. 18, P0.009). Tumor size (4.5 vs. 4.0 cm) and resection length (27 vs. 23 cm) were non-significantly larger after conversion compared to OS.

Table 1. Baseline and pathologic characteristics

	Laparoscopic surgery	Conversion	Open	P-value LS vs CS	P-value OS vs CS
n = 1347	505 (37.5%)	53 (3.9%)	789 (58.6%)		
Age	64.5 (52.8-75.4)	68.5 (60.1-78.1)	68.6 (57.0-79.5)	0.060	0.929
Male gender	245 (48.5%)	35 (66.0%)	392 (49.7%)	0.015	0.021
BMI	26.4 (23.2-30.0)	27.4 (24.9-30.6)	26.6 (23.0-31.6)	0.063	0.193
ASA	2.21 (±0.53)	2.45 (±0.64)	2.44 (±0.58)	0.004	0.918
Alcohol abuse	26 (5.1%)	7 (13.2%)	63 (8.0%)	0.018	0.182
Smoker, ever	223 (44.2%)	31 (58.5%)	426 (54.0%)	0.046	0.525
Prior abdominal surgery	171 (33.9%)	23 (43.4%)	374 (47.4%)	0.166	0.572
Tumor location					
Right-sided	290 (57.4%)	26 (49.1%)	476 (60.3%	0.242	0.105
Transverse	37 (7.3%)	7 (13.2%)	84 (10.6%)	0.132	0.561
Left-sided	41 (8.1%)	9 (17.0%)	78 (9.9%)	0.032	0.100
Sigmoid	168 (33.3%)	16 (30.2%)	206 (26.1%)	0.650	0.514
Stage					
0	23 (4.6%)	2 (3.8%)	30 (3.8%)	0.794	0.992
I	158 (31.3%)	6 (11.3%)	181 (22.9%)	0.002	0.049
II	141 (27.9%)	14 (26.4%)	240 (30.4%)	0.816	0.539
III	142 (28.1%)	22 (41.5%)	193 (24.5%)	0.042	0.006
IV	41 (8.1%)	9 (17.0%)	145 (18.4%)	0.032	0.799
T4 tumor	79 (15.6%)	12 (22.6%)	186 (23.6%)	0.190	0.877
N+	179 (35.4%)	27 (50.9%)	318 (40.3%)	0.026	0.127
M+	18 (3.6%)	5 (9.4%)	82 (10.4%)	0.041	0.824
High Grade	68 (13.5%)	11 (20.8%)	154 (19.5%)	0.148	0.826
EMVI	114 (22.6%)	21 (39.6%)	247 (31.3%)	0.006	0.208
LVI	153 (34.7%)	22 (52.4%)	248 (40.4%)	0.023	0.127
Perineural invasion	83 (16.4%)	16 (30.2%)	175 (22.2%)	0.013	0.178
Resection length, cm*	22 (16-28)	27 (19-36)	23 (17-30)	0.020	0.156
LN examined	21 (16-28)	18 (13-26)	19 (14-28)	0.009	0.320
Tumor size	3.9 (2.2-5.5)	4.5 (3.2-6.8)	4.0 (2.5-6.0)	0.030	0.091
R0-resection	479 (94.9%)	47 (88.7%)	724 (91.8%)	0.066	0.434

Proportions are presented for categorical data, means with SD for ASA-score, and median with IQR for all other continuous data.
Abbreviations: BMI: Body Mass Index (kg/m2), ASA: American Society of Anesthesiologists; EMVI: extramural vascular invasion; LVI: lymphovascular invasion
* Missing data: Resection length, n=867 ; Tumor size n=1290

INTRA-AND POSTOPERATIVE OUTCOMES

All perioperative outcomes are shown in Table 2. Median duration of operation in the CS group (180 minutes) was significantly longer than in both LS (130 min, P<0.001) or OS (119 min, P<0.001). Although the number of prior abdominal surgeries was comparable, conversion was associated with the presence of more adhesions (LS P0.002, OS P0.013). Additional-

ly, more multivisceral resections were performed in CS and OS patients (P<0.001 compared to LS).

Regarding postoperative morbidity, CS was associated with significantly worse short-term outcomes than LS patients. Length of stay (median 3 vs. 4 days, P<0.001), rates of in-hospital complications (21.2% vs. 41.5%, P0.001), and readmission rates (3.4% vs. 11.3%, P0.006) were higher after CS. More specifically, requirement for blood transfusion, and the number of patients with sepsis was significantly higher after CS than LS (P<0.001, P0.006, respectively). Compared to OS patients, outcomes were more comparable. However, conversion was correlated with more intra-abdominal abscesses/leaks, transfer to the ICU, and a higher rate of surgical site infections compared to both LS (P0.001, P<0.001, P0.001, respectively) and OS (P0.006, P0.047, P0.017, respectively). On the other hand, postoperative ileus tended to occur more often after OS than CS (5.7% vs. 12.7%, P0.131). Rates of reoperation as well as mortality rates were comparable (CS: 1.9% vs. LS: 0.6%, P0.289; vs. OS: 1.0%, P0.550).

The overall administration of adjuvant chemotherapy was not different between the groups. However, when analyzing stage-by-stage stage-III OS patients received less chemotherapy compared to stage-III LS patients (LS: 83.8% vs. OS: 68.2%, P0.002). A tendency toward less chemotherapy for stage-III CS patients was found (LS: 83.8% vs. CS: 69.4%, P0.078). This difference was on the one hand explained by differences in baseline characteristics, since 33.8% of all non-adjuvantly treated stage-III OS patients and 28.6% of stage-III CS patients underwent surveillance instead of chemotherapy due to a high comorbidity rate or age. However, the main reason for chemotherapy omission was patient's refusal, accounting for the majority in the CS cohort (57.1%) and 37.3% of the OS group. The median age in this cohort was 79.8 years. Moreover, 48.0% of all stage-III patients who declined further treatment developed a complication after surgery, ranging from more general events (including cardiac, respiratory and renal) in the OS group to anastomotic leakage and the need for reoperation in the CS group.

LONG-TERM OUTCOMES

Only patients with AJCC stage I-III disease were included for the long-term analysis (n=1097). Median follow-up duration was 47.8 months, and significantly longer for OS patients than LS patients (LS: 42.2 vs. CS: 49.2 vs. OS: 53.7 months, P<0.001). CS and OS patients had higher recurrence rates compared to LS patients (LS: 9.8% vs. CS: 21.4%, P0.020; vs. OS: 14.7%, P0.018). This difference was mainly explained by a greater difference in distant metastases in CS patients than LS patients (9.8% vs. 19.0%, P0.061) and a significantly higher rate of local recurrence after OS (0.5% vs. 2.3%, P0.017).

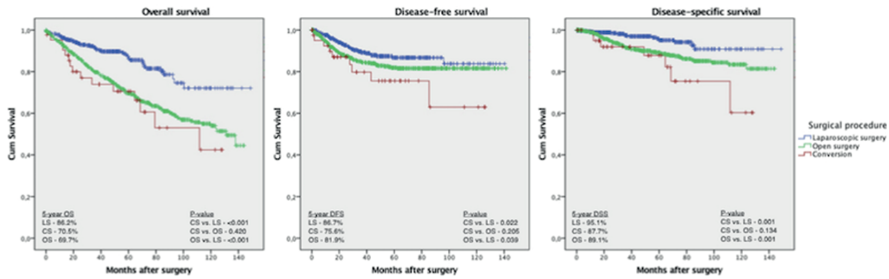
Kaplan-Meier survival curves emphasized the worse long-term outcomes for CS patients compared to LS patients (Figure 2). A poor prognosis was demonstrated in OvS (estimate 5 year: 86.2% vs. 70.5%, P<0.001), DSS (95.1% vs. 87.7%, P0.001), as well as DFS (86.7% vs. 75.6%, P0.022). All three long-term outcomes were also worse after OS compared to LS, whereas the outcomes were similar between CS and OS. When analyzing overall and disease-free survival stage-by-stage, we found significantly worse OvS after CS compared to LS in stage-I (91.0% vs. 80.0%, P0.026), and a tendency toward worse outcomes in stage II and III (P0.061, P0.060,

Table 2. Intra- and postoperative outcomes

	Laparoscopic surgery	Conversion	Open	P-value LS vs C	P-value OS vs C
n = 1347	505 (37.5%)	53 (3.9%)	789 (58.6%)		
Surgery					
Year of surgery, *after July 2009*	277 (54.9%)	23 (43.4%)	381 (48.3%)	0.112	0.490
Operation duration, *minutes*	130 (83-178)	180 (115-244)	119 (69-173)	<0.001	<0.001
Adhesions	137 (27.1%)	25 (47.2%)	243 (30.8%)	0.002	0.013
Multivisceral	14 (2.8%)	7 (13.2%)	127 (16.1%)	<0.001	0.578
Admission					
Admission duration, *days*	3 (3-5)	4 (3-7)	5 (4-8)	<0.001	0.073
Complications during admission	107 (21.2%)	22 (41.5%)	285 (36.1%)	0.001	0.430
Ileus	33 (6.5%)	3 (5.7%)	100 (12.7%)	0.805	0.131
Abscess/leak	10 (2.0%)	5 (9.4%)	21 (2.7%)	0.001	0.006
ICU transfer	5 (1.0%)	5 (9.4%)	30 (3.8%)	<0.001	0.047
Surgical site infection	10 (2.0%)	5 (9.4%)	25 (3.2%)	0.001	0.017
Sepsis	2 (0.4%)	2 (3.8%)	13 (1.6%)	0.006	0.257
Blood transfusion	50 (9.9%)	14 (26.4%)	193 (24.5%)	<0.001	0.749
Readmission	17 (3.4%)	6 (11.3%)	62 (7.9%)	0.006	0.370
Reoperation	9 (1.8%)	2 (3.8%)	21 (2.7%)	0.321	0.631
Death	3 (0.6%)	1 (1.9%)	8 (1.0%)	0.289	0.550

Proportions are presented for categorical data, median with IQR for all continuous data.

Figure 2. Kaplan-Meier curves for overall, disease-free, and disease-specific survival

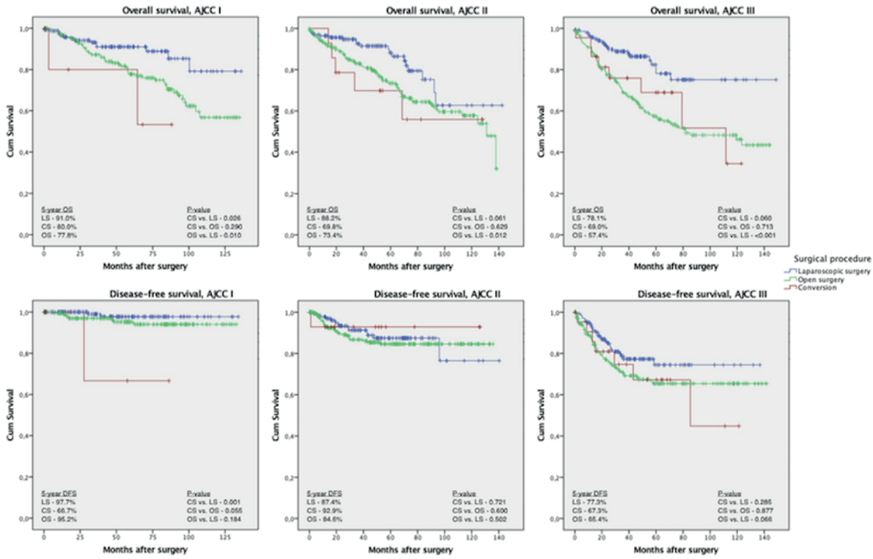


respectively) (Figure 3). Regarding DFS, only stage-I patients had a worse prognosis after conversion, compared to both LS (97.7% vs. 66.7%, P0.001) and OS (95.2% vs. 66.7%, P0.055). Otherwise, long-term outcomes were comparable in all stages between CS and OS.

PROPENSITY SCORE MATCHING

After propensity score matching we repeated the analysis, demonstrated in table 3. There were 48 patients in each subgroup. No differences were found in baseline characteristics, nor in pathology features. Nonetheless, intraoperative and postoperative outcomes remained slightly different. Duration of surgery was significantly longer when conversion was required (CS: 180 min vs. 139 min (LS, P0.020) and 141 min (OS, P0.029). The number of harvested lymph nodes was lower after CS compared to LS (18 vs. 23, P0.016), and while a multivisceral resection was not performed in the weighed LS group, 12.5% of CS underwent and extra procedure

Figure 3. Kaplan-Meier curves for overall, and disease-free survival, stage-by-stage



(P0.011) and 20.8% of the OS group. Concerning postoperative morbidity, we found significant differences in length of stay (median 4 vs. 3, P0.007) and the requirement for blood transfusion (P0.021) between CS and LS. Surgical site infections and sepsis only occurred in the CS group (P0.078, and P0.153, respectively). Furthermore, rates of readmission were higher after CS (10.4% vs. 2.1% (both LS and OS), P0.092). Long-term outcomes and Kaplan-Meier curves in the PSM cohort stage I-III were comparable between all groups. Mean 5-year survival for LS was 86.1 months, 86.1 for CS, and 99.8 months for OS (P0.559). Mean disease-specific survival was 96.8 months, 105.2 months, and 123.4 months, respectively (P0.474). Local recurrence did not occur in one of the weighted groups. Overall mean disease-free survival was 87.5 months, 98.4 months, and 119.3 months, respectively (P0.699).

MULTIVARIATE ANALYSIS

In the full cohort, univariate analysis demonstrated surgical procedure, age, ASA-score, EMVI, LVI, perineural invasion, AJCC stage, R1 resection, lymph-node harvest ≥12, complications during admission, blood transfusion and adjuvant treatment to be significant risk factors for OvS. After adjustment for these factors, CS (HR 2.04, 95% CI: 1.14-3.65, P0.017) and OS (HR 1.72, 95% CI: 1.27-2.34, P0.001) were still independent predictors for worse survival compared to LS. Ratios were comparable when comparing OS and CS (HR 0.84, 95% CI: 0.50-1.44, P0.534). Regarding DFS, surgical procedure, obesity, EMVI, LVI, perineural invasion, AJCC stage, and adjuvant treatment were significant factors after univariate analysis. However, after adjustment, only pathological features including EMVI, perineural invasion, and AJCC stage II and III were independent predictors for recurrence. DFS tended to be worse after OS compared to LS (HR 1.42, 95% CI: 0.99-2.05, P0.061) (Table 4 and 5).

Table 3. Baseline and postoperative outcomes after propensity score matching

	Laparoscopic surgery	Conversion	Open	P-value LS vs C	P-value OS vs C
n = 144	48 (33.3%)	48 (33.3%)	48 (33.3%)		
Baseline					
Age	65.3 (±13.2)	67.4 (±13.0)	65.6 (±13.5)	0.422	0.524
Male gender	34 (70.8%)	31 (64.6%)	26 (54.2%)	0.513	0.299
BMI	27.8 (24.7-31.8)	27.4 (24.9-30.6)	28.8 (22.6-35.0)	0.892	0.687
ASA	2 (2-3)	2 (2-3)	2 (2-3)	0.634	0.330
Pathology					
T4 tumor	14 (29.2%)	11 (22.9%)	16 (33.3%)	0.485	0.256
N+	27 (56.3%)	25 (52.1%)	26 (54.2%)	0.682	0.838
M+	4 (8.3%)	4 (8.3%)	8 (16.7%)	1.000	0.217
High Grade	7 (14.6%)	9 (18.8%)	10 (20.8%)	0.584	0.798
EMVI	16 (33.3%)	20 (41.7%)	23 (47.9%)	0.399	0.538
LVI	22 (45.8%)	26 (54.2%)	28 (58.3%)	0.414	0.681
Perineural invasion	15 (31.3%)	16 (33.3%)	18 (37.5%)	0.827	0.670
Resection length, cm*	21 (15-30)	27 (19 -37)	22 (18-29)	0.087	0.211
LN examined	23 (17-34)	18 (13-27)	19 (14-29)	0.016	0.375
Tumor size	4.3 (3.1-6.4)	4.5 (3.2-6.8)	5.0 (3.1-7.0)	0.752	0.641
R0-resection	42 (87.5%)	43 (89.6%)	46 (95.8%)	0.749	0.239
Intraoperative					
Operation duration, *minutes*	139 (95-181)	180 (123-241)	141 (95-194)	0.020	0.029
Adhesions	14 (29.2%)	23 (47.9%)	17 (35.4%)	0.059	0.214
Multivisceral	0 (0.0%)	6 (12.5%)	10 (20.8%)	0.011	0.273
Postoperative					
Admission duration, *days*	3 (3-5)	4 (3-7)	5 (4-8)	0.007	0.102
Ileus	3 (6.3%)	3 (6.3%)	4 (8.3%)	1.000	0.695
Abscess/leak	1 (2.1%)	3 (6.3%)	1 (2.1%)	0.307	0.307
ICU transfer	0 (0.0%)	3 (6.3%)	1 (2.1%)	0.078	0.307
Surgical site infection	0 (0.0%)	3 (6.3%)	0 (0.0%)	0.078	0.078
Sepsis	0 (0.0%)	2 (4.2%)	0 (0.0%)	0.153	0.153
Blood transfusion	3 (6.3%)	11 (22.9%)	13 (27.1%)	0.021	0.637
Readmission	1 (2.1%)	5 (10.4%)	1 (2.1%)	0.092	0.092
Long-term stage I-III					
Disease recurrence	6 (15.8%)	8 (20.5%)	5 (14.3%)	0.591	0.482
Deceased	7 (18.4%)	14 (35.9%)	12 (34.3%)	0.085	0.885
5-year overall survival	80.8%	71.7%	74.0%	0.286**	0.528**
5-year disease-specific survival	93.7%	87.4%	89.1%	0.436**	0.303**
5-year disease-free survival	78.1%	77.3%	82.8%	0.739**	0.401**

Proportions are presented for categorical data, mean with SD for age, and median with IQR for all other continuous data.
Abbreviations: BMI: Body Mass Index (kg/m^2), ASA: American Society of Anesthesiologists; EMVI: extramural vascular invasion; LVI: lymphovascular invasion
* Missing data: Resection length, n=92
** Log-rank test

With regards to the weighed cohort and overall survival, R0-resection, complications during admission and adjuvant chemotherapy were not contributory in univariate analysis and therefore not included in the logistic regression model. After adjustment, LVI (HR 4.40, 95% CI: 1.62-11.98, P0.004), lymph node harvest ≥12 (HR 0.17, 95% CI: 0.04-0.80, P0.025), and blood transfusion (HR 5.87, 95% CI: 1.89-18.20, P0.002) were the independent predictors for worse overall survival. Concerning disease-free survival, all factors except BMI were included in the logistic regression model. Perineural invasion (HR 3.40, 95% CI: 1.13-10.21, P0.030) and adjuvant therapy (HR 7.61, 95% CI: 2.02-28.60, P0.003) were the only independent predictors. The type of surgical procedure did not withstand the multivariate analysis of both overall and disease-free survival.

DISCUSSION

Laparoscopic surgery is a well-established approach in colon cancer, with equivalent oncological outcomes and lower morbidity rates compared to open surgery.[1-9] However, the need for conversion to open surgery reduces the benefits of a minimally invasive approach and may even lead to adverse oncological outcomes. Since most studies include converted patients in the laparoscopic group little is known about the impact of conversion to open surgery. Moreover, most studies that investigated short-term outcomes after conversion compared successful laparoscopic surgery with conversion, while only a comparison between planned open surgery and converted

Table 4. Multivariate analysis overall survival AJCC stage I-III

	Before PSM		After PSM	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
ASA III-IV	1.97 (1.51-2.55)	<0.001	2.27 (0.77-6.70)	0.139
Age >65 years	2.08 (1.51-2.86)	<0.001	2.58 (0.94-7.08)	0.065
Surgical procedure				
Conversion	Reference		Reference	
Successfully laparoscopic surgery	0.50 (0.27-0.88)	0.017	0.64 (0.18-2.25)	0.482
Planned open surgery	0.84 (0.50-1.44)	0.534	1.16 (0.36-3.73)	0.808
EMVI	1.42 (0.99-2.05)	0.060	0.88 (0.21-3.60)	0.855
Perineural invasion	1.86 (1.37-2.53)	<0.001	1.16 (0.35-3.82)	0.807
Lymphovascular invasion	1.41 (1.00-2.00)	0.054	4.40 (1.62-11.98)	0.004
AJCC stage				
I	Reference		Reference	
II	1.06 (0.75-1.49)	0.737	3.54 (0.30-42.36)	0.319
III	2.02 (1.39-2.94)	<0.001	6.37 (0.53-76.77)	0.145
R0-resection	0.61 (0.38-0.96)	0.033		NC
Lymph nodes harvested ≥ 12	0.44 (0.33-0.59)	<0.001	0.17 (0.04-0.80)	0.025
Complications during admission	1.07 (0.83-1.38)	0.630		NC
Requirement blood transfusion	1.45 (1.11-1.91)	0.007	5.87 (1.89-18.20)	0.002
Adjuvant therapy	0.35 (0.24-0.50)	<0.001		NC

Abbreviations: BMI: Body Mass Index (kg/m^2); EMVI: extramural vascular invasion; AJCC: American Joint Committee on Cancer
NC: not contributory in univariate analysis

Table 5. Multivariate analysis disease-free survival AJCC stage I-III

	Before PSM		After PSM	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
BMI ≥ 30 kg/m²	0.74 (0.50-1.09)	0.123		NC
Surgical procedure				
Conversion	Reference		Reference	
Successfully laparoscopic surgery	0.68 (0.33-1.39)	0.289	0.71 (0.19-2.68)	0.614
Planned open surgery	0.96 (0.48-1.91)	0.909	0.64 (0.16-2.57)	0.644
EMVI	2.51 (1.73-3.64)	<0.001	1.88 (0.59-6.01)	0.290
Perineural invasion	1.81 (1.24-2.63)	0.002	3.40 (1.13-10.21)	0.030
Lymphovascular invasion	1.31 (0.77-2.24)	0.315	1.41 (0.25-7.83)	0.697
AJCC stage				
I	Reference		Reference	
II	2.62 (1.34-5.16)	0.005	0.31 (0.02-4.21)	0.377
III	4.51 (2.30-8.82)	<0.001	0.50 (0.03-8.63)	0.629
Adjuvant therapy	0.92 (0.63-1.35)	0.673	7.61 (2.02-28.60)	0.003

Abbreviations: BMI: Body Mass Index (kg/m2); EMVI: extramural vascular invasion;
AJCC: American Joint Committee on Cancer
NC: not contributory in univariate analysis

patients will answer the question as to whether conversion should be considered a complication rather than a simple drawback.

In the current study, we reported a conversion rate of 9.5% with a slight decrease over the study period. The low incidence in comparison to previous studies, and the decline in conversion rates over time emphasizes our initial experience in laparoscopic surgery and even further progression over time. Although 20-30 laparoscopic procedures are often believed to be the standard to perform minimally invasive surgery safely, previous studies suggested a learning curve with a plateau after 40-80 laparoscopic procedures.[14,28] This study was conducted in a high-volume center and all procedures were performed by very experienced surgeons in minimally invasive colorectal surgery. Main reasons for conversion were adhesions, tumor size, and tumor adherence to adjacent organs. While prior abdominal surgery, and large tumor size are well known contraindications for a minimally invasive approach, the presence of a T4 tumor is debatable as laparoscopic surgery is often considered inadvisable. However, our study underlines the feasibility of LS in tumors with contiguous involvement of adjacent organs since no correlation between conversion and T4 tumors was found. Nonetheless, adhesions and a larger tumor size were correlated with conversion and are therefore potential contraindications for laparoscopic surgery.

The main finding in this study was the relatively similar overall postoperative outcome for converted patients in comparison to planned open surgery. In addition, although some studies have suggested comparable short-term outcomes after conversion and successfully completed laparoscopic surgery [22-23], most studies including the current study demonstrated adverse short-term outcomes for the converted group. In our study, converted patients had a longer length of stay, more complications during admission, and a higher readmission rate than LS patients. Moreover, compared to both laparoscopic and open surgery, the incidence of

intra-abdominal abscesses/leaks and surgical site infections, as well as the need for transfer to the intensive care-unit was higher in the converted group. A reasonable explanation could be that an intra-operative event led to these issues or led to a prolonged operative time, which is associated with adverse outcomes and infectious complications in particular.[29-30] Furthermore, similar to our findings, incidence of conversion was higher in left colectomies and male patients.[12,31] Both factors are well recognized as technical challenging, which may be explained by the limited visualization in a narrow pelvis and thus a higher risk of intraoperative complications or an incomplete oncological resection. Due to heterogeneity and selection bias, we repeated all analysis in a propensity score matched cohort. Although baseline and pathologic features were comparable between all groups, surgical duration, length of stay and the need for blood transfusion remained higher in the CS cohort compared to successfully laparoscopic surgery. While surgical site infections, ICU transfer and sepsis only occurred after conversion, the outcomes were not significantly different to LS. The same applied to readmission rates, which were non-significantly higher after CS (10.4% versus 2.1%). This underscores the potential negative impact of a longer surgical duration, since no differences in gender nor in tumor location existed in the weighed cohort.

Knowledge about long-term outcomes after conversion to open surgery is lacking. Only a few studies have addressed oncologic results, which suggested adverse outcomes in patients who required conversion to open surgery.[5, 25] In the present analysis, we found worse survival outcomes for converted patients and patients who had a planned open surgery compared to LS patients. However, the impact of distinct differences in baseline characteristics and stage of disease between laparoscopic and non-laparoscopic patients were underscored by our multivariate analyses and outcomes after propensity score matching. In the unweighted-cohort, surgical procedure withstood the multivariate analysis and CS and OS were independently related to poorer outcomes. Since long-term outcomes between CS and OS were comparable, the worse overall survival compared to LS is seemingly best explained by a combination of baseline and pathology-related factors, as well as procedure-related factors. Furthermore, a prolonged surgical procedure in combination with a more extensive adhesiolysis might lead to increased perioperative stress and could be an explanation of a more rapid initial decline in overall survival seen after conversion. This was stressed by the long-term outcomes in the PSM cohort. Kaplan-Meier curves demonstrated similar overall, disease-specific, and disease-free survival in all three groups. Moreover, only perioperative outcomes and pathologic features were found to be independently associated with survival in multivariate analysis. The same accounted for disease-free survival. After adjustment, only pathologic features including EMVI, perineural invasion and AJCC-stage were associated with worse outcomes in the unweighted cohort and perineural invasion and adjuvant chemotherapy in the propensity score matched cohort.

This study has its limitations. The retrospective design is inherent associated with risk of selection bias. There is an obvious bias in analyzing a group of patients who required conversion versus those who did not. Although patient characteristics were similar between the converted and open group, CS patients were older, had a higher comorbidity rate, and often a more advanced disease which could cause a higher postoperative

morbidity rate than LS patients. However, in practice, randomization of patients requiring conversion is not possible. To account for this obvious selection bias, we performed propensity score matching. Moreover, we minimized the risk of selection bias by performing adjusted analyses. It would be interesting to distinguish the conversion cohort in duration of laparoscopic surgery until conversion was required. Unfortunately, this data was not available in our data set.

To the best of our knowledge this study involved one of the largest series of patients undergoing surgical resection for colon cancer which addressed both short- and long-term outcomes after conversion to open surgery compared to both successfully laparoscopic and planned open surgery in a single institution. Another strength of the current study is the inclusion of only colon cancer patients, since long-term outcomes are different in colon and rectal cases [5], and the incidence of conversion is higher in rectal cases.[32]

CONCLUSION

Converting a laparoscopic procedure to an open one eliminates the benefits of a minimally invasive approach and is associated with poorer oncological outcomes. However, when accounting for the significant differences in baseline and pathologic features between LS and CS, oncologic outcomes were comparable and only length of stay and the requirement for blood transfusion were higher after CS. Furthermore, since outcomes were comparable between planned open surgery, this data supports a surgeon's attempt to perform a minimally invasive resection in patients with colon cancer.

REFERENCES

1. Clinical Outcomes of Surgical Therapy Study Group. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J Med.* 2004;350:2050–2059.

2. Guillou PJ, et al; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial): Multicentre, randomised controlled trial. *Lancet.* 2005;365:1718–1726

3. Veldkamp R, et al; Colon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol.* 2005;6:477-484

4. Buunen M, et al; Colon cancer Laparoscopic or Open Resection Study Group (COLOR). Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol*. 2009;10:44-52

5. Green BL, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. *Br J Surg.* 2013;100:75–82

6. Fleshman J, et al; Clinical Outcomes of Surgical Therapy Study Group. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg.* 2007;246:655-662

7. Jayne DG, et al. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg* 2010;97:1638–1645

8. Allaix ME, et al. Laparoscopic versus open resection for colon cancer: 10-year outcomes of a prospective clinical trial. *Surg Endosc.* 2015;29:916–924

9. Deijen CL, et al; COLOR (COlon cancer Laparoscopic or Open Resection) study group. Ten-year outcomes of a randomised trial of laparoscopic versus open surgery for colon cancer. *Surg Endosc.* 2017;31:2607-2615

10. Thorpe H, et al; Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer Trial Group. Patient factors influencing conversion from laparoscopically assisted to open surgery for colorectal cancer. *Br J Surg*. 2008;95:199–205

11. Bhama AR, et al. Factors associated with conversion from laparoscopic to open colectomy using the National Surgical Quality Improvement Program (NSQIP) database. *Colorectal Dis.* 2015;17:257-264

12. Masoomi H, et al. Risk factors for conversion of laparoscopic colorectal surgery to open surgery: Does conversion worsen outcome? *World J Surg.* 2015;39: 1240-1247

13. Tekkis PP, et al Evaluation of the learning curve in laparoscopic colorectal surgery. *Ann Surg.* 2005;242:83–91

14. Dincler S, et al. Multidimensional analysis of learning curves in laparoscopic sigmoid resection: eight-year results. *Dis Colon Rectum.* 2003;46:1371–1378

15. Allaix ME, et al. Does conversion affect short-term and oncologic outcomes after laparoscopy for colorectal cancer? *Surg Endosc.* 2013;27:4596–4607

16. Yerokun BA, et al. Does conversion in laparoscopic colectomy portend an inferior oncologic outcome? Results from 104,400 Patients. *J Gastrointest Surg.* 2016;20:1042–1048

17. Li J, et al. The impact of laparoscopic converted to open colectomy on short-term and oncologic outcomes for colon cancer. *J Gastrointest Surg.* 2015;19:335–343

18. Chan AC, et al. Impact of conversion on the long-term outcome in laparoscopic resection of colorectal cancer. *Surg Endosc*. 2008;22:2625–2630

19. Franko J, et al. Conversion of laparoscopic colon resection does not affect survival in colon cancer. *Surg Endosc.* 2008;22:2631–2634

20. Ptok H, et al; "Colon/Rectum Carcinoma (Primary Tumor)" Study Group. Conversion from laparoscopic to open colonic cancer resection - associated factors and their influence on long-term oncological outcome. *Eur J Surg Oncol.* 2009;35:1273–1279

21. Belizon A, et al. Converted laparoscopic colectomy: what are the consequences? *Surg Endosc.* 2006;20:947–951

22. Giglio MC, et al. Conversion during laparoscopic colorectal resections: a complication or a drawback? A systematic review and meta-analysis of short-term outcomes. *Int J Colorectal Dis* 2015;30:1445-1455

23. Casillas S, et al. Does conversion of a laparoscopic colectomy adversely affect patient outcome? *Dis Colon Rectum.* 2004;47:1680–1685

24. Gonzalez R, et al. Consequences of conversion in laparoscopic colorectal surgery. *Dis Colon Rectum.* 2006;49:197-204

25. Clancy C, et al. A meta-analysis to determine the oncological implications of conversion in laparoscopic colorectal cancer surgery. *Colorectal Disease.* 2014;17:482–490

26. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J.* 2009;51:171–184

27. Rassen JA, et al. Matching by propensity score in cohort studies with three treatment groups. *Epidemiology.* 2013;24:401-409

28. Schlachta CM, et al. Defining a learning curve for laparoscopic colorectal resections. *Dis Colon Rectum.* 2001;44:217–222

29. Jackson TD, et al. Does speed matter? The impact of operative time on outcome in laparoscopic surgery. *Surg Endosc*. 2011;25:2288-1895

30. Bailey MB, et al. Longer operative time: deterioration of clinical outcomes of laparoscopic colectomy versus open colectomy. *Dis Colon Rectum*. 2014;57:616-622

31. Tekkis PP, et al. Conversion rates in laparoscopic colorectal surgery: a predictive model with, 1253 patients. *Surg Endosc.* 2005;19:47-54

32. Arezzo A, et al. Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis. *Surg Endosc*. 2013;27:1485–1502

CHAPTER 6

The IMPACT of a MULTIVISCERAL RESECTION and ADJUVANT THERAPY in LOCALLY ADVANCED COLON CANCER

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ABSTRACT

BACKGROUND

Multivisceral resection for locally advanced colon cancer is mandatory to achieve complete tumor resection. We aimed to determine if local multivisceral resections (LMR) for pT4 and pT3 tumors impact perioperative and long-term oncological outcomes.

METHODS

All stage II or III colon cancer patients who had surgery between 2004-2014 were identified. We analyzed patients with non-multivisceral resections (NMR) for pT4 tumors versus pT4-LMR. In addition, outcomes were compared to both NMR and LMR pT3 patients.

RESULTS

LMR was performed in 55 (29.7%) of all patients with pT4 tumors and in 48 (8.9%) of all patients with pT3 tumors. The most commonly involved areas of extension were the abdominal wall and the small intestine. Transverse colon cancer was correlated with LMR. Morbidity rates were comparable between NMR and LMR, with the exception of higher rates of blood transfusion and postoperative ileus. Over one-third of all pT4-NMR patients developed recurrent disease, which was higher compared to all other groups. Subsequently, overall and disease-specific survival, as well as disease-free survival (DFS) were worse for pT4-NMR, even after adjustment for pTN-staging, adjuvant therapy, and R0-resection. Furthermore, when analyzing only curative resections, radial margin < 1 cm along with nodal disease were independent predictors for worse DFS. Long-term outcomes were comparable between pT4-LMR and pT3 patients.

CONCLUSIONS

Multivisceral resection for locally advanced colon cancer preserves long-term oncological outcomes without increased postoperative morbidity. Moreover, LMR in pT3 tumors does not contribute to postoperative morbidity. Our study underlines the feasibility and importance of performing LMR when locally advanced cancer is suspected.

INTRODUCTION

Colon cancer is one of the most common cancers worldwide, with an estimate of almost 100,000 new patients every year in the USA.[1] Approximately 10% of all primary colon cancer patients have contiguous involvement of adjacent organs at initial presentation, which is classified as locally advanced disease or pathological T4 tumors (pT4).[2-3] An R0 resection in these tumors is mandatory to achieve the best long-term outcomes and therefore a local multivisceral resection (LMR) is recommended when tumors invade adjacent organs.[4-6] Depending upon the location of the tumor, surgical treatment ranges from en bloc resection of involved organs in the upper abdomen to a pelvic exenteration.

Despite increased survival rates after LMR, the vast majority of the patients with locally advanced colon cancer do not receive an extended resection. Previous literature demonstrated that only 26-39% of patients with locally advanced colorectal cancer underwent a multivisceral resection.[7] Surgeons may be reluctant to perform a LMR because of the associated morbidity. Complication rates around 22-36% have been described after LMR for colon cancer [5,8-9], though there was substantial heterogeneity within studies. In addition, despite improvement in imaging techniques, it is not always clear preoperatively that LMR is required and therefore the decision to perform LMR often must be made intra-operatively. Furthermore, distinguishing oncological invasion from peri-tumorous inflammatory adhesions is often hard to discern and makes the intra-operative decision to perform an extended resection even more difficult.

In addition to complete surgical resection, adjuvant treatment plays an important role in locally advanced colon cancer. In node-positive disease, postoperative chemotherapy is clearly established, and previous research has shown benefit in overall and disease-free survival.[10-11] Additional treatment is therefore recommended for all patients with stage III disease operated on with curative intent.[12] This recommendation is less clear in stage II disease. Despite multiple clinical trials and meta-analyses over the past decades, the beneficial role of adjuvant chemotherapy in node-negative disease remains controversial. Several high risk factors have been introduced into the current guidelines, including T4 tumors. According to the NCCN guidelines, adjuvant chemotherapy can be considered for patients with high-risk features.

To assess the impact of LMR and R0-resections in locally advanced colon cancer, we evaluated the short- and long-term outcomes in patients with pT4 colon tumors who either did or did not undergo a multivisceral resection and additionally compared them to less advanced disease (T3). In order to evaluate whether a LMR compromises morbidity rates, patients who were thought clinically to be invasive or adhesive though not confirmed on pathology (T3) were assessed as well as another comparison-group.

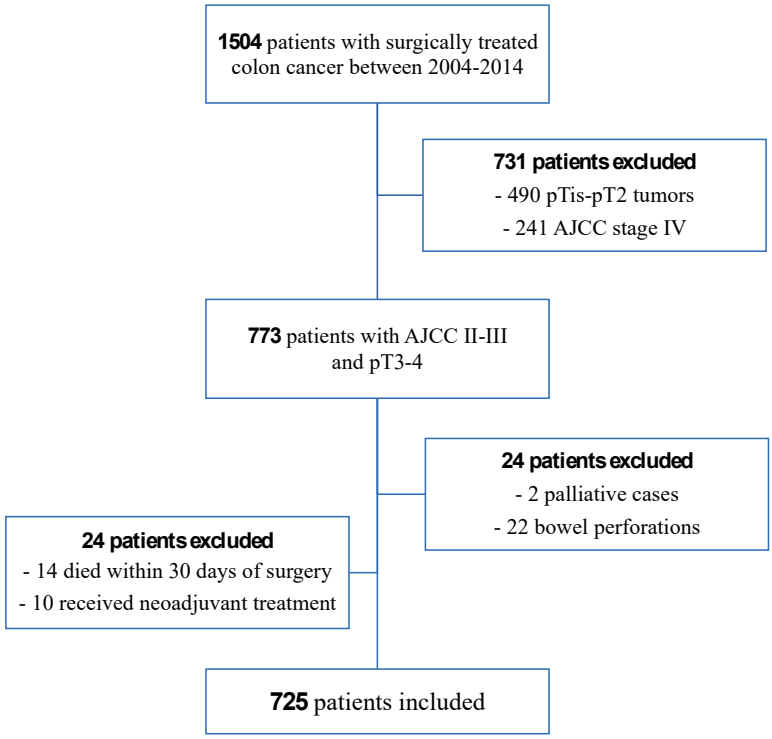
MATERIALS & METHODS

STUDY DESIGN AND POPULATION

We performed a retrospective analysis using a prospectively maintained database including all patients who had surgical treatment for primary colon cancer between January 2004 and December 2014 at Massachusetts General Hospital. This study was approved by the Institutional Review Board. A total of 773 patients underwent surgery for AJCC stage II or III, pT3-4 colon cancer during our study period. The majority had a pT3 tumor (562 patients had a pT3 tumor), 161 patients had a pT4a tumor and 50 patients a pT4b tumor. A multivisceral resection was performed in 117 patients, mostly for pT4 tumors (56.4%). Patients who were deemed unresectable were excluded, including palliative cases (n=2) and patients who presented with bowel perforation (n=22). To compare oncologic outcomes in pT3-4 tumors, patients who received neoadjuvant treatment (n=10) and patients who died within 30 days of surgery (n=14) were additionally excluded. Leaving a total of 725 patients for subsequent analyses [Figure 1]. We subdivided our cohort into four groups: patients with a pT3 tumor who either did (pT3-LMR) or did not (pT3-NMR) receive a multivisceral resection, and patients with a pT4 tumor who did (pT4-LMR) or did not undergo (pT4-NMR) a multivisceral resection.

The following data was prospectively obtained for each patient: patient demographics, comorbidities, pathological features, and both short- and long-term outcomes. Locoregional recurrence was defined as recurrent disease within the original tumor bed (perianastomotic, peritoneum, retroperitoneum, and pericolic mesenteric lymph nodes) [13-14], while

Figure 1. Inclusion flowchart of the study



distant recurrence included all recurrent disease at nonregional sites, such as liver or lung. Data on long-term outcomes were updated periodically by reviewing patient's records and the Massachusetts General Hospital cancer registry. In case this information was not recently updated, the Social Security Death Index was used for survival data. According to the NCCN guidelines, routine pre-operative work-up was completed for all patients. This included physical examination, total colonoscopy (unless an obstruction was the case), abdominal computed tomography (CT), chest X-ray, complete blood count and carcinoembryonic antigen (CEA). An anesthetic consultation was carried out to determine the American Society of Anesthesiologist score (ASA). In addition, adjuvant chemotherapy was recommended for all patients with lymph-node positive disease and considered for stage II patients with high-risk features (T4 tumors, poorly differentiated histology, vascular invasion, perineural invasion, <12 lymph nodes examined, bowel obstruction, or positive or indeterminate margins). The decision whether or not to administrate additional treatment was made on an individual basis, regardless of the tumor stage.

Local multivisceral resection was defined as en bloc resection of the primary tumor with adjacent organs or tissues. There were no patients who had direct invasion into the liver. Laparoscopic surgery was introduced before 2004 and therefore used throughout our study period. Short-term morbidity was classified as all complications within 30 days of surgery.

STATISTICAL ANALYSES

Differences in baseline characteristics and outcome variables between the groups were analyzed using a Chi-square test ($\chi 2$). Continuous data were compared using the Kruskal-Wallis test and presented as the mean with standard deviation or the median with an interquartile range according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Post-hoc adjusted comparisons were performed with Bonferroni correction to decrease the chance of incorrect rejection of the null hypothesis due to multiplicity. A Dunn's test was used after a Kruskal-Wallis test was rejected. Survival-analyses were determined using the Kaplan-Meier method and the differences between curves were assessed by the log-rank test. Cox proportional hazard models were used to determine the impact of multivisceral resection on oncologic outcomes, adjusted for potential confounders. A two-sided P-value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS *(IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.)*.

RESULTS

BASELINE CHARACTERISTICS

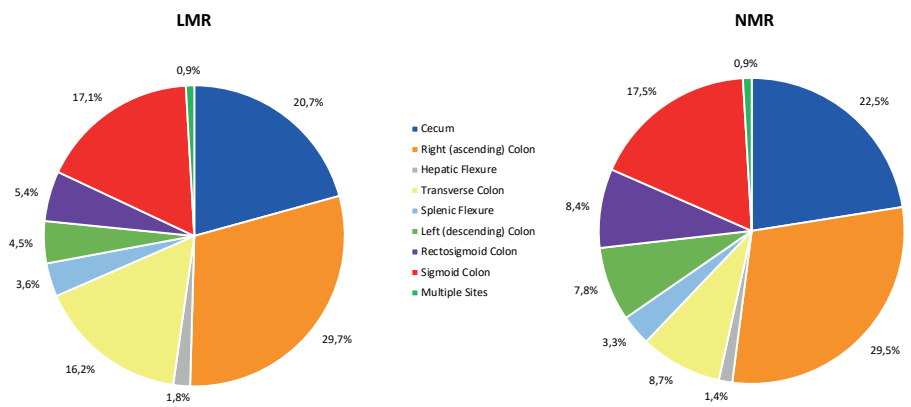
The study population consisted of 725 patients with a mean age of 69.4 years. A total of 540 patients (74.5%) had a pT3 tumor of whom 48 (8.9%) underwent a LMR. During the study period, 29.7% of patients with a pT4 tumor underwent a LMR. In patients with pathologically proven T4b disease, 66.0% underwent LMR, compared to 20.5% of all T4a tumors. Of the latter group, all the patients who had clinical T4b tumors (5.5%) underwent LMR. We also noted a slight increase in the number of LMR per-

formed over the time of our study period. In particular, 38.8% of all LMR resections and 40.0% of LMR in pT4 tumors were performed in the latter third. The main reason a multivisceral resection was not performed in cases where the tumor was found to invade adjacent organs (pT4b) was when surgeons encountered adhesions which were thought to be inflammatory (58.3%) and actually were microscopically invasive on pathology (33.3%). None of the pT4b-NMR procedures were emergent cases, and palliative cases were excluded beforehand.

R0 resection was achieved in almost all T3 tumors (NMR: 99.4%, LMR: 95.8%), whereas rates of tumor free margins were significantly lower in T4 tumors (NMR: 70.8%, LMR: 89.1%) (P<0.001). All incomplete resections, regardless of pT-stage, had positive radial margins. Transverse colon tumors were proportionally the most frequent in the LMR group (17.5%) [Figure 2]. The most involved organs were the abdominal wall (41.7%), small intestine (31.1%), reproductive organs (8.7%), and the bladder (6.8%). When analyzing the site of LMR by pT-stage, we found a higher frequency of small bowel resection in pT4b tumors (48.1%) compared to both pT4a (25.0%) and pT3 (25.0%) tumors. The latter two had more en bloc resections of the abdominal wall (46.4% and 52.1%, respectively, vs. 37.0% in pT4b). Baseline characteristics demonstrated significant difference in BMI, pre-operative CEA and clinical presentation between the groups [Table 1]. Post-hoc adjusted analysis with Bonferroni correction revealed that pT3-NMR patients had a significant higher BMI compared to pT3-LMR patients (mean 27.3 vs. 24.8 kg/m^2, P=0.003). Patients who underwent LMR presented more often with abdominal pain (P<0.001), without any differences in urgent admissions nor in related symptoms, including changes in stool habit, constipation, or bowel obstruction. Differences in pre-operative CEA within the groups were not significant after Bonferroni correction.

With regards to pathologic outcomes, the incidence of lymph-node positive disease was different between the groups with significantly more stage III patients in the pT4-NMR cohort compared to pT3-NMR (P<0.001). Patients who underwent a LMR had larger tumors than NMR patients, regardless of the T-stage (pT3: P=0.005; pT4: P<0.001). The surgical specimen was, as would be expected, larger, though colonic specimen length was comparable between the groups (P=0.541). Although

Figure 2. Primary tumor location in LMR and NMR patients



lymph node yield was higher after pT4-LMR, the difference compared to pT4-NMR was not significant after correction (P=0.257). Moreover, the vast majority in all groups had more than 12 lymph nodes retrieved. Concerning histopathological risk factors, both extramural vascular and lymphovascular invasion as well as perineural invasion were more often identified in pT4 tumors (P<0.001, P=0.034, P<0.001, respectively).

PERIOPERATIVE AND SHORT-TERM OUTCOMES

Table 2 demonstrates differences in perioperative outcomes and morbidity rates. Surgical approach was significantly different between the groups (P=0.024), with more laparoscopic surgery in the pT3-NMR group (34.1%). Duration of surgery was longer when a multivisceral resection

Table 1. Baseline characteristics

	NMR ρT3	LMR ρT3	NMR ρT4	LMR ρT4	P-value
	492 (67.9%)	48 (6.6%)	130 (17.9%)	55 (7.6%)	
Age	70.0 (57.7-79.8)	69.5 (62.6-81.2)	67.0 (59.9-80.2)	68.1 (58.9-83.2)	0.717
Gender, *male*	48.6	47.9	43.1	36.4	0.287
ASA	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	0.448
BMI	27.3 (23.6-30.8)	24.8 (21.9-27.4)	25.2 (22.7-30.6)	25.7 (21.4-29.5)	0.001$^{\beta}$
Prior abdominal surgery	45.3	47.9	40.8	43.6	0.774
Pre-operative CEA *	2.9 (1.6-5.9)	3.6 (2.0-13.6)	4.0 (2.3-6.5)	4.3 (2.0-16.7)	0.032
Symptoms					
Anemia	29.3	33.3	33.1	32.7	0.784
Abdominal pain	25.0	45.8	30.0	54.5	<0.001$^{\alpha\beta\gamma}$
Pathology					
Nodal disease	39.6	41.7	56.9	50.9	0.003$^{\delta}$
Tumor size, *cm*	4.5 (3.5-6.0)	5.9 (4.1-7.4)	4.5 (3.7-6.0)	7.0 (4.5-9.5)	<0.001$^{\alpha\beta\gamma}$
Colonic resection length, *cm**	21.5 (16.5-27.0)	22.0 (16.7-32.8)	21.0 (15.3-29.1)	21.0 (17.0-30.5)	0.541
Lymph-node harvested	21 (16-29)	23 (16-31)	21 (17-28)	25 (18-33)	0.042$^{\gamma}$
LN >12	91.5	91.7	93.8	98.2	0.300
Poor differentiation	18.9	27.7	25.8	25.9	0.443
EMVI	18.3	20.8	37.7	41.8	<0.001$^{\gamma\delta}$
LVI	46.7	39.6	68.5	61.8	0.001$^{\delta}$
Perineural invasion	18.0	12.5	41.5	38.2	<0.001$^{\gamma\delta}$
R0-resection	99.4	95.8	70.8	89.1	<0.001$^{\alpha\gamma\delta}$
Site of tumor					0.074
Right-sided	55.7	54.2	51.5	54.5	
Transverse	7.7	14.6	12.3	20.0	
Left-sided	10.6	8.3	15.4	9.1	
Sigmoid	26.0	22.9	20.8	16.4	

Proportions are presented for categorical data, median with IQR for continuous data.
Abbreviations: ASA: American Society of Anesthesiologists, BMI: Body Mass Index (kg/m^2), AJCC: American Joint Committee on Cancer, EMVI: extramural vascular invasion, LVI: lymphovascular invasion
* Missing data: CEA, n = 415; resection length, n = 717
α = pT4 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
β = pT3 NMR vs pT3 LMR: P<0.05 after Bonferroni correction
γ = pT3 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
δ = pT3 NMR vs pT4 NMR: P<0.05 after Bonferroni correction

was performed (P<0.001), and also significantly longer in pT4-LMR cases compared to pT3-LMR (P<0.001). Short-term outcomes were worse for patients who underwent a LMR, with significantly longer length of stay (P<0.001) and a higher requirement for blood transfusion (P<0.001). In addition, the overall morbidity rate (excluding the need for blood transfusion) was higher in pT4-LMR patients compared to pT4-NMR patients, which was mainly explained by more postoperative ileus (20.0% vs. 7.7%, P=0.064). Rates of readmission and reoperation were not different.

LONG-TERM ONCOLOGICAL OUTCOMES

Mean follow-up duration in the study was 48.5 months and significantly shorter in the pT4-NMR group compared to pT3-NMR (35.8 vs. 51.6 months, P=0.001) [Table 3]. In line with the current guidelines, we found higher rates of adjuvant chemotherapy in pT4 tumors (P<0.001) with a significant difference in node-negative disease (P<0.001) but not in stage III (P=0.065). No differences within the pT4 cohort nor in the pT3 cohort were found regarding postoperative treatment. As demonstrated in our results, not all patients with node-positive disease or T4 tumors received additional treatment. In stage II, the main reason to forgo further treatment was age. The median age of patients with stage II disease and T4 tumors who did not receive adjuvant treatment was 78.2 years compared to 63.2 years in the adjuvant T4 group (P<0.001). Furthermore, 17.7% of all eligible T4 stage II patients declined further treatment. With regards to stage III

Table 2. Perioperative and short-term outcomes

	NMR pT3	LMR pT3	NMR pT4	LMR pT4	P-value
Intraoperative					
Operation after July 2009	49.8	58.3	51.5	50.9	0.725
Surgery duration, min	120 (73-171)	164 (122-236)	109 (67-174)	170 (105-255)	<0.001$^{\alpha\beta\gamma}$
Laparoscopic approach	34.1	22.9	26.2	18.2	0.024
Conversion to open surgery	4.9	10.4	1.5	7.3	0.071
Admission					
Admission duration	4 (3-7)	7 (4-11)	4 (3-6)	7 (5-10)	<0.001$^{\alpha\beta\gamma}$
In-hospital morbidity	25.6	27.1	20.8	41.8	0.029$^{\alpha}$
Morbidity rate plus transfusion	39.4	62.5	33.8	69.1	<0.001$^{\alpha\beta\gamma}$
Ileus	10.2	16.7	7.7	20.0	0.046
Wound infection	6.1	2.1	3.1	3.6	0.354
Anastomotic leakage	1.6	4.2	3.1	1.8	0.534
Blood transfusion	19.1	43.8	17.7	41.8	<0.001$^{\alpha\beta\gamma}$
Cardiac	7.7	6.3	3.8	14.5	0.085
Respiratory	3.9	4.2	2.3	3.6	0.857
Renal failure	2.2	4.2	1.5	0.0	0.484
ICU Transfer	2.0	4.2	2.3	5.5	0.392
Readmission	7.1	6.3	5.4	5.5	0.886
Reoperation	1.8	4.2	1.5	1.8	0.705

Proportions are presented for categorical data, median with IQR for continuous data.
α = pT4 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
β = pT3 NMR vs pT3 LMR: P<0.05 after Bonferroni correction
γ = pT3 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
δ = pT3 NMR vs pT4 NMR: P<0.05 after Bonferroni correction

disease, 25.2% of all patients who did not receive adjuvant chemotherapy declined treatment (T3: 20.6%, T4: 34.4%). Similar to the node-negative cohort, median age was significantly higher in the non-adjuvant group (81.3 years versus 62.2 years, P<0.001).

While disease recurrence occurred as often in patients with pT4-LMR compared to pT3 tumors, we found a significantly higher rate in pT4-NMR patients compared to less advanced disease (P<0.001). This was especially true when analyzing locoregional recurrence only (P<0.001). In the majority of these cases, the location of recurrence was the peritoneum (53.3%) followed by the retroperitoneum (30.0%) and mesenteric lymph nodes (16.7%). When analyzing only patients who underwent an R0-resection, risk ratios of disease recurrence, both locoregional and distant, remained higher in the pT4-NMR group compared to pT4-LMR (local: RR 1.47 (0.7 – 3.06), distant: RR 1.81 (0.89 – 4.07)). A difference in median circumferential (radial) margin in patients who developed local recurrence was found between the pT4 groups (pT4-NMR median: 0.6 cm (0.2 – 4.3) versus pT4-LMR median 4.8 cm (0.6 – 5.9), P=0.061). Furthermore, rates of overall and colon cancer mortality were higher in the pT4-NMR group compared to pT4-LMR (overall mortality: 48.5% versus 34.5%, P=0.328, colon cancer mortality: 26.9% versus 10.9%, P=0.068). Survival outcomes were significantly worse after pT4-NMR compared to less advanced disease, whereas rates were comparable between pT4-LMR and T3 disease.

The poor prognostic outcomes were underlined by log-rank testing. Kaplan-Meier survival curves demonstrated significant differences in overall (OS), disease-specific (DSS) and in disease-free survival (DFS),

Table 3. Long-term oncological outcomes

	NMR pT3	LMR pT3	NMR pT4	LMR pT4	P-value
Follow-up duration, months	51.6 (25.1-81.9)	47.9 (22.7-70.2)	35.8 (16.3-59.4)	49.2 (22.5-82.8)	0.001$^{\delta}$
Recurrent disease	16.2	16.7	36.2	18.9	<0.001$^{\delta}$
Locoregional	5.1	8.3	21.5	14.5	<0.001$^{\delta}$
Distant	13.0	12.5	22.3	10.9	0.046$^{\delta}$
Adjuvant therapy	35.0	27.1	56.2	60.0	<0.001$^{\delta}$
Stage II	10.4	14.3	44.6	48.1	<0.001$^{\gamma\delta}$
Stage III	73.3	45.0	67.6	71.4	0.065
Deceased	25.2	31.3	48.5	34.5	<0.001$^{\delta}$
Deceased after R0	24.9	28.3	45.7	28.6	0.001$^{\delta}$
Colon cancer mortality	7.1	10.4	26.9	10.9	<0.001$^{\delta}$
Colon cancer mortality after R0	6.7	8.7	23.9	6.1	<0.001$^{\alpha\delta}$
5-year overall survival	78.6	63.3	46.3	70.0	<0.001*
5-year OS after R0	78.9	66.2	46.2	75.0	<0.001*
5-year disease-specific survival	92.8	85.3	67.2	89.6	<0.001*
5-year DSS after R0	93.4	87.2	67.7	92.7	<0.001*
5-year disease-free survival	82.8	81.9	52.7	74.1	<0.001*
5-year DFS after R0	83.2	81.9	53.2	78.1	<0.001*

Proportions are presented for categorical data, median with IQR for continuous data.
* Log-rank test
α = pT4 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
β = pT3 NMR vs pT3 LMR: P<0.05 after Bonferroni correction
γ = pT3 NMR vs pT4 LMR: P<0.05 after Bonferroni correction
δ = pT3 NMR vs pT4 NMR: P<0.05 after Bonferroni correction

regardless of accomplishment of clear tumor margins (all P<0.001) [Figure 3]. When comparing differences between the groups, we found significantly poorer outcomes after pT4-NMR compared to all other groups in both overall (vs. pT4-LMR: P=0.020, vs. pT3-NMR: P<0.001, vs. pT3-LMR: P=0.036) and colon cancer specific survival (P=0.007, P<0.001, P=0.018, respectively) as well as significantly worse DFS (P=0.034, P<0.001, P=0.010, respectively). Nevertheless, patients with pT4 tumors who underwent LMR had comparable outcomes to patients with less advanced disease. The significantly poorer outcomes in patients with locally advanced cancer who did not undergo a multivisceral resection also withstood multivariate analysis, as shown in the Cox proportional hazard models adjusted for pT-stage (subdivided into pT3, pT4a, and pT4b), pN-stage, adjuvant chemotherapy, and R0-resection [Figure 4]. Compared to patients with a pT4 tumor who did undergo a multivisceral resection, pT4-NMR patients had a 72% increase in the relative hazard of overall survival (HR 1.72, 95% CI: 1.02 – 2.90, P=0.041) and almost three-fold higher hazard ratios in the disease-specific survival model (HR 3.36, 95% CI: 1.40 – 8.09, P=0.007). Moreover, DFS remained significantly worse after adjustment (HR 2.47, 95% CI: 1.21 – 5.03, P=0.013). In addition to surgical approach, node-positive disease and clear tumor margins were independent predictors in all three models. Adjuvant chemotherapy was only predictive in overall survival. When adjusting for radial margin instead of radical resection, pT4-NMR was no longer a poor predictor for DFS. Radial margin <1 cm (HR 2.03, 95% CI: 1.16 – 3.53), P=0.013) was along with node-positive disease (HR 2.64, 95% CI:1.86 – 3.74, P<0.001) independently predictive for poor DFS.

A covariables included baseline pT-stage (subdivided into pT3, pT4a, pT4b)

DISCUSSION

There is clear evidence that an R0 resection is a strong predictor for both overall and disease-free survival in colon cancer.[5,15] A recent single-center study compared R0 with R1 resection in colon cancer and found a recurrence rate of 18.9% and 55.5%, respectively, with a corresponding 5-year survival of 60% and 25%.[16] However, R0 resection is more challenging to achieve if the tumor invades adjacent organs, which is the case in approximately 10% of all primary colon cancers. Multivisceral resection is then necessary to achieve complete tumor resection with negative margins. Although there is widespread knowledge of the importance of R0 resection, a recent population analysis demonstrated that the vast majority of the patients with locally advanced colon cancer did not receive LMR.[7] Our study underscored the problem of infrequently performed LMR for locally advanced colon cancer with a performance rate of 29.7%. In our cohort, the main reason to not perform a multivisceral resection was not reluctance of the surgeon, but a false discernment of oncological invasion as peri-inflammatory adhesions. An increase in LMR was seen over the study period, in particular in the latter third, which accounted for 40% of all multivisceral resections in locally advanced cancer. Perhaps more importantly, the majority of patients with pT4b tumors received LMR (66.0%) while the incidence of en bloc resections in tumors that did not invade the

Figure 3. Kaplan Meier survival curves

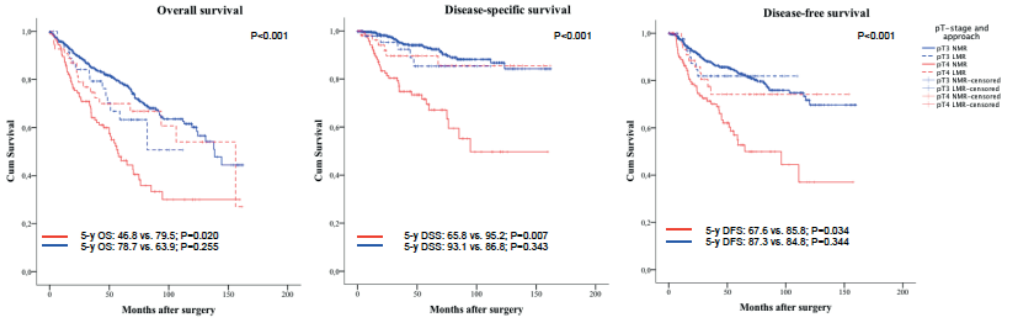
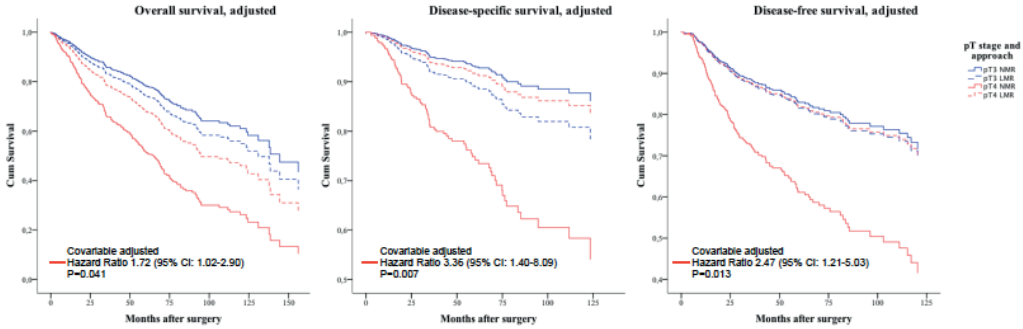


Figure 4. Multivariate Cox proportional hazards survival estimates



serosal surface on pathology was much lower (pT4a: 20.5%; pT3: 8.9%).

The benefit of LMR in locally advanced colon cancer was emphasized by our study with significantly better long-term outcomes in pT4-LMR patients compared to pT4-NMR patients and comparable oncologic outcomes to patients with less advanced disease. Overall survival, colon cancer mortality and disease-free survival were all worse in pT4-NMR patients compared to pT4-LMR, even after adjustment for potential confounders including pTN-stage, adjuvant therapy and the achievement of R0 resection. The estimated 5-year OS and DSS in our study was 70.0% and 89.6% when a multivisceral resection was performed in pT4 disease. These outcomes were comparable to previous reported outcomes [9,17] and even more notably, comparable to patients with less advanced disease and no tumor invasion (78.6%, 92.8%, respectively). On the contrary, when a patient with true tumor invasion did not receive LMR, both OS and DSS were significantly worse (46.3%, 67.2%). This poor prognosis remained true in the Cox proportional hazard models, including almost three-fold higher ratios of colon cancer mortality compared to pT4-LMR (HR 3.36, P=0.007).

In terms of disease-free survival, poorer outcomes were mainly explained by a higher rate of locoregional recurrence particularly the peritoneum, where the majority of recurrent disease was located. Despite free tumor margins, locoregional recurrence remained higher in patients with pT4 tumors who did not undergo a LMR. A possible explanation could be the limited circumferential clearance, which was less than 1 cm in pT4-NMR patients who developed locoregional recurrence. Although

the impact of radial margin clearance is extensively investigated for rectal cancer and has been demonstrated to be a poor prognostic factor, the outcomes in colon cancer are less well-detailed. The extent of a curative resection for colon cancer generally includes a proximal and distal margin of ≥5 cm.[18-19] However, knowledge about accurate circumferential margins in colon rectal cancer is lacking, other than recommendations to assess the radial margin in the current guidelines [12] and reported poor prognostic outcomes in patients with colon cancer and positive radial margins.[20] Our study demonstrated that a radial margin of less than 1 cm was independently predictive for disease recurrence, in particular locoregional recurrence. Additionally, lymph-node positive disease remained associated with worse outcomes after adjustment, which is in line with previous studies.[21] Because of the established risk factor of lymph node status in colon cancer, adjuvant therapy is highly recommended.[12] However, adjuvant therapy was only predictive for overall survival in the Cox proportional hazard model, which suggests that achieving accurate clearance of all tumor margins by LMR has a greater impact on disease-specific survival and recurrence than could be realized by postoperative therapy. Nonetheless, the number of patients that received additional treatment should be taken into account. In accordance with current guidelines, the administration of adjuvant therapy was higher in node-negative disease. However, about one-third of all stage III patients did not receive additional treatment mainly because of older age.

Despite our promising results, 34% of the patients with true tumor invasion on pathology did not receive a LMR. In the majority of those cases, invasion was misinterpreted as inflammatory adhesions. The problem remains that it is difficult to discern between true invasion and inflammatory adhesions. In our study, only 49.1% of all T4-LMR tumors had pathologic confirmed invasion. A multivisceral resection might not have been necessary in the remaining 50.9% of T4 tumors to achieve a complete resection. Since it is not possible to make this distinction through imaging, as of yet, the decision is based on a surgeon's perspective only.

Several factors may play an important role in the decision whether or not to perform an extended resection. First, the associated morbidity after a multivisceral resection. A recent systematic review reported a mean complication rate of 41.5% after multivisceral resections, which was significantly higher than the previously described morbidity rate of 20%-30% after surgery for colon cancer in general.[22] Morbidity rates in our study were in line with the systematic review by Longo et al, with higher complication rates compared to standard procedures. Nonetheless, this significant difference was mainly explained by a higher requirement of blood transfusion and more postoperative ileus. Differences in surgical approach and a longer operation duration in LMR cases might have led to these outcomes since open surgery is correlated with the need for blood transfusion and postoperative ileus. Additionally, a prolonged operative time is known to be a risk factor for ileus.[23-25] Other than these two factors, postoperative complications were comparable as were readmission and reoperation rates when comparing LMR to NMR. This underscores the safety of a multivisceral resection.

Previous studies found several baseline factors between patients who did and did not receive LMR, though disparities in our study were practically nonexistent. One might assume that surgeons are reluctant to

perform LMR in older patients with more comorbidities. Even though age per se is not a contraindication for more extensive surgical procedures, elderly patients are often deprived of aggressive surgical treatment.[7,26] Our study did not support this theory with a similar distribution of both age and ASA-score over all four groups. Nevertheless, patient's age was one of the reasons to forgo adjuvant therapy which might be considered as an incomplete treatment, in particular when an R0-resection is not achieved.

The inability to distinguish oncologic invasion from inflammatory adhesions is a well-known problem. These adhesions are often hard to discern from true tumor invasion [17,27], subsequently leading to compromised oncological outcomes when oncological invasion is misinterpreted as inflammatory adhesions. Nonetheless, achieving R0 resection with accurate tumor clearance remains most important. This is underlined by our study, demonstrating significantly poorer outcomes in terms of both disease recurrence and survival in patients with pT4 tumors who did not receive a multivisceral resection. On the other hand, when LMR was performed in T4 patients, oncologic outcomes were practically similar to those patients with less advanced disease. Furthermore, in patients with clinical tumor invasion but T3 disease on pathology, LMR does not compromise short-term outcomes as morbidity rates are comparable with NMR patients. Therefore, a resection with wide margins is recommended and should be the standard of care when tumor invasion is expected.

The limitations of this study are inherent to the retrospective design and the tertiary setting of our institute. The latter affects the generalizability of our results as patient and disease characteristics may differ from patients in non-referral centers. Furthermore, it is difficult to determine resectability in hindsight, since this may differ between surgeons and may change over time. Nevertheless, this study presents one of the few analyses of both short- and long-term outcomes in patients who did or did not receive LMR for true tumor invasion in colon cancer and in addition evaluates the potential harm of a LMR in patients who did not warrant it.

CONCLUSION

Our study confirms the importance of LMR in patients with extra-colonic extension. Patients with pT4 colon cancer who did not receive LMR had significantly worse prognosis in terms of disease recurrence and survival, even after adjustment for staging, adjuvant therapy, and R0 resection. The additional impact of adjuvant chemotherapy on oncologic outcomes was only confirmed on overall survival, which underlines the importance of clear tumor margins by LMR on disease-specific survival and recurrence. Furthermore, when LMR was performed in pT4 colon cancer long-term outcomes were practically similar to patients with less advanced disease. Postoperative morbidity was comparable between both LMR and NMR groups, with the exception of a higher requirement of blood transfusion and more frequent postoperative ileus. This emphasizes the safety and feasibility of a multivisceral resection and supports the decision to perform LMR in all cases when locally advanced cancer is suspected.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016

2. Gebhardt C, Meyer W, Ruckriegel S, Meier U. Multivisceral resection of advanced colorectal carcinoma. Langenbecks Arch Surg 1999;384:194-199

3. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010; 17:1471-1474

4. Zoucas E, Frederiksen S, Lydrup ML, Månsson W, Gustafson P, Alberius P. Pelvis exenteration for advanced and recurrent malignancy. World J Surg 2010;34:2177-2184

5. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: a systematic review. Ann Surg Oncol 2013;20:2929–2936

6. Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice Parameters for the Management of Colon Cancer. Dis Colon Rectum 2012;55:831-843

7. Govindarajan A, Coburn NG, Kiss A, Rabeneck L, Smith AJ, Law CH. Population based assessment of the surgical management of locally advanced colorectal cancer. J Natl Cancer Inst 2006;98:1474-1481

8. Courtney D, McDermott F, Heeney A, Winter DC. Clinical review: surgical management of locally advanced and recurrent colorectal cancer. Langenbecks Arch Surg 2014;399:33-40

9. Croner RS, Merkel S, Papadopoulos T, Schellerer V, Hohenberger W, Goehl J. Multivisceral resection for colon carcinoma. Dis Colon Rectum 2009;52:1381–1386

10. Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III co- lon carcinoma: a final report. Ann Intern Med 1995;122:321-326

11. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995;345:939-944

12. National Comprehensive Cancer Network. Colon Cancer (Version 2.2016).

13. Bowne WB, Lee B, Wong WD, Ben-Porat L, Shia J, Cohen AM, Enker WE, Guillem JG, Paty PB, Weiser MR. Operative salvage for locoregional recurrent colon cancer after curative resection: an analysis of 100 cases. Dis Colon Rectum 2005;48:897–909

14. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ Jr, Pemberton JH, Wolff BG. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 1992;174:27-32

15. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D, Sargent D; National Cancer Institute Expert Panel. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583-596

16. Khan MA, Hakeem AR, Scott N, Saunders RN. Significance of R1 resection margin in colon cancer resections in the modern era. Colorectal Dis 2015;17:943–953

17. Nakafusa Y, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K: Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. Dis Colon Rectum 2004;47:2055–2063

18. Hashiguchi Y, Hase K, Ueno H, Mochizuki H, Shinto E, Yamamoto J. Optimal margins and lymphadenectomy in colonic cancer surgery. Br J Surg. 2011;98:1171–1178

19. Rørvig S, Schlesinger N, Mårtensson NL, Engel S, Engel U, Holck S. Is the longitudinal margin of carcinoma-bearing colon resections a neglected parameter? Clin Colorectal Cancer. 2014;13:68–72

20. Amri R, Bordeianou LG, Sylla P, Berger DL. Association of radial margin positivity with colon cancer. JAMA Surg 2015;150:890-898

21. Radespiel-Troger M, Hohenberger W, Reingruber B. Improved prediction of recurrence after curative resection of colon carcinoma using tree-based risk stratification. Cancer 2004;100:958–967

22. Longo WE, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, Phelan MA, Henderson WG, Daley J, Khuri SF. Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum 2000;43:83-91

23. Artinyan A, Nunoo-Mensah JW, Balasubramaniam S, Gauderman J, Essani R, Gonzalez-Ruiz C, Kaiser AM, Beart RW Jr. Prolonged postoperative ileus-definition, risk factors, and predictors after surgery. World J Surg. 2008;32:1495–1500

24. Kiran RP, Delaney CP, Senagore AJ, Millward BL, Fazio VW. Operative blood loss and use of blood products after laparoscopic and conventional open colorectal operations. Arch Surg. 2004;139:39–42

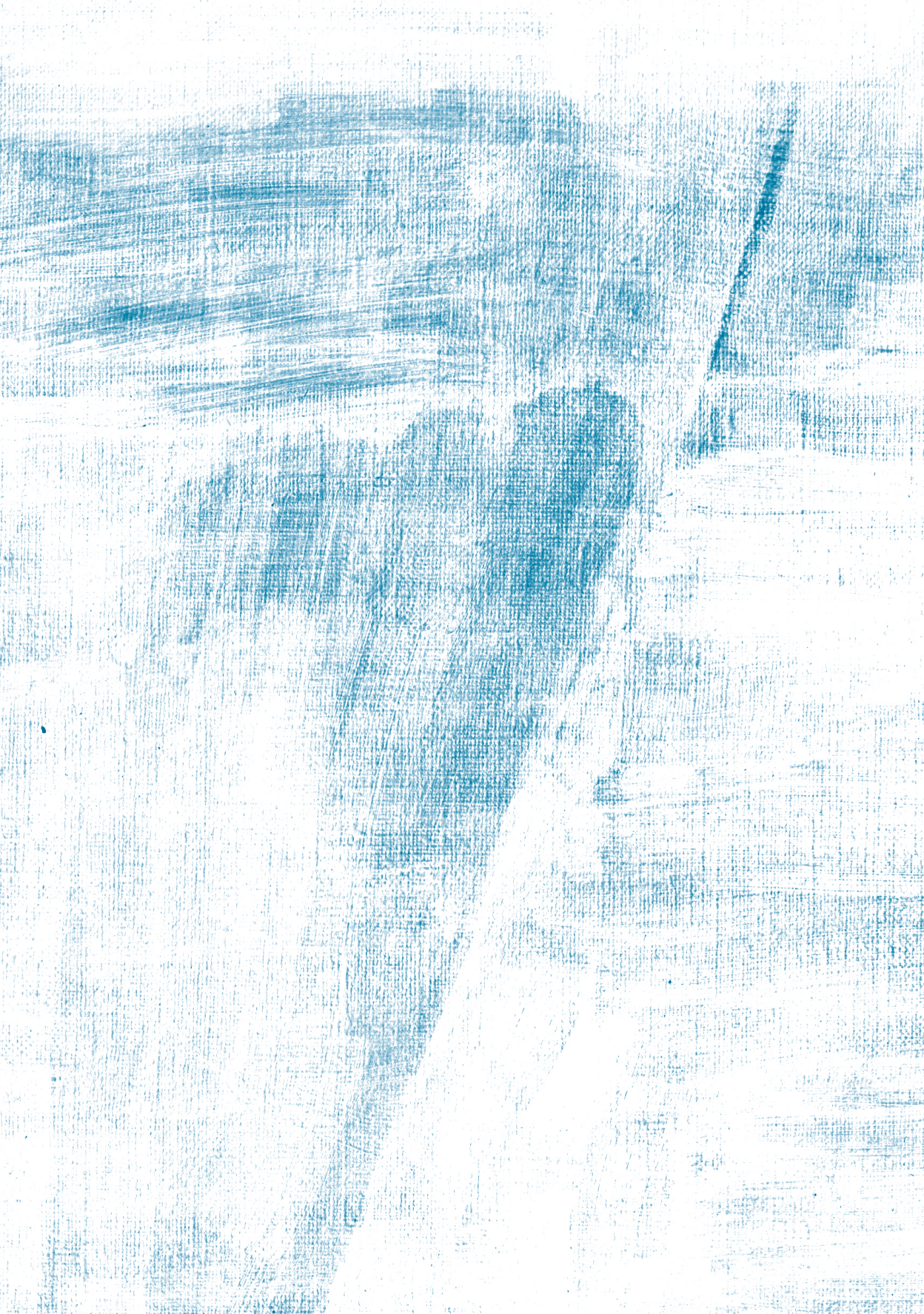
25. Halabi WJ, Jafari MD, Nguyen VQ, Carmichael JC, Mills S, Pigazzi A, Stamos MJ. Blood transfusions in colorectal cancer surgery: incidence, outcomes, and predictive factors: an American College of Surgeons National Surgical Quality Improvement Program analysis. Am J Surg 2013;206:1024-1032

26. Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. Lancet 2000;356:968-974

27. Chen YG, Liu YL, Jiang SX, Wang XS. Adhesion pattern and prognosis studies of T4N0M0 colorectal cancer following en bloc multivisceral resection: evaluation of T4 subclassification. Cell Biochem Biophys 2011;59:1–6

PART III

HISTO-PATHOLOGIC FEATURES and OUTCOMES in COLON CANCER



CHAPTER 7

PATHOLOGIC FACTORS are MORE IMPORTANT than TUMOR LOCATION in LONG-TERM SURVIVAL in COLON CANCER

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ABSTRACT

PURPOSE

Proximal and distal colon cancers differ in terms of epidemiology, clinical presentation, and pathologic features. The aim of our study was to evaluate the impact of right-sided (RC), transverse (TC), and left-sided (LC) colon cancer on morbidity rates and oncological outcomes.

METHODS

A retrospective analysis of patients with resected colon cancer between 2004-2014 was conducted. Cox proportional hazard models were used to assess predictors of overall (OS), and disease-specific survival (DSS), as well as disease-free survival (DFS).

RESULTS

A total of 1189 patients were included. RC patients (n=618) were older, predominantly women, and had a higher comorbidity rate. LC (n=454) was associated with symptomatic presentation and increased rates of laparoscopic surgery. Multivisceral resections were more frequently performed in TC tumors (n=117). This group was admitted one day longer and had a higher complication rate (RC 35.6% vs. TC 43.6% vs. LC 31.1%, P0.032). Although the incidence of abscess/leak was similar between the groups, the necessity of readmission and subsequent reoperation for a leak was significantly higher in LC patients. Pathology revealed more poorly differentiated tumors and microsatellite instability in RC. Kaplan Meier curves demonstrated worse 5-year OS for right-sided tumors (RC: 73.0%; TC: 76.2%. LC: 80.8%, P0.023). However, after adjustment no differences were found in OS, DSS, and DFS between tumor location. Only pathological features were independently correlated with prognosis, as were baseline characteristics for OS.

CONCLUSION

Tumor location in colon cancer was not associated with survival or disease recurrence. Pathological differences beyond tumor stage were significantly more important.

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers in both men and women worldwide. The decline in incidence and mortality rates over the last decades reflects the impact of the reduction of risk factors, the introduction of screening programs and altered treatment patterns.[1-2] Previous studies reported a shift in the distribution of colon cancer toward the proximal side of the colon.[3-4] Already in the early '90s, a distinction in clinical outcomes and pathological features within different segments of the colon relative to colon cancer was suggested.[5] Subsequent research elaborated on this topic and a discussion as to whether to consider proximal and distal colon cancer as two different diseases was raised.[6] However, up until now these results have had no consequences on screening or treatment patterns.

The proximal and distal parts of the large intestine are physiologically separate, due to different embryological origins. The right colon arises from the midgut, as does the proximal two-thirds of the transverse colon. The left colon, including the distal one-third of the transverse colon, derives from the hindgut. Consequently, there is not only a difference in blood supply, but also potentially in gene expression and clinical presentation.[6-7] In addition, the genetic carcinogenetic pathways may be different.[8-10] Three major pathways for sporadic colorectal cancer have been described: chromosomal instability (CIN), microsatellite instability (MSI) and more recently the serrated pathway classified as the CpG island methylator phenotype (CIMP). While CIN is observed in the vast majority of colorectal cancers, it is associated with distal cancers, whereas the latter two pathways have been linked to more proximal colon cancers.[8,11]

Although distinct differences exist, the influence on prognosis remains unclear. Some studies suggested higher mortality for right-sided tumors [7,12], while others found no differences.[13] Unfortunately, most of the conducted studies were limited in their ability to adjust for a wide range of potential confounders. Furthermore, to our knowledge, none of the studies compared transverse colon cancer as a separate entity. Therefore, the aim of our study was to determine clinicopathological differences and the prognostic impact of primary tumor location in colon cancer.

MATERIALS & METHODS

STUDY DESIGN AND POPULATION

A cohort study was designed from a prospectively maintained and IRB approved database that included all primary colon cancer patients who underwent surgical treatment at Massachusetts General Hospital between 2004 and 2014. Patients who underwent an emergency procedure (n=152), had a total colectomy (n=88), or received neoadjuvant therapy (n=62) were excluded. Patients were divided into three groups: right-sided, transverse, and left-sided colon cancer. TC was defined as the resection of the transverse colon only, while RC included the resection of the cecum, ascending colon, and hepatic flexure, and LC the resection of the splenic flexure, descending colon, and sigmoid.

The main outcome measures for this study were overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS). Data on

long-term outcomes was updated periodically by reviewing patient follow-up records and the Massachusetts General Hospital's cancer registry. Secondary outcomes included patient characteristics, pathological features, and perioperative outcomes. All time to events was calculated from date of surgery.

STATISTICAL ANALYSES

Continuous variables were analyzed using a Kruskal-Wallis H test for the differences between all three groups, while group-specific differences compared with the remainder of the population was performed through a Mann-Whitney U test. Continuous variables are presented as the mean with a standard deviation (SD) or the median with an interquartile range (IQR) according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Categorical variables are presented as the percentages of patients. Differences in dichotomous variables were assessed using a Chi-square (χ^2) test or Fisher's exact test where appropriate. Long-term outcomes were performed for stage I-III colon cancer only. Kaplan Meier curves for overall (OS), disease-specific survival (DSS), as well as disease-free survival (DFS) were assessed within each stage and all stages combined using log-rank testing. Multivariate analyses were performed using a Cox proportional hazard model to determine risk factors for overall, disease-specific, and disease-free survival. Variables significant in univariate analysis were entered into the model. Results are reported as Hazard Ratios (HR) with a 95% confidence interval (CI). All statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.). The threshold for statistical significance was set at a two-sided P-value of 0.05 or less.

RESULTS

Of the 1189 patients who underwent an elective single-segment colectomy for colon cancer at our tertiary center between 2004 and 2014, 52.0% (n=618) had right-sided colon cancer, 9.8% (n=117) a transverse colon cancer, and 38.2% (n=454) a left-sided colon cancer. Patient characteristics are summarized in Table 1. Median age (RC 71.4 vs. TC 70.3 vs. LC 62.6 years, P<0.001), and mean ASA-score (RC: 2.43 vs. TC 2.34 vs. LC 2.25, P<0.001), were significantly different between the three groups. In terms of group-specific differences compared with the remainder of the population, patients with RC were older, had a higher ASA-score (P<0.001), were more likely to be female (P0.003) and Caucasian (P0.014). LC patients were younger, had a lower ASA-score (P<0.001), were more often male (P0.003) and Asian (P0.004). When considering comorbidities, RC patients had more frequently a history of diverticulitis (P0.045), chronic pulmonary disease (P0.029), prior abdominal surgery (P0.011), and anemia (P<0.001). The incidence of anemia (P<0.001), congestive heart failure (P0.033), chronic pulmonary disease (P0.013), or prior abdominal surgery (P0.001) was significantly lower in LC patients. TC patients had a higher incidence of alcohol abuse (P0.041). A symptomatic presentation was more often seen in patients with left-sided tumors, including complaints of changes in stool habits (P0.002), constipation (P0.014), and hematochezia (P<0.001).

PATHOLOGY FEATURES

Statistically significant variations existed between the three groups in AJCC-stage, nodal disease, tumor grade, microsatellite instability, tumor size, colonic specimen length, and lymph-node harvest (Table 2). Poorly differentiated tumors were seen more often in right-sided colon cancer (RC 22.5% vs. TC 14.5% vs. LC 11.2%, P<0.001), as was high-microsatellite instability, and presence of both HPMS2 and HMLH1 loss (P<0.001). Lymph-node positive disease was correlated with left-sided cancer (RC 37.4% vs. TC 25.6% vs. LC 43.0%, P0.010). Furthermore, LC was associated with smaller tumor size, fewer lymph nodes harvested (P<0.001), and more perineural invasion (P0.022). TC was associated with a significantly longer colonic specimen length (median RC 20 vs. TC 30 vs. LC 23 cm, P<0.001), and less lymph-node positive disease (P0.003). R0 resections were achieved in comparable numbers (RC 92.1% vs. TC 96.6% vs. LC 93.6%, P0.182).

Table 1. Patient characteristics and comorbidities

N=1189	Right colectomy *N=618 (52.0%)*	Transverse *N=117 (9.8%)*	Left colectomy *N=454 (38.2%)*	P-value
Age	71.4 (60.9-80.3)***	70.3 (58.5-80.3)	62.6 (51.9-73.8)***	<0.001
Gender, *male*	273 (44.2%)**	57 (48.7%)	244 (53.7%)**	0.008
ASA	2.43 ±0.60 ***	2.34 ±0.51	2.25 ±0.55 ***	<0.001
BMI	26.5 (22.9 – 30.2)	26.5 (23.8 – 31.3)	26.9 (23.5 – 31.1)	0.348
Ethnicity				0.001
Caucasian	566 (91.6%)*	103 (88.0%)	396 (87.2%)*	
Asian	14 (2.3%)	1 (0.9%)	23 (5.1%)**	
Afro American	17 (2.8%)	6 (5.1%)	14 (3.1%)	
Other	21 (3.4%)	7 (6.0%)	21 (4.6%)	
Alcohol abuse	37 (6.0%)	13 (11.1%)*	29 (6.4%)	0.120
Nicotine dependence	55 (8.9%)	14 (12.0%)	51 (11.2%)	0.355
Comorbidity				
CHF	40 (6.5%)	9 (7.7%)	17 (3.7%)*	0.088
CPD	63 (10.2%)*	11 (9.4%)	27 (5.9%)*	0.045
DM II	111 (18.0%)	21 (17.9%)	65 (14.3%)	0.260
Diverticulitis	61 (9.9%)*	9 (7.7%)	29 (6.4%)	0.121
IBD	7 (1.1%)	0 (0.0%)	6 (1.3%)	0.467
Renal disease	35 (5.7%)	6 (5.1%)	22 (4.8%)	0.837
Anemia	221 (35.8%)***	25 (21.4%)	51 (11.2%)***	<0.001
Previous abdominal surgery	282 (45.6%)*	55 (47.0%)	164 (36.1%)**	0.004
Symptoms				
Hematochezia	42 (6.8%)***	9 (7.7%)	64 (14.1%)***	<0.001
Constipation	22 (3.6%)*	5 (4.3%)	31 (6.8%)*	0.047
Abdominal pain	152 (23.6%)	31 (24.8%)	106 (22.2%)	0.767
Change stool habit	16 (2.6%)***	8 (6.8%)	33 (7.3%)**	0.001

Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body Mass Index (kg/m^2); CHF, Congestive Heart Failure; CPD, Chronic Pulmonary Disease; DM II, Diabetes Mellitus type II; IBD, Irritable Bowel Disease
Asterisks denote values significantly different from the other resection regions; *P<0.05; **P<0.01; ***P<0.001

	Right colectomy	Transverse	Left colectomy	P-value
Tumor size	4.5 (2.8– 6.5)***	4.0 (2.5 – 6.0)	4.0 (2.2 – 5.2)***	<0.001
AJCC-stage				
0	33 (5.3%)*	5 (4.3%)	10 (2.2%)*	0.036
I	139 (22.5%)*	29 (24.8%)	132 (29.1%)*	0.049
II	207 (33.5%)	48 (41.0%)*	114 (25.1%)*	0.001
III	166 (26.9%)	22 (18.8%)*	142 (31.3%)*	0.021
IV	73 (11.8%)	13 (11.1%)	56 (12.3%)	0.926
T3-T4	424 (69.6%)*	80 (68.4%)	281 (61.9%)*	0.061
N+	231 (37.4%)	30 (25.6%)**	195 (43.0%)*	0.002
M+	42 (6.8%)	7 (6.0%)	20 (4.4%)	0.254
Poor differentiation	139 (22.5%)***	17 (14.5%)	51 (11.2%)***	<0.001
EMVI	165 (26.7%)	31 (26.5%)	134 (29.5%)	0.566
LVI	272 (44.0%)	46 (39.3%)	188 (41.4%)	0.527
Perineural involvement	114 (18.4%)	19 (16.2%)	107 (23.6%)*	0.063
Microsatellite instability				
High	71 (11.5%)***	11 (9.4%)	6 (1.3%)***	<0.001
Stable	114 (18.4%)**	16 (13.7%)*	130 (28.6%)***	<0.001
Unknown	433 (70.1%)	90 (76.9%)	318 (70.0%)	0.301
MRPE				
HPMS2 loss	76 (12.4%)***	13 (11.1%)	8 (1.8%)***	<0.001
HMLH1 loss	99 (16.1%)***	17 (14.5%)	8 (1.8%)***	<0.001
HMSH6 loss	10 (1.6%)	2 (1.7%)	5 (1.1%)	0.758
HMSH2 loss	10 (1.6%)	1 (0.9%)	3 (0.7%)	0.339
Tumor size	4.5 (2.8– 6.5)***	4.0 (2.5 – 6.0)	4.0 (2.2 – 5.2)***	<0.001
Resection length *	20 (15-26)***	30 (21-37)***	23 (17-27)**	<0.001
R0-resection	569 (92.1%)	113 (96.6%)	425 (93.6%)	0.182
Lymph node harvest	20 (16 – 28)***	20 (14 – 26)	18 (13 – 25)***	<0.001
R0-resection	569 (92.1%)	113 (96.6%)	425 (93.6%)	0.182

Abbreviations: AJCC, American Joint Committee on Cancer; EMVI, extramural vascular invasion; LVI, lymphovascular invasion; MRPE, mismatch repair protein expression
Asterisks denote values significantly different from the other resection regions; *P<0.05; **P<0.01; ***P<0.001
* Missing data: Resection length, n=753

PERI-OPERATIVE OUTCOMES

Analysis of peri-operative outcomes are demonstrated in Table 3. Left-sided colon cancer resections were completed more often laparoscopically (RC 31.9% vs. TC 30.8% vs. LC 39.0%, P0.010) with a subsequent significantly longer median time of surgery (RC 104 vs. TC 135 vs. LC 135 min, P<0.001). The overall laparoscopic conversion rate was 4.0%, with no difference between the groups (RC 3.1% vs. TC 6.8% vs. LC 4.6%, P0.119). The rate of adhesions was remarkably higher in RC patients (P<0.001). Although not significantly different, multivisceral resections were more frequently performed in TC resections (RC 10.4% vs. TC 15.4% vs. LC 8.8%, P0.054). Of all patients with transverse colon cancer, 44.4% underwent a transverse colectomy and 55.6% an extended right or left colectomy.

Median length of stay and rate of complications within 30 days of surgery was significantly different between the groups. TC patients were

admitted one day longer and developed more complications after surgery (RC 35.6% vs. TC 43.6% vs. LC 31.1%, P0.032). However, when including the requirement for blood transfusion in the complication rate, postoperative morbidity was comparable with RC but still significantly higher than the LC group (RC 46.1% vs. TC 51.3% vs. LC 35.9%, P0.049). On the contrary, although incidence of intra-abdominal abscess and/or anastomotic leakage was comparable between the groups, the rate of readmission was significantly higher in LC patients for abscess/leak (P0.038). This was reflected in higher reoperation rates after LC resection (P0.024), with anastomotic leakage (42.9%), colonic perforation (14.3%), bowel obstruction (14.3%), and fascial dehiscence (14.3%) as the main indications for reoperation. No differences were found regarding 30-day readmission and mortality rates.

ONCOLOGICAL OUTCOMES

Within the full study cohort, 999 patients were diagnosed with stage I-III disease and included in the long-term analysis (Table 4). Median follow-up duration was 48.6 months and comparable between the groups. During the study period, more patients with right-sided tumors died with a significantly worse 5-year overall survival (RC: 73.0%; TC: 76.2%. LC: 80.8%, P0.023). Nevertheless, colon cancer specific survival was not different between the groups (RC: 91.7%; TC: 94.2%. LC: 91.8%, P0.372) nor was disease recurrence (RC: 85.3%; TC: 89.4%. LC: 81.2%, P0.125). When analyzing stage-by-stage, no differences were found in either OS or DSS between the three groups. Despite a higher administration of adjuvant therapy in patients with left-sided tumors (P<0.001), the estimated 5-year disease-free survival tended to be worse for this group compared to the remainder of the population (LC 81.2% vs. RC/TC: 85.9%, P0.052). In addition, we found worse DFS for stage II left-sided colon cancer (LC 80.3% vs. RC/TC: 90.2%, P0.019).

To assess risk factors for both survival and disease recurrence, a multivariate analysis was performed. Relationships between patient characteristics, clinicopathological features and long-term outcomes in all patients undergoing curative resection for colon cancer are demonstrated in Table 5. On univariate analysis, left-sided colon cancer was associated with better overall survival compared to right-sided tumors (HR: 0.73, P0.025). However, after adjustment tumor location was no longer associated with worse outcomes. Factors independently related to overall mortality included patient-related (older age, higher ASA-score, BMI <25 kg/m^2, alcohol abuse), procedure-related (open surgery), as well as tumor-related characteristics (T3-T4 tumors, lymph-node positivity, high-grade disease, perineural invasion, R1 resection, less than 12 lymph nodes harvested) and the administration of adjuvant therapy. Regarding disease-specific survival, tumor location was not contributory in the univariate analysis. Pathological features including lymph-node disease, lymphovascular invasion, perineural invasion, and high grade disease as well as alcohol abuse were associated with worse colon cancer specific survival. When analyzing risk factors for disease-free survival, anastomotic type appeared to be a risk factor for poorer outcomes. Compared to ileo-colonic anastomoses, patients with a colo-colonic anastomosis had worse disease-free survival (HR 1.63, P0.048). Risk was non-significantly higher when compared to colo-rectal anastomoses (HR 1.37, P0.238).

Table 3. Perioperative outcomes

	Right colectomy	Transverse	Left colectomy	P-value
Laparoscopic approach	197 (31.9%)*	36 (30.8%)	177 (39.0%)*	0.036
Surgery duration, *min*	104 (60 – 155)***	135 (84 – 196)*	135 (88 – 182)***	<0.001
Conversion	19 (3.1%)	8 (6.8%)	21 (4.6%)	0.119
Adhesions	214 (34.6%)***	39 (33.3%)	97 (21.4%)***	<0.001
Multivisceral resection	64 (10.4%)	18 (15.4%)	40 (8.8%)	0.112
Admission duration	4 (3-7)	5 (3-9) **	4 (3-6)***	<0.001
Complication rate	220 (35.6%)	51 (43.6%)*	141 (31.1%)*	0.031
Complication rate, *including blood transfusion*	285 (46.1%)*	60 (51.3%)*	163 (35.9%)***	0.001
In-hospital morbidity	193 (31.2%)	44 (37.6%)	119 (26.9%)*	0.034
Ileus	56 (9.1%)	13 (11.1%)	38 (8.4%)	0.651
Intra-abdominal abscess/leak	12 (1.9%)	2 (1.7%)	12 (2.6%)	0.691
Wound infection	36 (5.8%)	4 (3.4%)	28 (6.2%)	0.514
Peritonitis	9 (1.5%)	0 (0.0%)	3 (0.7%)	0.225
GI bleeding	8 (1.3%)	3 (2.6%)	1 (0.2%)*	0.046
Fascial dehiscence	5 (0.8%)	2 (1.7%)	5 (1.1%)	0.650
Cardiac	49 (7.9%)	12 (10.3%)	22 (4.8%)*	0.050
Respiratory	28 (4.5%)	4 (3.4%)	10 (2.2%)	0.124
Renal	57 (9.2%)	11 (9.4%)	26 (5.7%)*	0.091
Urinary tract infection	32 (5.2%)*	3 (2.6%)	11 (2.4%)*	0.051
DVT	5 (0.8%)	2 (1.7%)	7 (1.5%)	0.467
PE	2 (0.3%)	2 (1.7%)**	0 (0.0%)	0.017
Blood transfusion	138 (22.3%)**	26 (22.2%)	60 (13.2%)***	0.001
Intravenous fluids	47 (7.6%)	11 (9.4%)	17 (3.7%)**	0.013
TPN	17 (2.8%)	6 (5.1%)	15 (3.3%)	0.402
ICU admission	17 (2.8%)	3 (2.6%)	14 (3.1%)	0.930
Readmission	30 (4.9%)	10 (8.5%)	29 (6.4%)	0.233
Reoperation	7 (1.1%)*	2 (1.7%)	14 (3.1%)*	0.071
Death	7 (1.1%)	1 (0.9%)	3 (0.7%)	0.725

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; TPN, total parenteral nutrition
Asterisks denote values significantly different from the other resection regions; *P<0.05; **P<0.01; ***P<0.001

Table 4. Long-term oncological outcomes in stage I-III colon cancer

N=999	Right colectomy *N=512 (51.3%)*	Transverse *N=99 (9.9%)*	Left colectomy *N=388 (38.8%)*	P-value
Follow-up duration, months	48.6 (22.2-77.4)	50.0 (23.5-71.9)	48.1 (22.4-85.4)	0.884
Disease-free duration, months	43.1 (17.1-71.5)	45.0 (18.3-65.0)	36.0 (16.6-74.6)	0.819
Disease recurrence	58 (11.3%)	9 (9.1%)	58 (14.9%)	0.148
Local	5 (1.0%)	2 (2.0%)	7 (1.8%)	0.497
Distant	57 (11.1%)	7 (7.1%)	54 (13.9%)	0.134
Adjuvant therapy	104 (20.3%)**	18 (18.2%)	123 (31.7%)***	<0.001
Deceased	142 (27.7%)*	22 (22.2%)	81 (20.9%)*	0.052
Colon cancer death	35 (6.8%)	5 (5.1%)	35 (9.0%)	0.290
Estimate 5-year OS	73.0%*	76.2%	80.8%*	0.070
Estimate 5-year DSS	91.7%	94.2%	91.8%	0.372
Estimate 5-year DFS	85.3%	89.4%	81.2%	0.125

Abbreviations: OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival
Asterisks denote values significantly different from the other resection regions; *P<0.05; **P<0.01; ***P<0.001

DISCUSSION

Over the last several years, there has been increased interest in identifying the differences between proximal and distal colon cancer. Differences in epidemiology, patient demographics, and histological features relative to tumor site in colon cancer are observed, yet the location of the tumor is often not considered as a separate entity when outcomes are discussed. In addition, transverse colon cancers are often excluded altogether or included in either the right- or left-sided group for analysis. Therefore, the aim of our study was to assess the differences in clinicopathological characteristics as well as long-term outcomes in patients who were diagnosed with either a right-sided, left-sided, or transverse colon cancer.

In our study, patients with right-sided colon cancer were older, more likely to be female and had poorer histopathological features including more T3-T4 tumors and poor differentiation. This is fully consistent with previous data.[7,13-14] On the other hand, lymph-node positive disease was more frequent in LC tumors. Transverse cancer was correlated with stage II disease, but the requirement for a multivisceral resection was higher in this group due to contiguous involvement of adjacent organs. Regarding short-term outcomes, most studies have investigated the rate of complications during admission and these tend to be higher for right-sided procedures.[7,15-16] Benedix et al demonstrated a higher rate of general postoperative complications for RC patients, including pulmonary and cardiovascular complications while surgery-related complications were almost equally distributed. Other studies concluded that risk of major complications was comparable between the two locations.[15-18] However, knowledge of differences in short-term outcomes after surgery for transverse colon cancer is scarce. Since transverse colon cancer requires either an extended colectomy or a transverse colectomy with the need for a colo-colonic anastomosis, we hypothesized that this might lead to a higher comorbidity rate and differences in short-term outcomes exist depending on the type of resection. Our study demonstrated a longer length of stay

Table 5. Cox proportional Hazard Ratios and 95% CIs for overall, disease-specific, and disease-free survival (N=999)

		Overall survival			
	Patients (%)	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Tumor site					
Right colon	51.3	1.00		1.00	
Transverse colon	9.9	0.80 (0.51-1.26)	0.342	1.17 (0.58-2.34)	0.666
Left colon	38.8	0.73 (0.56-0.96)	0.025	1.53 (0.60-3.93)	0.374
Trans vs. Left		1.10 (0.69-1.76)	0.692	0.76 (0.38-1.52)	0.439
Age (≥65 vs. <65 y)	59.5	3.47 (2.51-4.79)	<0.001	2.06 (1.45-2.92)	<0.001
Female sex	51.8	1.05 (0.81-1.35)	0.725		
ASA-score III-IV (vs. I-II)	36.3	2.96 (2.30-3.82)	<0.001	2.29 (1.74-3.02)	<0.001
BMI (≥25 vs. <25)	64.2	0.68 (0.53-0.87)	0.003	0.71 (0.54-0.93)	0.014
Alcohol abuse	5.7	2.06 (1.34-3.17)	0.001	1.70 (1.09-2.66)	0.019
Smoking (current or hx)	49.8	1.31 (1.02-1.69)	0.034	1.08 (0.83-1.41)	0.571
Surgical approach (laparoscopic vs. open)	30.1	0.44 (0.28-0.69)	<0.001	0.45 (0.28-0.72)	0.001
Surgical procedure (extended vs. segmental)	13.1	1.41 (1.01-1.97)	0.045	1.17 (0.80-1.71)	0.413
Multivisceral resection	8.4	1.50 (1.03-2.19)	0.034	0.86 (0.57-1.28)	0.452
Anastomotic type					
Ileo-colonic	55.8	1.00		1.00	
Colo-colonic	12.6	0.83 (0.56-1.23)	0.350	0.75 (0.33-1.71)	0.500
Colo-rectal	31.6	0.70 (0.52-0.94)	0.017	0.60 (0.23-1.59)	0.307
Colonic vs. rectal		1.19 (0.77-1.83)	0.443	1.25 (0.73-2.16)	0.420
T3-T4 stage (vs. T1-T2)	64.7	1.97 (1.46-2.65)	<0.001	1.60 (1.12-2.27)	0.009
N+ disease	32.9	1.61 (1.25-2.07)	<0.001	1.62 (1.19-2.22)	0.002
High-grade disease	15.2	2.30 (1.72-3.08)	<0.001	1.60 (1.16-2.22)	0.004
MSI (stable vs. high)	22.3	0.59 (0.32-1.11)	0.104		
EMVI	23.1	2.34 (1.81-3.04)	<0.001	1.42 (0.96-2.12)	0.082
LVI	38.6	2.07 (1.61-2.67)	<0.001	1.34 (0.92-1.96)	0.130
Perineural invasion	15.8	2.42 (1.83-3.20)	<0.001	1.69 (1.22-2.34)	0.002
R0-resection	95.7	0.62 (0.38-0.99)	0.048	0.55 (0.33-0.93)	0.025
LN harvest ≥12	89.6	0.47 (0.35-0.65)	<0.001	0.37 (0.26-0.51)	<0.001
Adjuvant therapy	24.5	0.53 (0.38-0.75)	<0.001	0.34 (0.23-0.51)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; BMI, Body Mass Index (kg/m^{2}); MSI, microsatellite instability; EMVI, extramural vascular invasion; LVI, lymphovascular invasion

and a higher complication rate when the requirement for blood transfusion was excluded. However, when blood transfusion was incorporated in the morbidity rate, outcomes were similar with RC patients but still worse than after LC surgery. Our relatively high blood transfusion rate could be explained by the fact that we incorporated all patients who received blood whether or not this was pre-operative, intra-operative or post-operative., This was especially true in right-sided colon cancer, since these patients often presented with anemia. LC patients had a better postoperative course with shorter admission duration and less complications, including less general postoperative complications as cardiac and renal events. Although the incidence of intra-abdominal abscesses and/or leaks was equally distributed, the necessity of readmission and subsequent reoperation for a leak was significantly higher in LC patients. This is in line with the overall belief that LC procedures are technically more challenging and due to differences in vascularization prone to develop anastomotic leak-

Disease-specific survival				Disease-free survival			
Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
1.00				1.00			
0.74 (0.29-1.88)	0.525			0.79 (0.39-1.60)	0.511		
1.28 (0.80-2.05)	0.295			1.37 (0.95-1.97)	0.093		
0.57 (0.23-1.47)	0.246			0.58 (0.29-1.17)	0.127		
1.38 (0.86-2.21)	0.186			0.92 (0.64-1.30)	0.627		
1.03 (0.65-1.62)	0.908			0.92 (0.64-1.30)	0.620		
1.45 (0.92-2.31)	0.113			0.99 (0.69-1.45)	0.980		
0.99 (0.62-1.60)	0.980			0.96 (0.67-1.38)	0.812		
3.02 (1.55-5.88)	0.001	3.35 (1.68-6.66)	0.001	2.69 (1.57-4.61)	<0.001	2.81 (1.62-4.85)	<0.001
1.27 (0.81-2.01)	0.302			1.24 (0.87-1.76)	0.238		
0.63 (0.35-0.11)	0.110			0.63 (0.36-1.12)	0.116		
1.45 (0.80-2.64)	0.222			1.04 (0.62-1.74)	0.877		
1.26 (0.60-2.62)	0.541			1.26 (0.71-2.24)	0.429		
1.00				1.00		1.00	
1.10 (0.55-2.21)	0.792			1.71 (1.06-2.76)	0.029	1.63 (1.01-2.65)	0.048
1.21 (0.74-1.98)	0.454			1.22 (0.82-1.81)	0.329	1.19 (0.78-1.83)	0.419
0.91 (0.44-1.88)	0.798			1.40 (0.84-2.34)	0.195	1.37 (0.81-2.31)	0.238
3.88 (1.99-7.55)	<0.001	2.05 (0.94-4.46)	0.070	4.85 (2.78-8.45)	<0.001	2.27 (1.24-4.14)	0.008
3.94 (0.26-6.31)	<0.001	2.02 (1.14-3.59)	0.017	3.89 (2.70-5.59)	<0.001	2.02 (1.30-3.16)	0.002
3.03 (1.84-4.98)	<0.001	1.73 (1.03-2.92)	0.040	1.76 (1.16-2.69)	0.008	1.10 (0.71-1.73)	0.665
0.99 (0.31-3.24)	0.997			1.76 (0.77-4.02)	0.180		
5.30 (3.35-8.38)	<0.001	1.45 (0.78-2.68)	0.239	4.69 (3.29-6.67)	<0.001	1.78 (1.06-3.00)	0.029
6.04 (3.52-10.38)	<0.001	2.56 (1.23-5.30)	0.012	4.12 (2.81-6.03)	<0.001	1.43 (0.82-2.51)	0.210
4.80 (3.04-7.58)	<0.001	2.08 (1.24-3.48)	0.005	4.18 (2.92-6.00)	<0.001	1.78 (1.19-2.66)	0.005
0.56 (0.24-1.29)	0.172			0.90 (0.40-2.04)	0.796		
0.60 (0.33-1.10)	0.097			0.84 (0.49-0.144)	0.527		
1.70 (1.06-2.70)	0.027	0.65 (0.38-1.10)	0.106	2.17 (1.52-3.10)	<0.001	0.88 (0.58-1.34)	0.547

age. However, outcomes are contradictory with more recent studies suggesting no difference in incidence of anastomotic leak between right-sided and left-sided colectomies.[15-16]

The main finding in our study was the worse overall but comparable disease-specific survival for right-sided colon cancer. However, when analyzing stage-by-stage, the prognostic impact of tumor location was no longer observed. After adjusting for multiple variables, only patient characteristics and pathological features were independently related to overall and disease-specific survival. This is in contrast with previous studies including a recent systematic review and meta-analysis that reported worse overall survival for right-sided colon cancer.[7,12,19] Most of the studies included in the systematic review and meta-analysis evaluated only overall survival. The higher comorbidity rate and older age in the proximal colon cancer group are a reasonable explanation for the worse outcomes, especially since colon cancer specific survival was found to be

similar. Although most studies adjusted for baseline characteristics as age and ASA-score, information about adjuvant therapy was often lacking. Furthermore, we excluded patients who underwent neoadjuvant therapy, patients with distant metastasis and we were able to adjust for known histopathological risk factors besides TNM-stage. The latter proved to be an important factor, since pathologic features such as poor differentiation, perineural invasion, and lymphovascular invasion were independent predictors for worse oncological outcomes.

The influence of tumor location and disease recurrence is poorly investigated. Lim et al found worse DFS for stage III right-sided tumors, but this effect disappeared after adjusting for patient and tumor characteristics.[20] In our study, left-sided colon cancer patients tended to have a worse 5-year disease-free survival, with a significant difference in stage II disease. No differences in admission of adjuvant therapy between LC and the remainder of the population were found. After adjusting for multiple variables, risk factors for worse DFS included advanced TNM-stage, extramural vascular invasion and perineural invasion as well as type of anastomosis. Compared to ileo-colonic anastomoses, patients with a colo-colonic anastomosis had worse disease-free survival (HR 1.63, P0.048). Outcomes were comparable between colo-colonic and colo-rectal anastomoses (HR 1.37, P0.238) as well as colo-rectal and ileo-colonic anastomoses (HR 1.19, P0.419). Previous studies demonstrated that anastomoses close to the anal verge were at risk for developing anastomotic leakage.[21-22] In rectal cancer, anastomotic leakage is associated with an increased risk of local recurrence, whereas the impact of distant recurrence remains debatable.[23-25] Knowledge about the impact of anastomotic leakage and recurrent disease in colon cancer is limited. Although previous studies demonstrated conflicting results, there is some evidence that anastomotic leakage is associated with reduced disease-free survival.[26-27]

Our study has several strengths and limitations. To our knowledge, this is the first study that assessed differences in clinicopathological and long-term outcomes between different segments in colon cancer and included transverse colon cancer as a separate entity. Moreover, only one study reported disease-free survival concerning this topic. Due to a prospectively maintained single-center database, another major strength of our study is the ability to adjust for multiple confounders. However, selection bias is inherent to the retrospective design and although we adjusted for important clinicopathological factors, the determination of MSI status was not yet routine management during our study period. Consequently, the prognostic impact of MSI, associated with right-sided colon cancer, might be underestimated in our analysis.

CONCLUSION

Although distinct differences were found between right-sided, transverse, and left-sided colon cancer in terms of patient characteristics, histopathological features and 30-day morbidity, tumor location in colon cancer was not independently associated with survival and disease recurrence. Nonetheless, pathological differences beyond tumor stage were significantly more important. Future research should elaborate on differences in disease characteristics leading to potential different optimal treatments in colon cancer.

REFERENCES

1. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544-573.

2. Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JD, Zauber AGl. How much can current interventions reduce colorectal cancer mortality in the US? Mortality projections for scenarios of risk-factor modification, screening, and treatment. Cancer 2006;107:1624-1633.

3. Cucino C, Buchner AM, Sonnenberg A. Continued rightward shift of colorectal cancer. Dis Colon Rectum 2002;45:1035–1040.

4. Saltzstein SL, Behling CA. Age and time as factors in the left-to-right shift of the subsite of colorectal adenocarcinoma: a study of 213,383 cases from the California Cancer Registry. J Clin Gastroenterol 2007;41:173–177.

5. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113:779–788.

6. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004;88:261– 266.

7. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H; Colon/Rectum Carcinomas (Primary Tumor) Study Group. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010;53:57-64.

8. Azzoni C, Bottarelli L, Campanini N, Di Cola G, Bader G, Mazzeo A, Salvemini C, Morari S, Di Mauro D, Donadei E, Roncoroni L, Bordi C, Sarli L. Distinct molecular patterns based on proximal and distal sporadic colorectal cancer: arguments for different mechanisms in the tumorigenesis. Int J Colorectal Dis 2007;22:115–126.

9. Nawa T, Kato J, Kawamoto H, Okada H, Yamamoto H, Kohno H, Endo H, Shiratori Y. Differences between right- and left- sided colon cancer in patient characteristics, cancer morphology and histology. J Gastroenterol Hepatol 2008;23:418–423.

10. Ponz de Leon M, Sacchetti C, Sassatelli R, Zanghieri G, Roncucci L, Scalmati A. Evidence for the existence of different types of large bowel tumor: suggestions from the clinical data of a population-based registry. J Surg Oncol 1990;44:35–43.

11. Ogino S, Odze RD, Kawasaki T, Brahmandam M, Kirkner GJ, Laird PW, Loda M, Fucks CS. Correlation of pathologic features with CpG island methylator phenotype (CIMP) by quantitative DNA methylation analysis in colorectal carcinoma. Am J Surg Pathol 2006;30:1175–1183.

12. Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left- sided colon cancers? Ann Surg Oncol 2008;15:2388-2394.

13. Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G, Smith MA. Mortality by stage for right-versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results–medicare data. J Clin Oncol 2011;29:4401-4409.

14. Powell AG, Wallace R, McKee RF, Anderson JH, Going JJ, Edwards J, Horgan PG. The relationship between tumour site, clinicopathological characteristics and cancer-specific survival in patients undergoing surgery for colorectal cancer. Colorectal Dis. 2012;14:1493-1499.

15. Campana JP, Pellegrini PA, Rossi GL, Ojea Quintana G, Mentz RE, Vaccaro CA. Right versus left laparoscopic colectomy for colon cancer: does side make any difference? Int J Colorectal Dis 2017;32:907-912.

16. Masoomi H, Buchberg B, Dang P, Carmichael JC, Mills S, Stamos MJ. Outcomes of right vs. left colectomy for colon cancer. J Gastrointest Surg 2011;15:2023–2028.

17. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, Passalacqua R, Sgroi G, Barni S. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol 2017;3:211-219.

18. Kwaan MR, Al-Refaie WB, Parsons HM, Chow CJ, Rothenberger DA, Habermann EB. Are right-sided colectomy outcomes different from left-sided colectomy outcomes?: study of patients with colon cancer in the ACS NSQIP database. JAMA Surg 2013;148:504–510.

19. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. J Gastrointest Surg. 2016;20:648-655.

20. Lim DR, Kuk JK, Kim T, Shin EJ. Comparison of oncological outcomes of right-sided colon cancer versus left-sided colon cancer after curative resection. Medicine (Baltimore) 2017;96:e8241.

21. Trencheva K, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T, Michelassi F, Charlson ME, Milsom JW. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg 2013;257:108-113.

22. Veyrie N, Ata T, Muscari F, Couchard AC, Msika S, Hay JM, Fingerhut A, Dziri C; French Associations for Surgical Research. Anastomotic leakage after elective right versus left colectomy for cancer: prevalence and independent risk factors. J Am Coll Surg 2007;205:785-793.

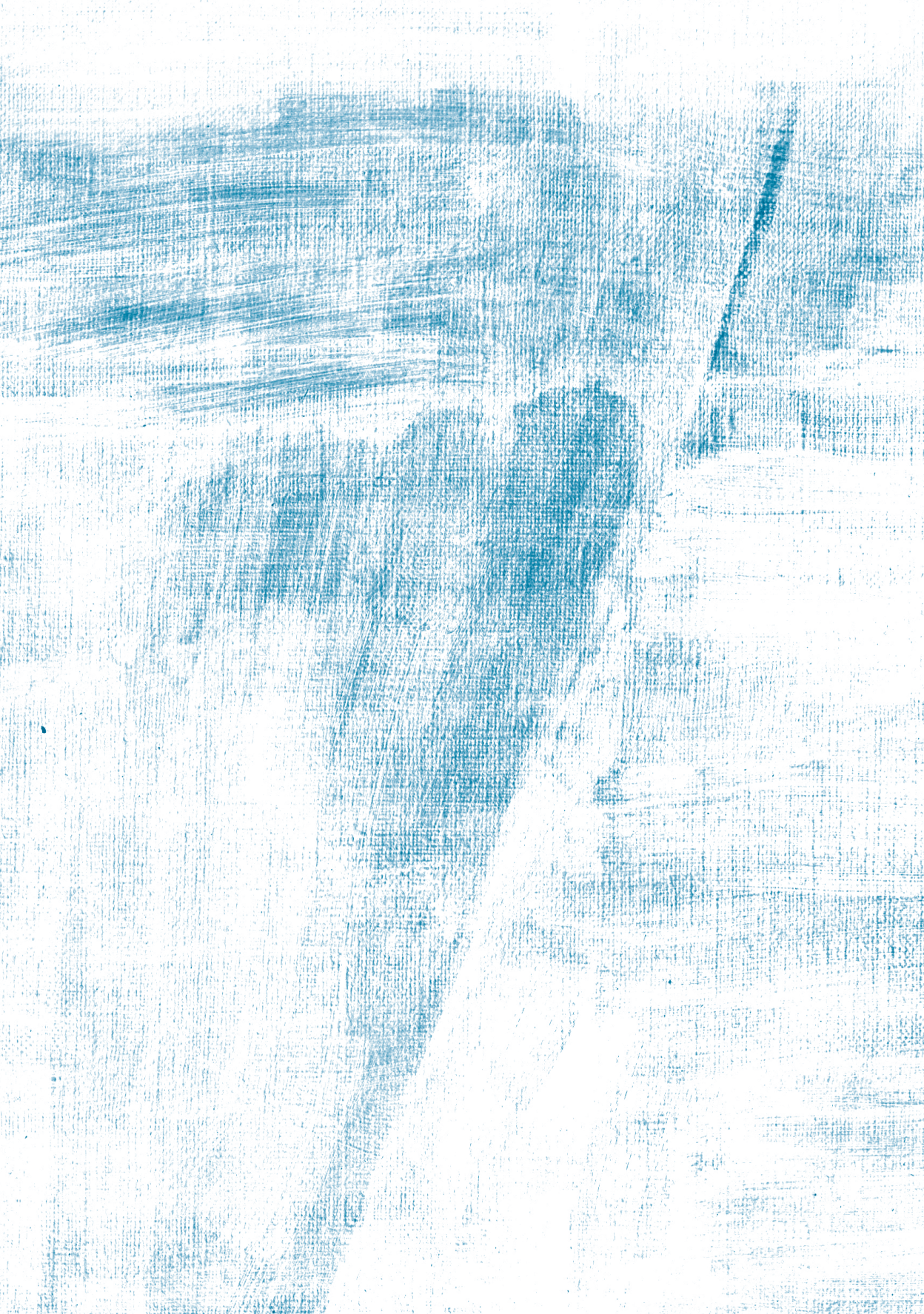
23. Eberhardt JM, Kiran RP, Lavery IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum. 2009;52:380–386.

24. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg. 2011;253:890–899.

25. Bertelsen CA, Andreasen AH, Jørgensen T, Harling H; Danish Colorectal Cancer Group. Anastomotic leakage after curative anterior resection for rectal cancer: short and long-term outcome. Colorectal Dis. 2010;12:e76-81.

26. Kube R, Mroczkowski P, Granowski D, Benedix F, Sahm M, Schmidt U, Gastinger I, Lippert H. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol. 2010;36:120–124.

27. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. Ann Surg. 2014;259:930-938.



CHAPTER 8

IMPACT of INTRAMURAL and EXTRAMURAL VASCULAR INVASION on STAGE II-III COLON CANCER OUTCOMES

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ABSTRACT

BACKGROUND AND OBJECTIVES

Vascular invasion, in particular extramural venous invasion (EMVI), is a pathologic characteristic that has been extensively studied in rectal cancer but rarely in colon cancer. This study aims to evaluate its prognostic role in stage II-III colon cancer.

METHODS

All stage II-III colon cancer patients who underwent surgery between 2004-2015 were reviewed. We divided the study group into patients without invasion, with intramural invasion only (IMVI), EMVI only, and both IMVI/EMVI (n=923).

RESULTS

EMVI was associated with other high-risk features, including T4, N+ disease, lymphatic, and perineural invasion (P<0.001). EMVI+ patients had considerably higher rates of locoregional and distant recurrence and subsequently disease-specific mortality (stage-II: odds ratio (OR) 3.64, P=0.001, stage-III OR:1.94, P=0.009), whereas outcomes were comparable between IMVI and no vascular invasion (OR:1.21, P=0.764, OR:1.28, P=0.607, respectively). The adjusted hazard ratios for EMVI+ patients on disease-free survival, and disease-specific survival were 2.07 (P<0.001), 1.67 (P=0.027), respectively. Moreover, EMVI+ stage-II patients fared worse than EMVI– stage-III patients, even after adjusting for adjuvant chemotherapy.

CONCLUSION

EMVI is a strong predictor for worse oncologic outcomes in stage II-III colon cancer patients, whereas IMVI is not. It is also associated with worse outcomes compared in patients with higher stage disease who are EMVI negative.

INTRODUCTION

Colorectal cancer is one of the most prevalent malignancies in both men and women worldwide. Survival and recurrence rates vary considerably depending on baseline staging and tumor characteristics.[1] Available adjuvant and neoadjuvant treatment options surrounding operative treatment range from surveillance to chemoradiation regimens. The decision whether or not to treat needs to be made on a case-by-case basis, considering the risks of both under and over treatment. To address this, efforts have been made to identify factors beyond the standard Tumor, Node, Metastasis (TNM) classification to stratify risks of recurrence and mortality. As a result, pathological and molecular features including poorly differentiated cancers, lymphovascular invasion, perineural invasion, and microsatellite instability have been validated as risk factors.[2-4]

Traditionally, validation of prognostic factors is done in cohorts grouping colon and rectal cancer together, rather than separately, for the sake of statistical power even though treatment approaches and tumor biology are markedly different.[5-7] It is necessary to ensure that such factors are valid for colon cancer as well as rectal cancer. An example of this discrepancy is extramural vascular invasion (EMVI) or vascular invasion beyond the muscularis propria. In large part due to the potential finding of EMVI during preoperative magnetic resonance imaging (MRI) in rectal cancer [8,9], a diagnostic modality that is not routinely performed in tumors of the colon. EMVI has been well scrutinized in rectal cancer [10-12] but far less so in tumors of the colon.[13] Nonetheless, the College of American Pathologists recommend recording the status of vascular invasion during routine pathologic examination in both colon and rectal cancer patients [14] because of the unfavorable outcomes and increased risk of hepatic metastasis.[15] Current guidelines also incorporate vascular invasion as a histologic risk feature in colon cancer, for which adjuvant therapy could be considered. Besides lacking data on colon cancer specific outcomes, little is known about the importance of separating intramural and extramural venous invasion. Therefore, the aim of this study was to evaluate the impact of vascular invasion, both intramural and extramural, on long-term oncologic outcomes in stage II and III colon cancer patients without distant metastasis.

METHODS

PATIENTS

All patients treated surgically for a primary colorectal carcinoma at Massachusetts General Hospital between 2004 and 2015 (n=2287) were included in a prospectively maintained survival and outcomes database after institutional review board approval. Data on patients was gathered from patient visit records, the institutional research patient data repository, the social security death index, as well as patient records from our healthcare network.

Due to the significant differences in treatment approach, tumor biology, and the intent to specifically explore the impact of vascular invasion on colonic tumors, we exclusively focused on colon cancer and did not include patients with tumors of the rectum (n=642). We excluded

all patients with intramucosal tumors (n=174) and patients with baseline metastatic disease (n=246). Furthermore, as only 14 out of 285 patients with stage I disease[16] revealed either intra- or extramural vascular invasion, we decided to exclude patients with stage I disease as well, leaving 923 patients for final analysis. We divided patients into four groups: no invasion, intramural vascular invasion (IMVI) only, extramural vascular invasion (EMVI) only, and both IMVI and EMVI.

PATHOLOGIC EXAMINATION

Standardized pathologic examination was performed by a team of dedicated gastrointestinal pathologists during the full length of our study. For the purpose of this paper, tumors of the colon were defined as any tumor more than 15 centimeters from the anal verge. Right-sided tumors included those located from the cecum to the hepatic flexure, transverse colon cancer included transverse tumors only, tumors located from the splenic flexure proximal to the sigmoid were defined as left-sided cancer, and (recto)sigmoid tumors were located from the sigmoid to the rectosigmoid. Tumor stage was assessed according to the seventh edition of the American Joint Committee on Cancer.[16] Tumor grading was categorized according to the classification designed by the World Health Organization.[17]

The presence of vascular invasion was assessed on hematoxylin and eosin-stained (H&E) slides. Vessels with an unequivocal endothelial lining were considered lymphatic (small), whereas large vessels (venous) included all with a muscular wall. In suspicious cases, sections at multiple levels and elastic stains have been used to confirm venous invasion. Intramural vascular invasion (IMVI) was defined as the presence of large vessel invasion in the submucosal and/or muscular layer. Venous invasion beyond the muscularis propria was considered extramural vascular invasion (EMVI). [Figure 1]

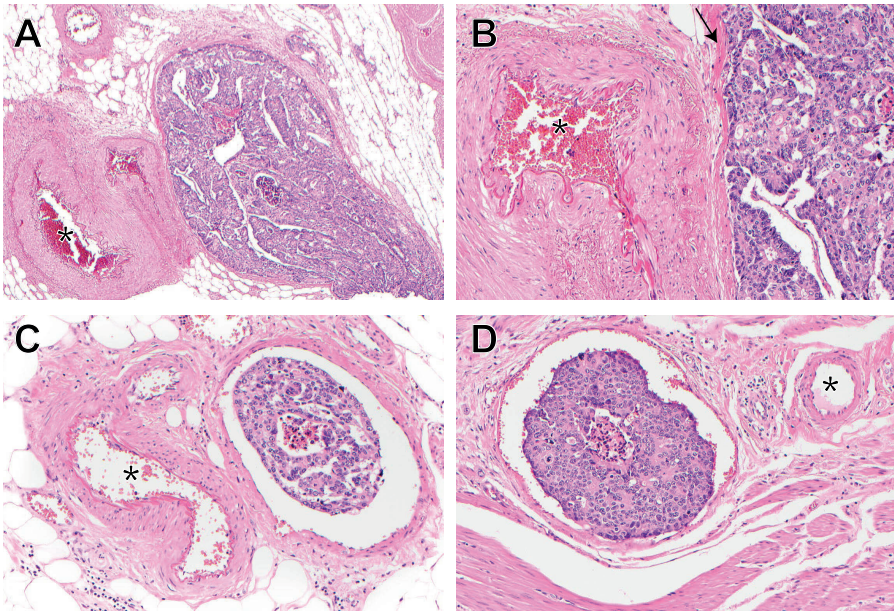
PRIMARY AND SECONDARY OUTCOMES

Disease recurrence was our primary outcome, divided into locoregional recurrence, including all recurrences within the original tumor bed (contiguous to the original site of the tumor, peri-anastomotic, peritoneum, and retroperitoneum), and distant recurrence (liver, lung, and other non-regional organs). Determination of disease recurrence was made by histological or clinical and radiological examinations.

Secondary outcomes were time to disease recurrence, and overall and disease-specific survival. Data on long-term outcomes and survival were periodically updated by reviewing patient's records and the US Social Security Death Index. The last status review of survival and follow-up was on March 1st, 2018. Patients alive at the closure of the study or lost to follow-up were censored. All time to events were expressed in months, measured from date of surgery. Recurrent or metastatic disease within 30 days of the original admission was considered baseline metastases and therefore excluded from our study cohort.

All patients underwent a standardized surveillance according to the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines.[6,18] Postoperative treatment was considered for all patients. The decision whether or not to administrate adjuvant chemotherapy was made on an individual basis after reviewing pathology results and assessing the performance status of the patients and their consent to the therapy.

Figure 1. Histology of intramural and extramural vascular invasion.



A: EMVI in a large vein, x40
B: Higher magnification of A (x200) highlights vein wall (arrow)
C: EMVI in a smaller vein, x200
D: IMVI, x200.
* in all panels highlights muscular artery

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (*Version 24.0; SPSS Inc, Chicago, IL, USA)*. A two-tailed P-value below 0.05 was considered the threshold for statistical significance. Descriptive statistics (percentage, medians with interquartile range or means with standard deviation) were used to illustrate differences in baseline characteristics, if any. Subsequently, outcomes were compared among EMVI positive and negative patients. Outcomes analyzed were, metastatic recurrence, and overall and disease-specific mortality, expressed as percentage outcomes, compared for significance using a chi-square (X^2) coefficient. Kaplan-Meier survival estimates were compared using Log-Rank tests.

Additionally, multivariate analyses using Cox proportional hazard regression models were performed to analyze the impact of vascular invasion on disease recurrence and colon cancer specific survival. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were estimated. Variables included in the model were: age, ASA-score, vascular invasion (no invasion – IMVI only – EMVI only – both IMVI and EMVI), TN-stage, tumor location, lymphatic invasion, high grade disease (including poorly differentiated adenocarcinomas, mucinous and signet-cell carcinomas), perineural invasion, microsatellite instability, bowel obstruction at presentation, R0-resection, and adjuvant chemotherapy. Lastly, differences in long-term outcomes were also demonstrated per AJCC substage using Kaplan-Meier survival analyses, as well as for the EMVI-subgroup only.

RESULTS

BASELINE CHARACTERISTICS

A consecutive cohort of 923 patients with AJCC stage II or stage III was included, of whom 59 patients had intramural vascular invasion only on surgical pathology, 163 patients had extramural vascular invasion, and 59 patients had both IMVI and EMVI. None of the baseline characteristics, including age, gender, ethnicity, BMI, and emergency admissions differed significantly based on vascular invasion status. Patients with vascular invasion, regardless of the precise location, presented more often with a large bowel obstruction (10.7% vs. 5.9%; P=0.011), while perforation at presentation rates were comparable. Table 1 shows baseline characteristics in detail.

Tumor location did not differ between the groups. Rates of R0-resections tended to be lower when IMVI and EMVI were both present (P=0.057). Patients with EMVI+ tumors or both IMVI/EMVI demonstrated significantly higher rates of node-positive disease as well as higher incidences of T4 tumors, lymphatic invasion, and perineural invasion. Numbers of examined lymph nodes were not different between the groups; neither did the number of patients in whom less than 12 lymph nodes were examined.

OUTCOMES

Vascular invasion was present in 21.1% of stage II patients and 40.0% of stage III patients (Table 2 and 3). An increasing rate was in particular true for EMVI+ patients (stage II: 11.0%; stage III: 24.5%). The detection rate of vascular invasion, however, slightly increased over the study period from 27.5% in the first half (stage II: 16.7%, stage III: 38.6%) to 33.3% (25.3%, 41.3%, respectively) in the latter. Lymphatic invasion was far more prevalent in EMVI+ or IMVI/EMVI+ patients, with a significant higher rate than IMVI+ patients in stage II (P<0.001). Moreover, presence of small vessel invasion in vascular negative patients was lower, though certainly not absent (stage II: 19.1%; stage III: 45.1%).

In line with current guidelines, rates of adjuvant chemotherapy were higher in stage III disease. A total of 332 stage III patients (72.5%) received postoperative treatment compared to 89 (19.1%) stage II patients. The most common reasons to forego further treatment were comorbidity or age (49.0%) and patient's refusal (40.8%). In stage II disease, rates of postoperative chemotherapy admission were significantly higher in patients with EMVI (P=0.001), whereas no differences were found in stage III disease (P=0.909)

Regardless of stage, the presence of vascular invasion was strongly associated with locoregional and distant recurrence. In stage II, EMVI+ and IMVI/EMVI+ patients had significantly higher rates of locoregional and distant recurrence compared to patients without invasion or IMVI only (P=0.004, P=0.042, respectively), subsequently leading to impaired disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS). With regards to stage III disease, rates of distant recurrence increased substantially in all groups, but remained higher in the EMVI+ group (P<0.001).

Table 1. Baseline and Tumor Characteristics

	Total n = 923	No invasion n = 642	IMVI only n = 59	EMVI only n = 163	Both n = 59	P-value
Age, *years*	69.0 (57.7-79.8)	69.4 (57.8-79.8)	74.9 (60.2-82.6)	68.1 (58.0-78.6)	65.9 (55.1-78.7)	0.329
Female gender	487 (52.8%)	342 (53.3%)	35 (59.3%)	83 (50.9%)	27 (45.8%)	0.481
Caucasian	826 (89.5%)	575 (89.6%)	55 (93.2%)	143 (87.7%)	53 (89.8%)	0.782
ASA score	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	0.314
BMI, *kg/m²*	26.7 (23.2-30.7)	26.8 (23.3-30.8)	27.2 (23.1-31.7)	26.4 (23.3-29.8)	26.9 (22.7-33.2)	0.797
Inflammatory Bowel disease	27 (2.9%)	19 (3.0%)	1 (1.7%)	5 (3.1%)	2 (3.4%)	0.946
Urgent admission	99 (10.7%)	66 (10.3%)	8 (13.6%)	16 (9.8%)	9 (15.3%)	0.566
Bowel obstruction	68 (7.4%)	38 (5.9%)	6 (10.2%)	17 (10.4%)	7 (11.9%)	0.084
Bowel perforation	25 (2.7%)	18 (2.8%)	1 (1.7%)	4 (2.5%)	2 (3.4%)	0.941
Tumor location						0.140
Right-sided	479 (51.9%)	336 (52.3%)	38 (64.4%)	82 (50.3%)	23 (39.0%)	
Transverse colon	83 (9.0%)	60 (9.3%)	3 (5.1%)	12 (7.4%)	8 (13.6%)	
Left-sided	94 (10.2%)	67 (10.4%)	8 (13.6%)	12 (7.4%)	7 (11.9%)	
(Recto)sigmoid colon	250 (27.1%)	166 (25.9%)	9 (15.3%)	54 (33.1%)	21 (35.6%)	
Multiple sites	17 (1.8%)	13 (2.0%)	1 (1.7%)	3 (1.8%)	0 (0.0%)	
R0-resection	890 (96.4%)	625 (97.4%)	57 (96.6%)	154 (94.5%)	54 (91.5%)	0.057
Tumor characteristics						
Stage II disease	465 (50.4%)	367 (57.2%)	33 (55.9%)	51 (31.3%)	14 (23.7%)	<0.001
Tumor size	5.0 (3.5-7.5)	5.2 (3.5-7.7)	4.7 (3.5-7.5)	5.0 (3.5-7.0)	5.3 (3.5-10.9)	0.604
High grade	239 (26.1%)	154 (24.2%)	13 (22.4%)	51 (31.3%)	21 (36.2%)	0.073
T4 tumor	237 (25.7%)	130 (20.2%)	12 (20.3%)	67 (41.1%)	28 (47.5%)	<0.001
Lymphatic invasion	376 (40.7%)	194 (30.2%)	27 (45.8%)	107 (65.6%)	48 (81.4%)	<0.001
Perineural invasion	211 (22.9%)	90 (14.0%)	15 (25.4%)	69 (42.6%)	37 (62.7%)	<0.001
Lymph nodes examined	21 (16-29)	21 (16-29)	21 (16-29)	20 (16-29)	23 (17-35)	0.605
<12 lymph nodes examined	69 (7.5%)	48 (7.5%)	3 (5.1%)	12 (7.4%)	6 (10.2%)	0.775
Microsatellite instability						0.061
High	125 (13.5%)	95 (14.8%)	7 (11.9%)	14 (8.6%)	9 (15.3%)	
Low	39 (4.2%)	31 (4.8%)	3 (5.1%)	5 (3.1%)	9 (0.0%)	
Stable	392 (42.5%)	251 (39.1%)	32 (54.2%)	79 (48.5%)	30 (50.8%)	
Not tested	367 (39.8%)	265 (41.3%)	17 (28.8%)	65 (39.9%)	20 (33.9%)	

Proportions are presented for categorical data, median with IQR for all continuous data.
Abbreviations: ASA: American Society of Anesthesiologists, BMI: Body Mass Index (kg/m2)

SUBGROUP ANALYSIS

In stage II disease, time to disease recurrence was comparable between patients with no invasion and IMVI only (5-year DFS: 85.5% vs. 93.3%, P=0.332). Overall survival and disease-specific survival were also comparable between these two groups (OS: P=0.601, DSS: P=0.208). Nonetheless, EMVI+ patients demonstrated worse outcomes compared to no invasion (DFS: P=0.002, OS: P=0.001, DSS: P<0.001) (Figure 2).

The poor prognosis for EMVI+ tumors was emphasized in stage III disease. Time to disease recurrence, overall survival, as well disease-free survival was all worse when extramural vascular invasion was present (P<0.001), while no differences between the IMVI group and no invasion group were found. Interestingly, the estimated survival rates of stage III patients without vascular invasion or IMVI+ only were comparable with stage II EMVI+ patients (DFS: P=0.281, DSS: P=0.101), indicating once more the importance of EMVI.

Table 2. Outcome differences by vascular invasion status, stage II (n=465)

Stage II patients	No invasion n = 367	IMVI only n = 33	EMVI only n = 51	Both n = 41	P-value
Lymphatic invasion	70 (19.1%)	8 (24.2%)	21 (41.2%)	9 (64.3%)	<0.001
Adjuvant chemotherapy	60 (16.3%)	5 (15.2%)	17 (33.3%)	7 (50.0%)	0.001
Locoregional recurrence	26 (7.1%)	0 (0.0%)	10 (19.6%)	2 (14.3%)	0.004
Distant recurrence	42 (11.4%)	2 (6.1%)	12 (23.5%)	3 (21.4%)	0.042
Disease-free survival					0.004
K-M 3-year estimate / NAR	88.6% | 238	93.3% | 28	67.5% | 23	71.8% | 7	
K-M 5-year estimate / NAR	85.2% | 174	93.3% | 28	67.5% | 23	71.8% | 7	
Overall survival					<0.001
K-M 3-year estimate / NAR	85.4% | 239	85.9% | 20	69.6% | 28	36.9% | 2	
K-M 5-year estimate / NAR	78.6% | 154	79.8% | 13	57.3% | 16	36.9% | 2	
Colon cancer specific survival					<0.001
K-M 3-year estimate / NAR	96.5% | 239	93.2% | 27	81.8% | 28	69.2% | 5	
K-M 5-year estimate / NAR	95.0% | 156	93.2% | 27	77.0% | 16	69.2% | 5	

Abbreviations: IMVI: Intramural Vascular Invasion; EMVI: Extramural Vascular Invasion; K-M: Kaplan Meier. NAR: Number at risk
Survival estimates calculated by log-rank

Table 3. Outcome differences by vascular invasion status, stage III (n=458)

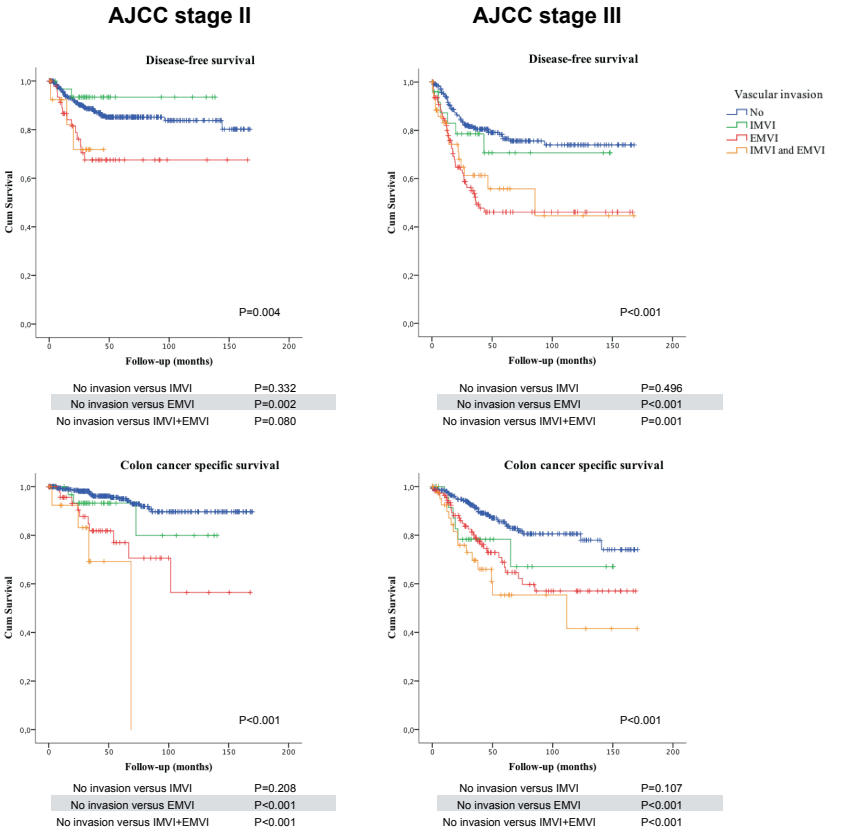
Stage III patients	No invasion n = 275	IMVI only n = 26	EMVI only n = 112	Both n = 45	P-value
Lymphatic invasion	124 (45.1%)	19 (73.1%)	86 (76.8%)	39 (86.7%)	<0.001
Adjuvant chemotherapy	197 (71.6%)	20 (76.9%)	83 (74.1%)	32 (71.1%)	0.909
Locoregional recurrence	35 (12.7%)	6 (23.1%)	29 (25.9%)	8 (17.8%)	0.015
Distant recurrence	49 (17.8%)	6 (23.1%)	49 (43.8%)	14 (31.1%)	<0.001
Disease-free survival					<0.001
K-M 3-year estimate / NAR	81.0% | 153	78.5% | 18	52.3% | 37	61.4% | 18	
K-M 5-year estimate / NAR	76.6% | 90	70.7% | 9	46.1% | 28	55.8% | 10	
Overall survival					0.009
K-M 3-year estimate / NAR	79.3% | 173	68.0% | 17	67.7% | 62	55.7% | 22	
K-M 5-year estimate / NAR	68.0% | 100	60.4% | 8	55.2% | 32	44.3% | 10	
Colon cancer specific survival			78.8% | 62	69.6% | 22	<0.001
K-M 3-year estimate / NAR	91.3% | 173	78.3% | 18	66.8% | 32	55.4% | 10	
K-M 5-year estimate / NAR	85.5% | 106	78.3% | 18			

Abbreviations: IMVI: Intramural Vascular Invasion; EMVI: Extramural Vascular Invasion; K-M: Kaplan Meier. NAR: Number at risk Survival estimates calculated by log-rank

SURVIVAL AND MULTIVARIATE ANALYSES

Median follow-up was 43.9 months, which was not significantly different between stage (II: 46.2 months vs. III: 40.7 months, P=0.122). In multivariate Cox proportional hazard models, time to disease recurrence remained significantly shorter in patients who were EMVI+ compared to those without (HR=2.07; 95% CI: 1.46 – 2.93, P<0.001)(Table 4). Although hazard ratios were higher in the IMVI/EMVI+ cohort, outcomes were not significantly different after adjustment (HR=1.52; 95% CI: 0.88 – 2.63, P=0.135). This was different in colon cancer specific survival, with more than two-fold higher hazard ratios for the IMVI/EMVI+ cohort (HR=2.39; 95% CI:1.31 – 4.36, P=0.005). Similarly to DFS, EMVI+ withstood adjustment in the DSS model (HR 1.67; 95% CI: 1.06 – 2.64, P=0.027). Along with vas-

Figure 2. Survival outcomes per AJCC stage.



cular invasion, ASA-score, T4 tumors, lymph-node positive disease, high grade tumors, perineural invasion, and bowel obstruction at presentation were all found to be independent predictors for both DFS and DSS. Moreover, time to disease-specific mortality was shorter in patients with distal tumors and patients in patients with an incomplete tumor resection. The administration of adjuvant chemotherapy did not have a significant effect in adjusted Cox regression models for aforementioned survival outcomes.

The negative impact of EMVI on disease-free and disease-specific survival was underlined by univariate stage-by-stage Kaplan Meier curves focusing on patients with or without EMVI positive tumors (Figure 3). Both DFS and DSS were worse for EMVI+ patients, regardless of stage (P<0.001). Moreover, DFS was comparable between stage II EMVI+ and stage III EMVI- patients (P=0.098), but DSS was significantly worse for the first group (P=0.021). When adjusting for adjuvant chemotherapy, outcomes remained similar to the univariate analyses including a non-significant difference in DFS between stage II EMVI+ and stage III EMVI-, but higher hazard ratios for colon cancer specific survival in stage II EMVI+ (HR=2.02; 95% CI: 1.10 – 3.71, P=0.024).

Outcomes are based on unadjusted (upper) and adjusted (lower) analyses. AJCC stage II-patients are represented with blue lines (solid line is EMVI +, dotted line is EMVI -), AJCC stage III-patients are represented with red lines (solid line is EMVI +, dotted line is EMVI -).

Table 4. Cox proportional regression models of disease-free survival and disease-specific survival

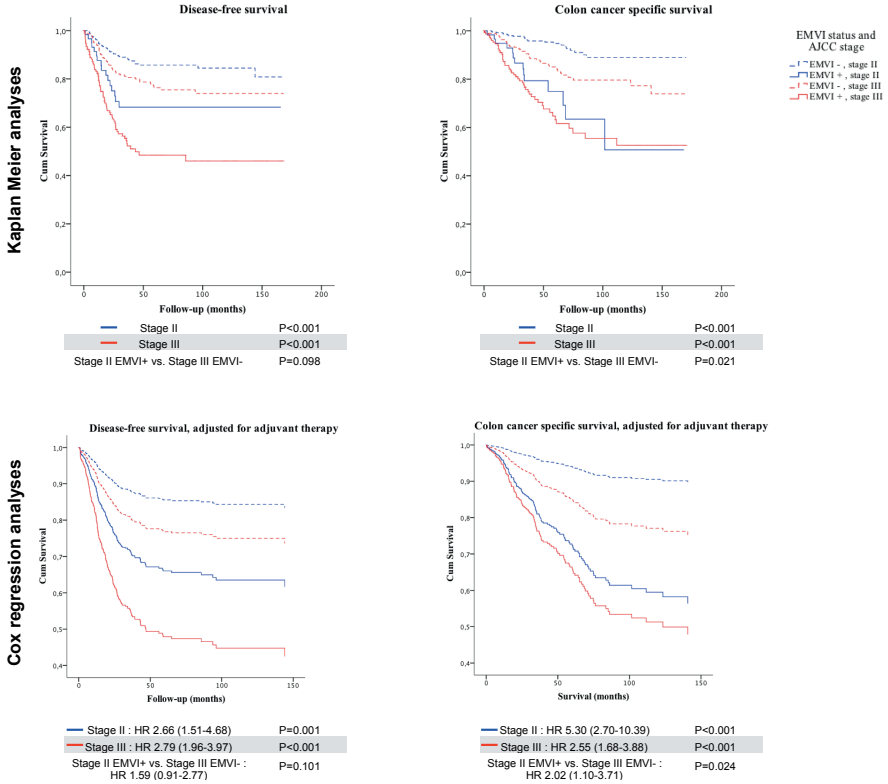
	Disease-free survival		Colon cancer specific survival	
Variable	HR (*95% CI*)	P-value	HR (*95% CI*)	P-value
Age	1.00 (0.99-1.01)	0.949	1.01 (0.99-1.02)	0.172
ASA-score, *III-IV*	1.36 (1.00-1.83)	0.048	1.46 (1.01-2.10)	0.044
Vascular invasion				
Absent	Reference		Reference	
IMVI only	0.74 (0.34-1.59)	0.436	1.53 (0.72-3.25)	0.270
EMVI only	2.07 (1.46-2.93)	<0.001	1.67 (1.06-2.64)	0.027
IMVI + EMVI	1.52 (0.88-2.63)	0.135	2.39 (1.31-4.36)	0.005
T4 tumors	1.50 (1.09-2.06)	0.012	2.14 (1.46-3.13)	<0.001
Lymph-node disease	1.56 (1.12-2.16)	0.008	1.61 (1.04-2.48)	0.033
Tumor location				
Right-sided	Reference		Reference	
Transverse	0.84 (0.45-1.57)	0.581	1.24 (0.60-2.56)	0.561
Left sided	1.60 (0.99-2.57)	0.052	1.58 (0.86-2.91)	0.144
(Recto)Sigmoid	1.38 (0.97-1.95)	0.076	1.75 (1.13-2.73)	0.013
Multiple	2.09 (0.83-5.25)	0.116	2.41 (0.73-7.91)	0.148
Lymphatic invasion	1.30 (0.93-1.83)	0.130	1.48 (0.95-2.30)	0.080
High grade	1.64 (1.18-2.28)	0.003	1.77 (1.21-2.59)	0.003
Perineural invasion	1.72 (1.23-2.41)	0.002	1.59 (1.05-2.42)	0.028
MSI-high versus stable/low	0.69 (0.40-1.17)	0.167	0.82 (0.41-1.61)	0.555
Bowel obstruction	1.87 (1.18-2.96)	0.008	2.40 (1.43-4.03)	0.001
R0-resection	0.61 (0.34-1.12)	0.112	0.42 (0.23-0.77)	0.005
Adjuvant chemotherapy	1.16 (0.81-1.68)	0.421	0.95 (0.57-1.60)	0.852

Abbreviations: ASA: American Society of Anesthesiologists; IMVI: Intramural Vascular Invasion; EMVI: Extramural Vascular Invasion; HR: Hazard Ratio; CI: Confidence Interval

DISCUSSION

In this study, extramural venous invasion proved to be a strong and independent predictor of disease-free and disease-specific survival, while patients with only intramural venous invasion had comparable outcomes to those without any invasion. Patients with EMVI positive tumors were almost three times as likely to develop disease recurrence or die from colon cancer compared to patients with no vascular invasion detected. This remained true after adjusting for potentially confounding factors including baseline staging, demographics, histologic high risk features, and postoperative treatment. The prognostic impact of EMVI on colon cancer mortality was comparable to that of other risk factors, including lymph-node positive disease, high grade disease, and perineural invasion, stronger than the impact of lymphatic invasion, but inferior to T4 tumors, bowel obstruction and tumor clearance. Differences in oncologic outcomes were present in both stage II as stage III disease, though more profound in the latter. All outcomes were found to be independent of adjuvant chemotherapy status. Additionally, although EMVI+ patients received adjuvant treatment in stage II disease twice as often as patients without invasion or with only IMVI, patients with stage II and EMVI positive tumors still fared worse. In fact, the effect was of such a magnitude that stage II patients with EMVI had worse disease-specific survival than stage III patients with-

Figure 3. Survival outcomes per EMVI status, univariate and adjusted for adjuvant chemotherapy.



out EMVI, independent of adjuvant therapy. This reiterates the finding that extramural vascular invasion is a poor prognostic sign in colon cancer, for which more targeted approaches or a more aggressive follow-up may be needed to truly benefit patients with EMVI positive tumors.

CURRENT PERSPECTIVE

Extramural vascular invasion is already an important baseline characteristic in rectal cancer.[19-20] As a prognostic factor, it is used to potentially predict high-risk disease or in some institutions to determine the need for preoperative chemoradiation. These tumors have an increased potential for vascular seeding: as the tumor is aggressive enough to directly invade blood vessels, it makes sense that these patients are at higher risk of having occult disease. Although the impact of EMVI is less well understood in colon cancer, vascular invasion should be taken into consideration as a high risk feature in stage II disease for which adjuvant therapy could be considered. Moreover, this study emphasized the difference between intramural and extramural vascular invasion, as only the latter was associated with poor outcomes.

Magnetic resonance imaging has made preoperative detection of EMVI in rectal cancer an important item of the baseline assessment.[21] This approach is not useful for tumors of the colon, as magnetic resonance imaging cannot account for the location and colonic peristalsis. Computed tomography is the only alternative but does not have sufficient resolution or tissue differentiation to identify vascular invasion reliably. Our hypoth-

esize that vascular invasion detected on histopathologic examination is a very important prognostic factor to predict recurrence and colon cancer-specific mortality proved to be true in this study comprising a large cohort of stage II and III colon cancer patients spanning over a decade.

LIMITATIONS AND FURTHER RESEARCH

As most metastatic disease presents within 24 months of baseline treatment, many patients may already have metastatic disease which is impossible to detect on presentation. These cases may or may not benefit from the prognostic value of EMVI. This study demonstrated that EMVI positive stage II patients did not seem to benefit substantially from adjuvant chemotherapy; however, the analyses demonstrating the lack of effect of chemotherapy on long term outcomes for these patients might be caused by type II errors, due to relatively small numbers in these subanalyses. Nevertheless, outcomes tended to be worse for EMVI positive stage II patients who received contemporary adjuvant therapy. Therefore, studies regarding targeted adjuvant therapy in EMVI positive colon cancer are needed. Chand et al demonstrated an association between response of extramural venous invasion to neoadjuvant therapy and better disease-free survival for rectal cancer patients.[22] Although the administration of neoadjuvant therapy for colon cancer is not standard of practice, the finding of Chand and colleagues may give insights for therapy to which extramural invasion in colon cancer may respond. Furthermore, although this is a single institution study, results could be generalizable to all hospitals reporting extramural invasion. Extramural vascular invasion should be part of pathology reports, as the College of American Pathologists recommends reporting EMVI in their Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum.[14]

Concluding from these findings, it is clear that extramural vascular invasion is an important prognostic feature of disease recurrence and disease-specific mortality of patients with surgically treated stage II or stage III colon cancer. Even within patients of higher AJCC stage, the presence of EMVI is associated with worse outcomes. Research regarding targeted therapy for EMVI positive disease is needed.

REFERENCES

1.
Siegel RL, Miller KD, Fedewa SA, et al A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017 May 6;67(3):177-193.

2.
Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *Journal of Clinical Oncology*. 2006;24(33):5313–5327.

3.
Compton CC. Colorectal carcinoma: diagnostic, prognostic, and molecular features. *Mod Pathol*. 2003;16(4):376–388.

4.
Alotaibi AM, Lee JL, Kim J, et al. Prognostic and oncologic significance of perineural invasion in sporadic coloretcal cancer. *Ann Surg Oncol.* 2017;24(6):1625-1634

5.
Labianca R, Nordlinger B, Beretta GD, et al. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. *Ann Oncol*. 2010;21 Suppl 5:v70–7.

6.
Benson AB 3rd, Venook AP, Cederquist L, et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(3):370-398.

7.
Li M, Li JY, Zhao AL, Gu J. Colorectal cancer or colon and rectal cancer? Clinicopathological comparison between colonic and rectal carcinomas. *Oncology*. 2007;73(1-2):52–57.

8.
Smith NJ, Shihab O, Arnaout A, et al. MRI for detection of extramural vascular invasion in rectal cancer. *AJR Am J Roentgenol*. 2008;191(5):1517–1522.

9.
Chand M, Swift RI, Tekkis PP, et al. Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br J Cancer*. 2014;110(1):19–25.

10.
Smith NJ, Barbachano Y, Norman AR, et al. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229–236.

11.
Chand M, Bhangu A, Wotherspoon A, et al. EMVI-positive stage II rectal cancer has similar clinical outcomes as stage III disease following pre-operative chemoradiotherapy. *Ann Oncol*. 2014;25(4):858–863.

12.
Bhangu A, Fitzgerald JEF, Slesser A, et al. Prognostic significance of extramural vascular invasion in T4 rectal cancer. *Colorectal Dis*. 2013;15(11):e665–671.

13.
Dighe S, Blake H, Koh M, et al. Accuracy of multidetector computed tomography in identifying poor prognostic factors in colonic cancer. *The British Journal of Surgery.* 2010;97(9):1407-1415.

14.
Kakar S, Shi C, Berho ME, et al; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Version 4.0.0.0, 2017 (June).

15.
Blenkinsopp WK, Stewart-Brown S, Blesovsky L, et al. Histopathology reporting in large bowel cancer. *J Clin Pathol*. 1981;34(5):509–513

16.
Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17(6):1471-1474

17.
Hamilton SR, Aaltonen LA, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. IARC Press: Lyon 2000

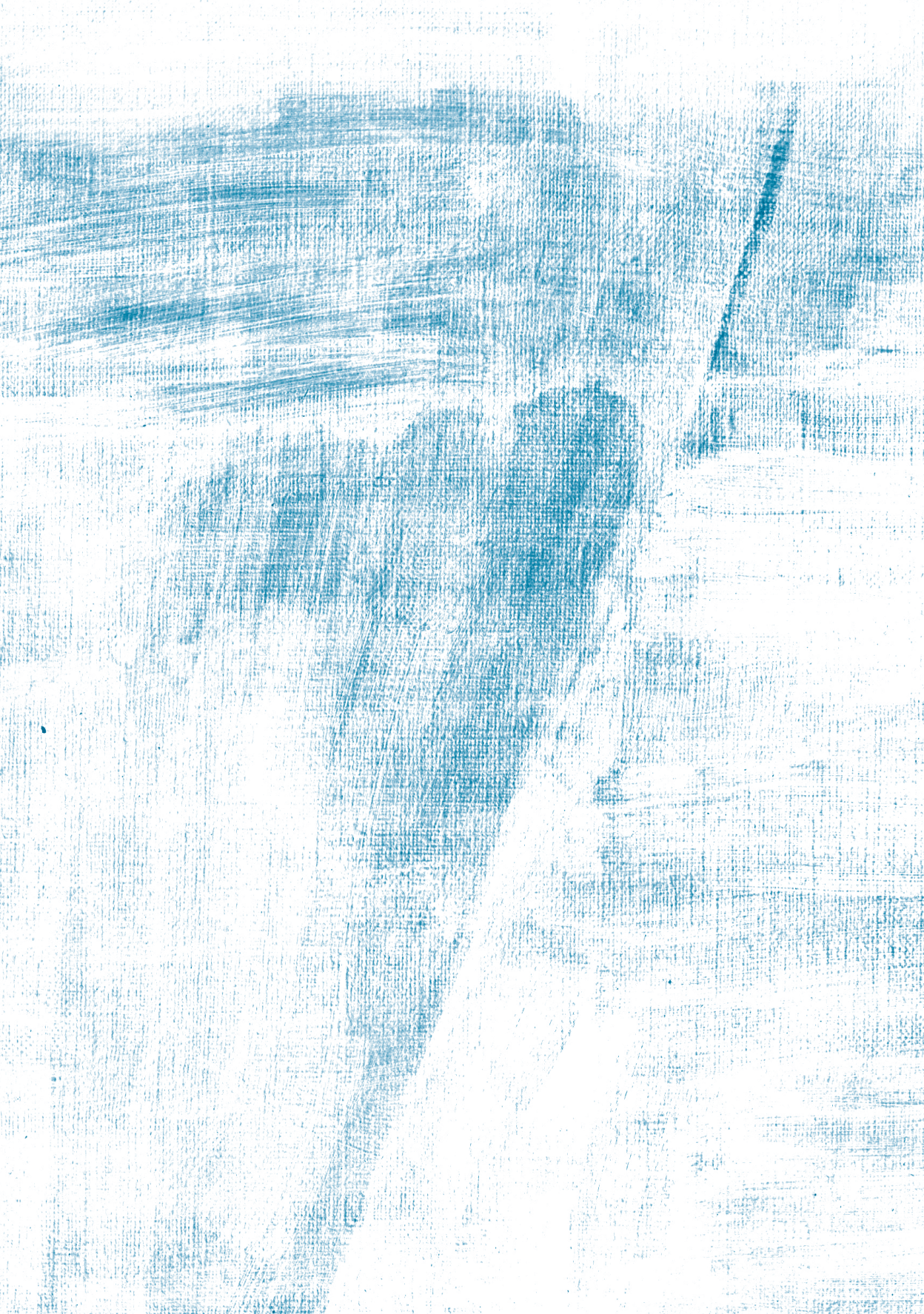
18.
National Comprehensive Cancer Network. Colon Cancer (Version 2.2018).

19.
Talbot IC, Ritchie S, Leighton M, et al. Invasion of veins by carcinoma of rectum: method of detection, histological features and significance. *Histopathology*. 1981;5(2):141–163.

20.
Prabhudesai A, Arif S, Finlayson CJ. Impact of Microscopic Extranodal Tumor Deposits on the Outcome of Patients with Rectal Cancer. *Diseases of the colon & Rectum.* 2003;46(11):1531-1537.

21.
Jhaveri KS, Hosseini-Nik H. MRI of Rectal Cancer: An Overview and Update on Recent Advances. *American Journal of Roentgenology*. 2015;205(1):W42-55.

22.
Chand M, Swift RI, Tekkis PP, et al. Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br J Cancer*. 2014;110(1):19-25.



CHAPTER 9

PERINEURAL INVASION is a PROGNOSTIC but not a PREDICTIVE FACTOR in NON-METASTATIC COLON CANCER

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ABSTRACT

BACKGROUND

Perineural invasion is associated with adverse oncological outcomes in colorectal cancer. However, data regarding the prognostic and predictive impact in colon cancer are scarce. The aim of this study was to clarify the role of PNI in patients with non-metastatic colon cancer.

METHODS

Patients with stage I-III colon cancer who underwent elective surgery at our tertiary center between 2004-2015 were extracted from a prospectively maintained database (n=1145). Long-term outcomes were compared, and differences were determined by multivariate Cox regression models.

RESULTS

Perineural invasion was identified in 215 patients (18.8%) and associated with emergency procedures, male gender, and advanced disease. Histopathological features including lymphatic and extramural vascular invasion, poor differentiation, and infiltrating tumor borders were correlated with perineural invasion. Compared with perineural invasion-negative tumors, perineural invasion-positive patients had worse disease-free, overall, and disease-specific survival (all P<0.001). Moreover, patients with perineural invasion-positive node-negative disease had worse overall survival than perineural invasion-negative node-positive patients (P<0.001). After adjustment, perineural invasion remained significantly associated with worse disease-free survival (HR: 1.45, 95% CI: 1.03 – 2.03, P=0.033), overall survival (HR: 1.75, 95% CI: 1.33 – 2.31, P<0.001), as well with worse disease-specific survival (HR: 1.52, 95% CI: 1.00 – 2.30, P=0.048). However, we did not find a significant predictive response with adjuvant chemotherapy in perineural invasion-positive node-negative tumors (HR: 2.10, 95% CI: 0.80 – 5.51, P=0.122). The predictive value was only demonstrated in stage-III disease with a significant impaired overall survival in patients with perineural invasion-positive tumors who did not receive adjuvant therapy (HR: 0.23, 95% CI: 0.13 – 0.40, P<0.001).

CONCLUSION

Our study confirms the prognostic value of perineural invasion in stage I-II and III colon cancer. However, patients with node-negative disease and perineural invasion did not significantly benefit from adjuvant therapy. More information regarding post-operative treatment in node-negative perineural invasion-positive colon cancer is required.

INTRODUCTION

The current standard for clinical prediction of survival and recurrence in colon cancer is principally based on pathological staging per the Tumor-Node-Metastasis (TNM) classification. Current treatment guidelines are based on this baseline staging, since survival and recurrence rates vary considerably.[1] In localized colon cancer, the 5-year survival rate is up to 90% which declines to 70% when regional lymph nodes are involved.[2] Adjuvant chemotherapy has a clearly established benefit in patients with locoregional lymph node metastasis (AJCC stage III), with improved survival and lower recurrence rates. However, the role of adjuvant therapy in non-metastatic colon cancer is disputable and complete surgical resection remains the gold standard of care.[3] Most clinical trials that enrolled both stage II and III patients demonstrated only a marginal benefit in overall survival, not higher than 5% in lymph-node negative disease.[4,5]

To identify patients with early stage disease who may benefit from chemotherapy, more explicit staging is necessary. TNM-staging is not accurate enough to stratify patients with stage I-II disease, which is noted in previous studies demonstrating the impact of various histopathologic features on survival and disease recurrence. Vascular involvement is one of those high risk factors, which is well explained by the established and most frequent route of tumor spread, namely through venous and lymphatic vessels.[6] Although less common, tumor spread along nerves is an established mode, and previous research has shown the impact of perineural invasion (PNI) on long-term outcomes in colorectal cancer.[7-10] As a result, PNI was incorporated as an accessory factor in the 7th edition of the AJCC Cancer Staging Manual, and included as a high-risk factor in the National Comprehensive Cancer Network (NCCN) guideline for which adjuvant therapy could be considered.[3,11] The College of American Pathologists also underlined the importance of PNI and has recommend reporting PNI in patients with primary carcinoma of the colon and rectum since 2009.[12]

Despite all changes in the guidelines over the last decade, the decision to give additional treatment in node-negative cancer needs to be made on an individual basis, in particular when considering the risk of both undertreatment and the potential harm of chemotherapy. This is especially true in early stage disease where there are considerable questions about the benefit of additional therapy. With regards to perineural invasion, previous studies indicate the need for adjuvant therapy in patients with colorectal tumors and the presence of PNI.[7-10, 13-16] Unfortunately, a distinction in tumor location was rarely made. It is to be expected that the detection rate of PNI would be higher in rectal cancer due to its anatomic localization and more extensive examination of the mesorectal fat. Moreover, the prognostic impact of perineural invasion has been studied more often than the predictive impact. Therefore, the aim of our study was to establish both the prognostic and predictive value of PNI in stage I-III colon cancer.

MATERIALS & METHODS

STUDY DESIGN AND PATIENTS

All patients treated surgically for primary colon cancer at Massachusetts General Hospital in the decade covering January 1st, 2004 through December 31st, 2015 were included in a prospectively maintained survival and outcomes database after institutional review board approval (n=1645). We included only patients with pathologic AJCC stage I-III and those treated with curative intent (n=1222). All patients with hereditary cancer (n=29), a personal history of colorectal cancer (n=31), synchronous or recurrent colon cancer (n=11), or patients who received neoadjuvant treatment were excluded (n=14), leaving 1145 patients.

Adjuvant chemotherapy was considered for all patients. The decision whether to administer postoperative therapy was made after reviewing pathology results and assessing the performance status of the patients and their consent to the therapy. Due to distinct differences in epidemiology, tumor biology, and treatment patterns, we exclusively focused on colon cancer and did not include patients with rectal cancer. Based on tumor location, we divided the study group into patients with right-sided tumors (including any tumor proximal to the splenic flexure) and left-sided tumors (splenic flexure to 15 cm of the anal verge).

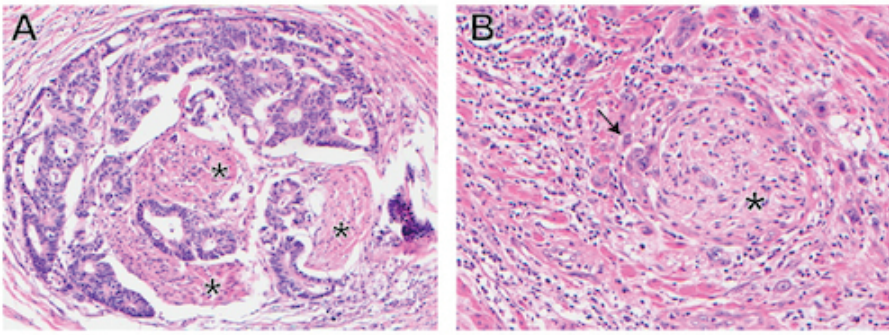
HISTOPATHOLOGICAL EXAMINATION

All specimens from the resection were analyzed by a team of board-certified gastrointestinal pathologists at Massachusetts General Hospital. Pathologic analysis was performed per current recommendations of the College of American Pathologists.[12] Staging was performed per the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system [11] and tumors were graded per the World Health Organization guidelines (WHO).[17] Perineural invasion (PNI) was defined as presence of cancer cells inside the perineurium of any nerve (Auerbach's plexus, Meissner plexus, or in peripheral nerves in intramural or extramural tissues) (Figure 1).

SURVEILLANCE AND SURVIVAL

All patients underwent a standardized follow-up per the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines.[3,18] The decision whether or not to administrate postoperative therapy was made after reviewing pathology results and assessing the performance status of the patients and their consent to the therapy. Determination of disease recurrence was made by histological or clinical and radiological examinations. Local recurrence was defined as colon cancer within or contiguous to the original site of the tumor. Regional recurrence included all recurrent disease within the original tumor bed (including perianastomotic, peritoneum, retroperitoneum, and pericolic mesenteric lymph-nodes), while recurrence at nonregional sites, such as liver or lung, were considered distant recurrences. Recurrent or metastatic disease within 30 days of the original admission was considered baseline metastases and therefore excluded from our study cohort.

Data on long-term outcomes are periodically updated by reviewing patient follow-up record and the US Social Security Death Index. The last status review of survival and follow-up was on December 1st 2017. All time to events (in months) were measured from date of surgery.



A: An example of PNI in an extramural nerve in a moderately-differentiated colonic adenocarcinoma (original magnification x200). The tumor both surrounds the circumference of the nerve (perineural) and infiltrates the nerve (intraneural).
B: PNI in the Auerbach plexus in a poorly differentiated colonic carcinoma. The tumor (arrow) surrounds the nerve bundle (perineurial invasion) (original magnification x 300).
*: Nerve (both panels)

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS *(Version 24.0; SPSS Inc, Chicago, IL, USA).* A two-tailed P-value of 0.05 or less was considered the threshold for statistical significance. Categorical variables are presented as the percentage of patients and compared by the Chi- square (χ^2) test, while continuous variables are presented as the median [IQR] and analyzed using the Mann-Whitney *U* test. Survival times were censored at either the time of last encounter with the patient or date of death (OS and DSS) or date of disease recurrence (DFS). All three survival outcomes were estimated by the Kaplan-Meier method using a Log-Rank test. Additionally, a multivariate Cox regression analysis was performed to identify factors related to survival outcomes. Explanatory variable with significant univariate P-values were included in the model. The results are reported as hazard ratios (HR) with a 95% confidence interval (CI). The predictive value of PNI was assessed in node-negative and node-positive patients, who underwent an R0 resection.

RESULTS

BASELINE CHARACTERISTICS

The baseline and clinical outcomes of the study cohort are demonstrated in table 1. A total of 1145 patients were included, with a median age of 68.9 years and an equal distribution in gender. More tumors were located proximal to the splenic flexure (62.3%). Emergent admission occurred in 9.6% of all cases, mainly due to bowel obstruction. Open procedures were performed in the majority of cases (54.1%), though the rate of laparoscopic surgery increased significantly over the study period; the last third of the study accounted for 49.5% of all laparoscopic procedures. PNI positive tumors were identified in 18.8% of all included patients, with a significant increase over tumor staging (stage I: 2.3%, stage II: 14.0%, stage III: 32.8%, P<0.001). Moreover, the incidence of PNI was higher in left-sided tumors (22.7% of all

left-sided tumors versus 16.4% in the right-sided cohort, P=0.008). The detection rate of PNI remained stable over the study period, with only a slight increase in node-negative disease (8.7% in the first half, 10.8% in the latter). As demonstrated in table 2, 52.0% of the study population had a pT3 tumor and 61.0% node-negative disease. With regard to other histologic risk factors incorporated in the current guidelines, extramural venous invasion was found in 19.0% of all patients, lymphatic invasion in 35.3%, and 21.6% of all tumors were poorly differentiated.

CORRELATION BETWEEN PNI AND CLINICOPATHOLOGICAL PARAMETERS

The correlations between PNI and clinicopathological parameters are demonstrated in table 1 and 2. Male patients were at higher risk of having PNI-positive tumors (Odds Ratio: 1.40, 95% CI: 1.04 – 1.89, P=0.026). Moreover, bowel obstruction had a strong correlation with presence of PNI (OR: 2.77, 95% CI: 1.66 – 4.61, P<0.001). Other than gender and urgent admission, no differences in patient characteristics or in tumor location were found. However, PNI was found to be strongly associated with pathological and molecular risk features, including T4 tumors, N+ disease (P<0.001), poor differentiation (P=0.002), infiltrating border configuration (P<0.001), lymphatic invasion (P<0.001), and EMVI (P<0.001). Adjuvant chemotherapy was given more often in PNI-positive patients (30.1% vs. 60.9%, P<0.001). The main reasons to omit further treatment was high age or comorbidity (58.2%), deceased (13.1%) or declination of further treatment (8.0%).

Table 1. Correlation between PNI, patient demographics and clinical features in patients with stage I-III colon cancer

	Overall N = 1145	PNI – *N = 930*	PNI + *N = 215*	P-value
Age, *years*	68.9 (58.1 – 79.6)	69.1 (57.9 – 79.8)	68.1 (58.5 – 78.2)	0.490
Male Gender	550 (48.0%)	432 (46.5%)	118 (54.9%)	0.026
Caucasian	1028 (89.8%)	835 (89.8%)	193 (89.8%)	0.604
ASA-score, *III-IV*	2 (2 – 3)	2 (2 – 3)	2 (2 – 3)	0.661
Preoperative BMI, *kg/m²*	26.8 (23.4 – 30.9)	26.8 (23.4 – 31.0)	26.6 (22.9 – 30.7)	0.449
Alcohol abuse	72 (6.3%)	57 (6.1%)	15 (7.0%)	0.644
Smoking – *current or history of*	559 (48.8%)	449 (48.3%)	110 (51.2%)	0.446
Preoperative CEA, *ng/mL**	3.4 (1.7 – 10.4)	3.2 (1.7 – 9.9)	3.9 (2.2 – 14.1)	0.129
Tumor location				0.008
Right-sided	713 (62.3%)	596 (64.1%)	117 (54.4%)	
Left-sided	432 (37.7%)	334 (35.9%)	98 (45.6%)	
Urgent admission	110 (9.6%)	81 (8.7%)	29 (13.5%)	0.032
Bowel obstruction	70 (6.1%)	44 (4.7%)	26 (12.1%)	<0.001
Bowel perforation	23 (2.0%)	18 (1.9%)	5 (2.3%)	0.713
Open surgical approach	628 (54.8%)	508 (54.6%)	120 (55.8%)	0.414
Multivisceral resection	101 (8.8%)	74 (8.0%)	27 (12.6%)	0.032
Adjuvant chemotherapy	411 (35.9%)	280 (30.1%)	131 (60.9%)	<0.001

Proportions are presented for categorical data (%), median with IQR for all continuous data.
Abbreviations: ASA: American Society of Anesthesiologists, BMI: Body Mass Index (kg/m²), CEA: Carcinoembryonic antigen
* Missing data preoperative CEA: n = 630

Table 2. Correlation between PNI, pathological and molecular features in patients with stage I-III colon cancer

	Overall N = 1145	PNI – *N = 930*	PNI + *N = 215*	P-value
Depth of tumor invasion (pT stage)				<0.001
pT1	145 (12.7%)	142 (15.3%)	3 (1.4%)	
pT2	176 (15.4%)	169 (18.2%)	7 (3.3%)	
pT3	595 (52.0%)	485 (52.2%)	110 (51.2%)	
pT4	229 (20.0%)	134 (14.4%)	95 (44.2%)	
Nodular stage				<0.001
N0	699 (61.0%)	631 (67.8%)	68 (31.6%)	
N1	305 (26.6%)	229 (24.6%)	76 (35.3%)	
N2	141 (12.3%)	70 (7.5%)	71 (33.0%)	
AJCC stage				<0.001
I	257 (22.4%)	251 (27.0%)	6 (2.8%)	
IIA	343 (30.0%)	307 (33.0%)	36 (16.7%)	
IIB	75 (6.6%)	56 (6.0%)	19 (8.8%)	
IIC	19 (1.7%)	13 (1.4%)	6 (2.8%)	
IIIA	56 (4.9%)	53 (5.7%)	3 (1.4%)	
IIIB	295 (25.8%)	202 (21.7%)	93 (43.3%)	
IIIC	100 (8.7%)	48 (5.2%)	52 (24.2%)	
R0 resection	1111 (97.0%)	913 (98.2%)	198 (92.1%)	<0.001
Tumor size, cm	4.5 (3.0 – 7.0)	4.5 (3.0 – 6.9)	4.5 (3.2 – 7.1)	0.194
LN harvest	20 (16 – 28)	20 (16 – 28)	21 (16 – 29)	0.256
< 12 LN examined	99 (8.6%)	79 (8.5%)	20 (9.3%)	0.704
Tumor differentiation				0.002
WD/MD	867 (75.7%)	718 (77.2%)	149 (69.3%)	
PD	247 (21.6%)	183 (19.7%)	64 (29.8%)	
Unknown	31 (2.7%)	29 (3.1%)	2 (0.9%)	
Tumor border configuration				<0.001
Infiltrating	706 (61.8%)	523 (56.4%)	183 (85.1%)	
Pushing	396 (34.6%)	365 (39.3%)	31 (14.4%)	
Unknown	41 (3.6%)	40 (4.3%)	1 (0.5%)	
Lymphatic invasion	404 (35.3%)	264 (28.4%)	140 (65.1%)	<0.001
Intramural venous invasion	66 (5.8%)	50 (5.4%)	16 (7.4%)	0.324
Extramural venous invasion	217 (19.0%)	112 (12.0%)	105 (48.8%)	<0.001
Microsatellite instability				0.577
MSS/MSI-L	506 (44.2%)	405 (43.5%)	101 (47.0%)	
MSI-H	135 (11.8%)	113 (12.2%)	22 (10.2%)	
Not tested	504 (44.0%)	412 (44.3%)	92 (42.8%)	

Proportions are presented for categorical data (%), median with IQR for all continuous data.
Abbreviations: AJCC: American Joint Committee on Cancer, LN: lymph nodes, WD: well-differentiated, MD: moderately differentiated, PD: poorly differentiated, MSS: microsatellite stable, MSI-L: microsatellite instability-low, MSI-H: microsatellite instability-high

PNI AS A PROGNOSTIC FACTOR OF ONCOLOGIC OUTCOMES IN STAGE I-III COLON CANCER

Median follow-up duration was 45.7 months, which was significantly shorter in patients with PNI positive tumors (median 46.7 vs. 37.1 months, P=0.001). Also, duration of disease-free survival was significantly reduced when PNI was present (42.8 vs. 26.7 months, P<0.001). Table 3 demonstrates the correlation between PNI and oncological outcomes in the study cohort. The strong association between PNI and disease recurrence was mainly explained by more regional and distant recurrence (P<0.001).

Log-rank tests underlined the worse outcomes, demonstrated in the Kaplan-Meier curves (Figure 2).

PNI-positive patients not only did worse compared to PNI-negative patients in the same stage of disease, but overall survival was significantly worse in PNI-positive node-negative patients compared to PNI-negative node-positive patients (5-year estimate 55.0% vs. 71.0%, P<0.001).

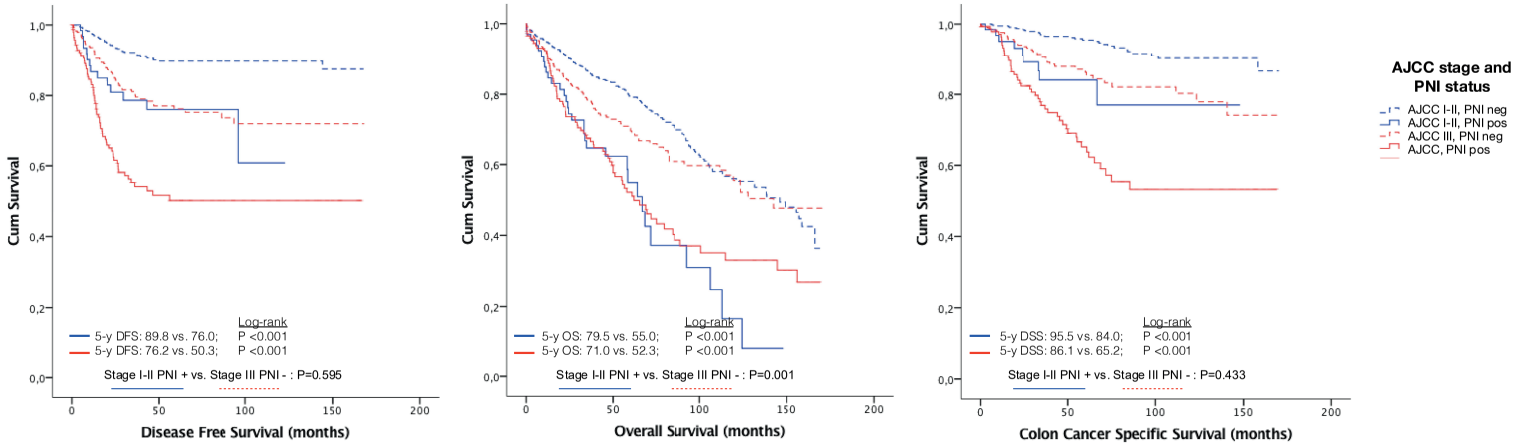
PNI AS AN INDEPENDENT PROGNOSTIC FACTOR OF ONCOLOGIC OUTCOMES IN STAGE I-III COLON CANCER

To assess the influence of all significant covariates on oncologic outcomes, a Cox regression model was completed (Table 4). With regards to DFS, PNI remained a significant predictor for a shorter time to disease recurrence after adjusting for all other significant univariate covariates (Hazard Ratio: 1.45, 95% CI: 1.03 – 2.03, P=0.033), along with alcohol abuse, bowel obstruction, open surgery, advanced staging (T3-T4, N+ disease), infiltrating tumors, and EMVI. PNI also withstood the multivariate analysis of overall survival with almost two-fold higher hazard ratios (HR: 1.75, 95% CI: 1.33 – 2.31, P<0.001), as well as colon cancer specific mortality (HR: 1.52, 95% CI: 1.00 – 2.30, P=0.048). Adjuvant chemotherapy was only independently associated with worse overall survival.

Table 3. Correlation between PNI and oncological outcomes in patients with stage I-III colon cancer

	Overall N = 1145	**PNI – *N = 930***	**PNI + *N = 215***	**P-value**
Disease recurrence	186 (16.3%)	111 (12.0%)	75 (34.9%)	<0.001
Local	30 (2.6%)	20 (2.2%)	10 (4.7%)	0.039
Locoregional	98 (8.6%)	50 (5.4%)	48 (22.3%)	<0.001
Distant	175 (15.3%)	102 (11.0%)	73 (34.0%)	<0.001
Disease-free survival, months	39.7 (17.4 – 72.4)	42.8 (21.6 – 77.9)	26.7 (11.1 – 52.7)	<0.001
5-year estimate DFS		85.4%	57.8%	<0.001
Stage I		*95.4%*	*100%*	*0.648*
Stage IIA		*88.2%*	*77.6%*	*0.039*
Stage IIB-IIC		*76.6%*	*65.9%*	*0.211*
Stage III		*76.2%*	*50.3%*	*<0.001*
Deceased	369 (32.2%)	262 (28.2%)	107 (49.8%)	<0.001
Colon cancer death	124 (10.8%)	69 (7.4%)	55 (25.6%)	<0.001
Follow-up duration, months	45.7 (25.8 – 78.9)	46.7 (27.4 – 82.7)	37.1 (17.6 – 63.9)	0.001
5-year estimate OS		76.6%	53.2%	<0.001
Stage I		*82.7%*	*53.3%*	*0.257*
Stage IIA		*81.1%*	*63.8%*	*<0.001*
Stage IIB-IIC		*60.3%*	*55.0%*	*0.352*
Stage III		*69.6%*	*52.3%*	*<0.001*
5-year estimate DSS		92.5%	70.2%	<0.001
Stage I		*99.0%*	*100%*	*0.813*
Stage IIA		*95.5%*	*87.6%*	*0.084*
Stage IIB-IIC		*82.1%*	*74.7%*	*0.190*
Stage III		*86.1%*	*65.2%*	*<0.001*

Proportions are presented for categorical data (%), median with IQR for all continuous data.
Abbreviations: DFS: disease-free survival, OS: overall survival, DSS: disease-specific survival
a Log-rank test



Numbers at risk															
AJCC I-II, PNI neg	627	577	577	576	567	627	538	483	464	460	627	610	598	597	596
AJCC I-II, PNI pos	67	54	53	53	53	67	45	38	35	35	67	59	58	58	58
AJCC III, PNI neg	303	243	242	242	242	303	231	215	208	208	303	274	268	265	265
AJCC III, PNI pos	148	92	88	88	88	148	95	77	74	73	148	113	102	102	102

Figure 2. Kaplan Meier curves for disease-free survival, overall survival, and colon cancer specific survival. Divided by stage

Table 4. Cox proportional Hazard Ratios and 95% CIs for overall, disease-specific, and disease-free survival stage I-III

	5-year disease free survival			5-year overall survival			5-year disease specific survival		
	Univariate P-value [1]	Multivariate HR (95% CI)	*P-value* [2]	Univariate P-value [1]	Multivariate HR (95% CI)	*P-value* [2]	Univariate P-value [1]	Multivariate HR (95% CI)	*P-value* [2]
PNI	<0.001	1.45 (1.03 – 2.03)	0.033	<0.001	1.75 (1.33 – 2.31)	<0.001	<0.001	1.52 (1.00 – 2.30)	0.048
Age (≥65 vs. <65 y)	0.832			<0.001	2.42 (1.80 – 3.26)	<0.001	0.072		
Male sex	0.221			0.427			0.984		
ASA-score III-IV (vs. I-II)	0.160			<0.001	1.76 (1.40 – 2.20)	<0.001	0.049	1.38 (0.95 – 2.01)	0.093
BMI (≥25 vs. <25)	0.490			<0.001	0.75 (0.60 – 0.94)	0.011	0.226		
Alcohol abuse	0.002	2.12 (1.32 – 3.40)	0.002	<0.001	1.68 (1.15 – 2.45)	0.007	0.013	2.67 (1.46 – 4.91)	0.001
Smoking (current or hx)	0.501			0.103			0.770		
Bowel obstruction	<0.001	1.93 (1.21 – 3.07)	0.006	<0.001	1.64 (1.12 – 2.39)	0.010	<0.001	2.10 (1.23 – 3.59)	0.006
Bowel perforation	0.003	2.04 (0.98 – 4.27)	0.057	<0.001	2.54 (1.32 – 4.92)	0.005	0.001	2.69 (1.12 – 6.46)	0.027
Surgical approach (laparoscopic vs. open)	0.036	0.72 (0.53 – 0.97)	0.033	<0.001	0.70 (0.55 – 0.90)	0.006	0.003	0.55 (0.36 – 0.84)	0.006
Tumor location	0.013		0.318	0.218			0.016		0.187
Right-sided		1.00						1.00	
Left-sided		1.17 (0.86 – 1.59)						1.23 (0.89 – 1.87)	
pT stage	<0.001			<0.001			<0.001		
T1		1.00			1.00			1.00	
T2		2.62 (0.72 – 9.59)	0.146		1.10 (0.65 – 1.86)	0.735		1.56 (0.40 – 6.14)	0.526
T3		4.85 (1.49 – 15.80)	0.009		1.31 (0.81 – 2.12)	0.274		2.10 (0.62 – 7.09)	0.235
T4		6.18 (1.86 – 20.53)	0.004		2.23 (1.32 – 3.77)	0.003		3.98 (1.16 – 13.71)	0.029
pN stage	<0.001			<0.001			<0.001		
N0		1.00			1.00			1.00	
N1		1.48 (1.03 – 2.14)	0.036		1.55 (1.14 – 2.12)	0.005		1.43 (0.88 – 2.32)	0.146
N2		2.96 (1.97 – 4.44)	<0.001		3.33 (2.28 – 4.85)	<0.001		3.29 (2.01 – 5.39)	<0.001
Poor differentiation	<0.001	1.34 (0.97 – 1.86)	0.077	<0.001	1.40 (1.10 – 1.79)	0.007	<0.001	1.67 (1.13 – 2.47)	0.011
Tumor border configuration (pushing vs. infiltrating)	<0.001	0.55 (0.36 – 0.83)	0.005	0.006	0.91 (0.71 – 1.16)	0.436	<0.001	0.58 (0.34 – 1.00)	0.051
MSI (high vs. stable/low)	0.185			0.032	1.18 (0.80 – 1.73)	0.413	0.696		
EMVI	<0.001	1.84 (1.32 – 2.58)	<0.001	<0.001	0.97 (0.72 – 1.31)	0.852	<0.001	1.55 (1.01 – 2.37)	0.045
IMVI	0.312			0.267			0.244		

Lymphatic invasion	<0.001	1.22 (0.81 – 1.83)	0.343	<0.001	1.38 (1.07 – 1.79)	0.014	<0.001	2.40 (1.47 – 3.92)	<0.001
R0-resection	0.004	0.92 (0.49 – 1.74)	0.793	0.001	0.83 (0.53 – 1.31)	0.430	<0.001	0.66 (0.34 – 1.31)	0.237
LN harvest ≥12	0.290			<0.001	0.51 (0.38 – 0.70)	<0.001	0.078		
Adjuvant chemotherapy	<0.001	1.08 (0.74 – 1.58)	0.697	<0.001	0.37 (0.27 – 0.50)	<0.001	<0.001	0.74 (0.46 – 1.18)	0.202

To assess whether PNI is a pathologic characteristic that predicts response to adjuvant chemotherapy, we performed additional analyses on PNI positive patients with complete tumor resection (Figure 3). Among PNI positive patients with node-negative disease (n=66), the estimated 5-year OS was 54.7% for patients who did not receive adjuvant therapy versus 70.5% in patients who were treated postoperatively (P=0.122). Although outcomes were not significant, not administrating adjuvant chemotherapy doubled the hazard of death in PNI positive N0 tumors (HR: 2.10, 95% CI: 0.80 – 5.51, P=0.130), with the effect attributable to deaths in the first two years after surgery (Figure 3, panel B1). The predictive value of PNI was not present for DSS (HR: 2.41, 95% CI: 0.60 – 9.67, P=0.200), nor in the DFS analysis (HR: 1.61, 95% CI: 0.54 – 4.84, P=0.389). Outcomes were more clear in stage III disease (n=132). Receiving adjuvant chemotherapy was associated with a 77% reduction in the hazard of overall mortality (HR: 0.23, 95% CI: 0.13 – 0.40, P<0.001). Nonetheless, we did not find a significant impact on colon cancer specific mortality (HR: 0.58, 95% CI: 0.23 – 1.50, P=0.255).

DISCUSSION

Although extensive research has been performed over the last decades, the role for adjuvant chemotherapy in node-negative colorectal cancer remains debatable. Some studies advocate postoperative treatment, especially when high-risk features are present. The international guidelines agree on some of these factors and recommend consideration of adjuvant therapy in cases with T4 tumors, inadequately sampled lymph nodes, bowel perforation or obstruction, poorly differentiated histology and lymphovascular invasion. However, the effect of adjuvant therapy on these additional features including perineural invasion are not yet established. Because of increasing evidence on prognostic impact of PNI in colorectal cancer, reporting perineural invasion has been recommended by the CAP for a decade now.[12] Although underreporting was an issue before the recognition of the CAP, a recent systematic review did not find a difference in percentages of PNI between studies that extracted PNI from pathology reports and studies that reexamined pathologic slides, suggesting that this biomarker is well reported in routine practice.[10] Our findings support those suggestions with a stable detection rate over our study period of 12 years. With regards to treatment recommendations, PNI is considered a high-risk factor for disease recurrence in the current guidelines for which adjuvant chemotherapy could be considered. Despite the widespread recognition of the prognostic impact of PNI, the impact of postoperative chemotherapy is less clear. The incremental benefit of adjuvant chemotherapy in lymph-node negative colorectal cancer in general is small, and therefore the advantage of treatment in patients with high-risk features should be weighed against the risks of overtreatment. A personalized approach of eligible patients is an important goal in today's practice, for which more evidence about the predictive impact of all recognized biomarkers is needed.

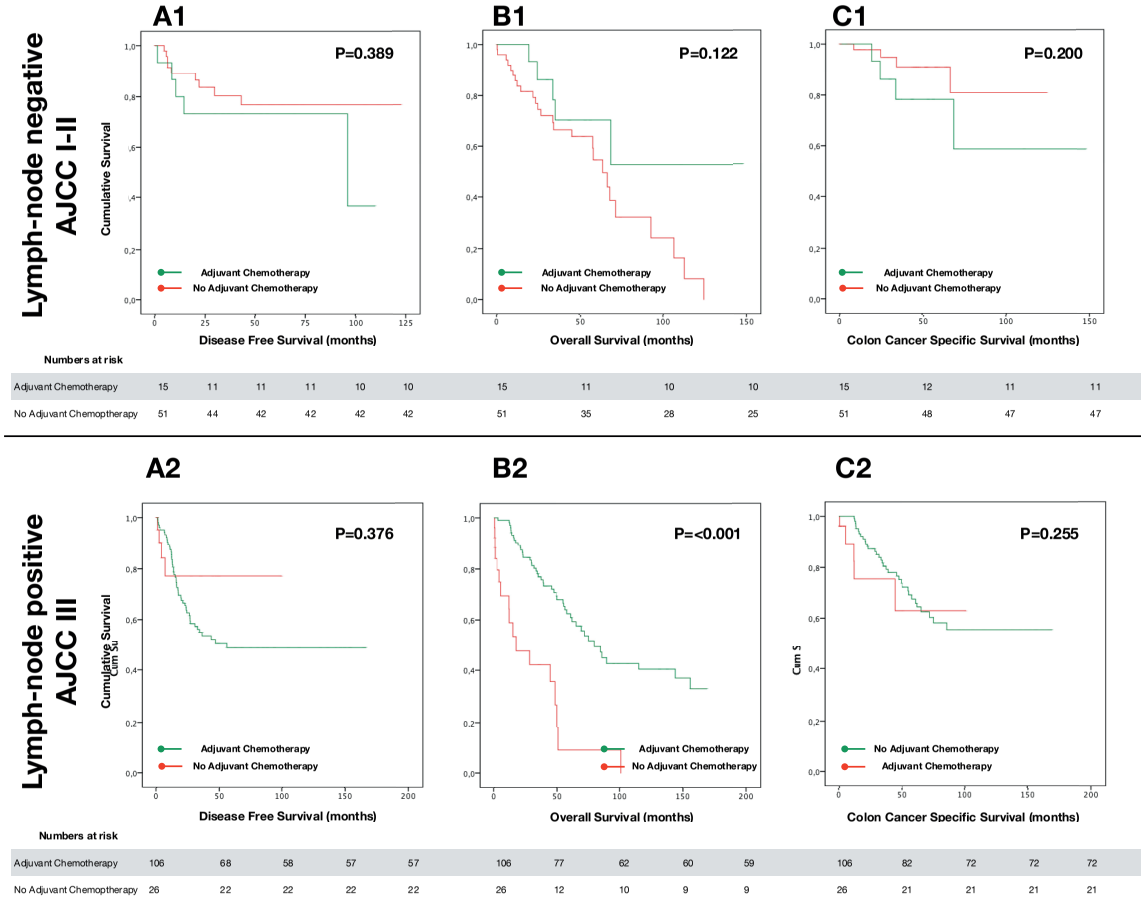


Figure 3. Kaplan Meier curves for disease-free survival, overall survival, and colon cancer specific survival in patients with PNI positive tumors and R0 resection. Divided by adjuvant chemotherapy status.

PNI seems a reasonable risk factor when incorporating all possible ways of tumor spread. The incidence of PNI in the current study was 18.8%, which increased from 9.7% in node-negative disease to 32.8% in AJCC stage III. Those rates are in line with previous studies [13-16], and notably higher than the rates reported in studies conducted before the inclusion of PNI in the CAP protocol.[7] The prognostic impact of PNI has been demonstrated in various studies so far, though most of them included both colon and rectal cancer patients. We hypothesized that the incidence of PNI may be higher in rectal cancer, due to anatomic differences and the autonomic nerve plexuses that surround the rectum in the pelvis, but also the more extensive tissue investigation in rectal cancer. The higher incidence of PNI positive tumors in left-sided colon cancers in our study stresses this hypothesis. Therefore, to minimize potential bias, we focused on colon cancer only. In our study, PNI was related to more aggressive tumor markers, including T4 and N+ disease, poor differentiation, infiltrating tumor configuration, lymphatic invasion, and EMVI. The prognostic impact on overall survival was clear, with 75% higher hazard ratios compared to PNI negative tumors after adjustment for multiple confounders. To our knowledge, this is the first study investigating the prognostic impact of PNI on colon cancer specific mortality, which was significantly related (HR: 1.52, P=0.048). Factors such as TN-staging, emergency procedures, lymphovascular invasion, and poor differentiation were stronger correlated to DSS. Similar findings were seen in the multivariate analysis of DFS. Although independently associated with a shorter time to disease recurrence, the impact of PNI was less than other well-established risk factors including bowel obstruction, T4 tumors, N+ disease, and EMVI.

The aforementioned results might suggest that the established prognostic effect of PNI is less evident than previous studies suggest. This was further emphasized by our results for the predictive value of PNI. In node-negative colon cancer, we found non-significant higher hazard ratios of overall mortality and a deeper incline of the Kaplan-Meier overall survival curve in patients with PNI positive tumors who did not receive adjuvant chemotherapy. This is most likely best explained by a higher age and comorbidity rate in patients who did not receive adjuvant therapy, since the predictive value on DFS and colon cancer specific mortality remained absent. Our findings are in contrast with previous studies that focused on PNI positive tumors and demonstrated a significant benefit of adjuvant chemotherapy.[13-16] The inclusion of rectal cancer might have influenced those findings. It is well-known that rates of disease recurrence are higher in rectal cancer than colon cancer. This was emphasized by previous studies, demonstrating a strong correlation between PNI and local tumor progression in rectal cancer despite tumor free margins.[19,20] Nevertheless, we are not the first study who failed to detect a predictive benefit in PNI positive tumors.[21,22] On the contrary, the effect of adjuvant chemotherapy in stage III colon cancer in our study was significant with a reduction of 77% on overall mortality when chemotherapy was received.

To our knowledge, this study represents one of the few analyses of the prognostic and predictive value of PNI on colon cancer only. Nevertheless, our study has limitations inherent to the retrospective origin. The advantage, on the other hand, is a large and homogeneous cohort treated in the same fashion without the limits of a multicenter trial. Due to detailed data, we could adjust for multiple confounders, including both

patient characteristics and pathologic features. This study demonstrated the prognostic effect of PNI, but node-negative colon cancer patients with PNI did not seem to benefit from adjuvant chemotherapy. The lack of effect of postoperative treatment might reflect the true effect, but could also be cause by type II errors, due to relatively small numbers. Not all patients received adjuvant chemotherapy. The decision to administrate postoperative therapy was made on an individual basis, driven by pathology results, the performance status of the patients and their consent to the therapy. This led to an administration rate of almost two-thirds of all PNI-positive patients. High comorbidity score and age were the main reasons to omit further treatment. Moreover, the predictive value of PNI is best investigated by a randomized controlled trial. The Quasar trial, for example, determined the benefit of adjuvant therapy in all stage II colorectal cancer patients and randomly assigned postoperative treatment.[4] Similar trials are needed to confirm our findings.

CONCLUSION

Perineural invasion in stage I-III colon cancer is associated with an aggressive tumor phenotype, by strong correlations with advanced TN-staging, poor differentiation, infiltrating tumor borders, and lymphovascular invasion. Although PNI was found to be an independent prognostic factor for disease-free survival, disease-specific and overall survival, the predictive value was only demonstrated in node-positive disease. Incorporating the potential harm of postoperative chemotherapy, our results do not support adjuvant treatment in node-negative colon cancer when PNI is detected. More research regarding adjuvant therapy in PNI positive colon cancer is needed to underscore our results.

REFERENCES

1.
Siegel RL, Miller KD, Fedewa SA, et al. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:177-193.

2.
Noone AM, Howlader N, Krapcho M, et al (eds). *SEER Cancer Statistics Review*, 1975-2015, National Cancer Institute. Bethesda MD https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

3.
National Comprehensive Cancer Network. Colon Cancer (Version 2.2018).

4.
Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;370:2020-2029.

5.
Wilkinson NM, Yothers G, Lopa S, Costantino JP, Petrelli NJ, Wolmark N. Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. *Ann Surg Oncol.* 2010;17:959-966.

6.
Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. *Cell* 2011;147:275-292.

7.
Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol*. 2009;27:5131-5137.

8.
Ueno H, Shirouzu K, Eishi Y, et al; Study Group for Perineural Invasion projected by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Characterization of perineural invasion as a component of colorectal cancer staging. *Am J Surg Pathol*. 2013;37:1542-1549.

9.
Gomez D, Zaitoun AM, De Rosa A, et al. Critical review of the prognostic significance of pathological variables in patients undergoing resection for colorectal liver metastases. *HPB (Oxford).* 2014;16:836-844.

10.
Knijn N, Mogk SC, Teerenstra S, Simmer F, Nagtegaal ID. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. *Am J Surg Pathol.* 2016;40:103–112.

11.
Edge SB, Byrd SR, Compton CC, et al., editors. *AJCC Cancer Staging Manual*. 7th edition Springer-Verlag; New York (NY): 2010. pp. 143–164.

12.
Washington MK, Berlin J, Branton P, et al; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med.* 2009;133:1539-1551.

13.
Cienfuegos JA, Martinez P, Baixauli, et al. Perineural Invasion is a Major Prognostic and Predictive Factor of Response to Adjuvant Chemotherapy in Stage I–II Colon Cancer. *Ann Surg Oncol.* 2017;24:1077-1084.

14.
Suzuki T, Suwa K, Ogawa M, et al Adjuvant chemotherapy for the perineural invasion of colorectal cancer. *J Surg Res.* 2015;199:84-89.

15.
Alotaibi AM, Lee JL, Kim J, et al. Prognostic and Oncologic Significance of Perineural Invasion in Sporadic Colorectal Cancer. *Ann Surg Oncol.* 2017;24:1626-1634.

16.
Huh JW, Kim HR, Kim YJ. Prognostic Value of Perineural Invasion in Patients with Stage II Colorectal Cancer. *Ann Surg Oncol.* 2010;17:2066-2072.

17.
Hamilton S, Bosman F, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban R, Theise ND, eds. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: *International Agency for Research on Cancer*; 2010:134–146.

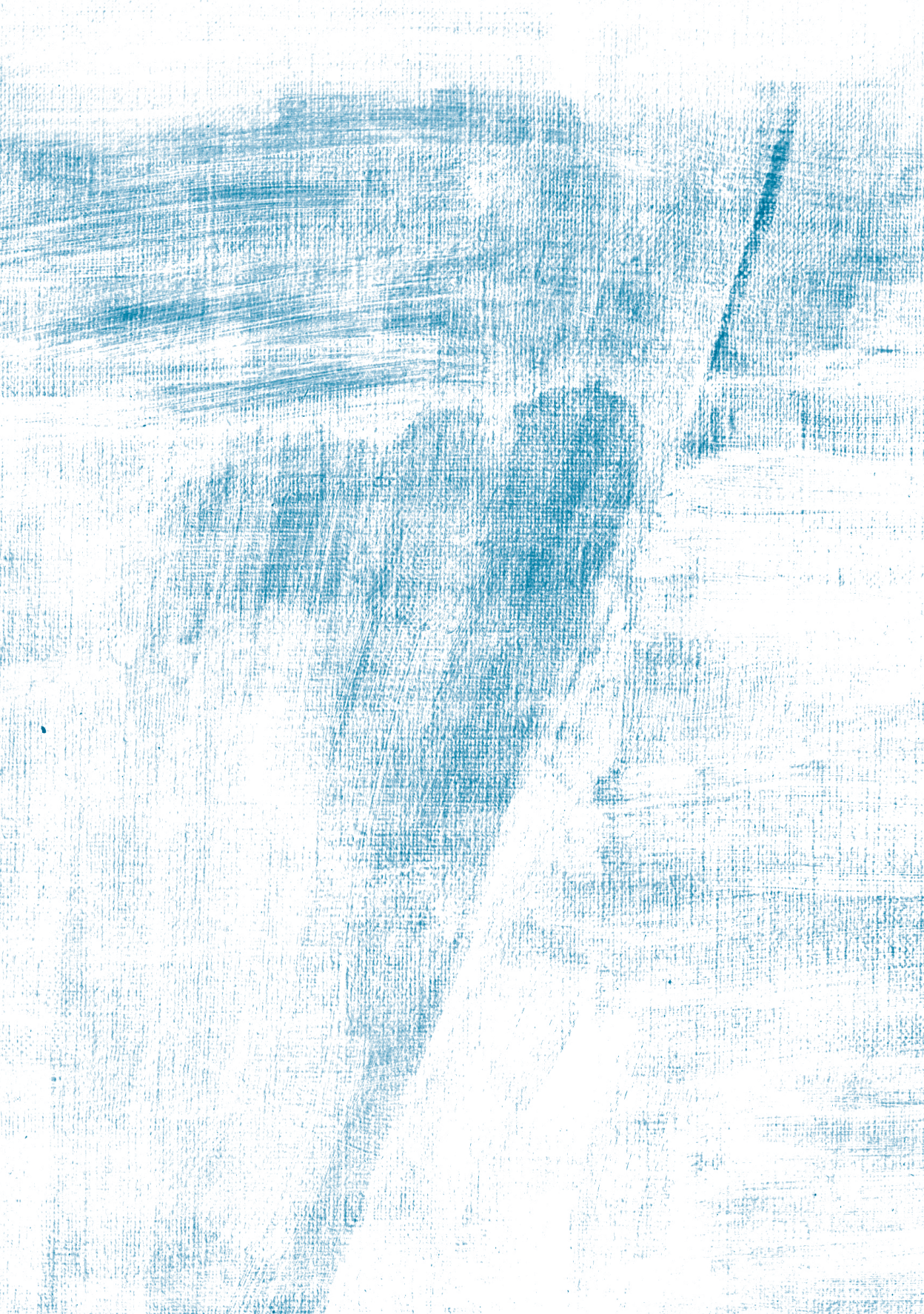
18.
Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol.* 2004;22:3408–3419.

19.
Poeschl EM, Pollheimer MJ, Kornprat P, et al. Perineural invasion: correlation with aggressive phenotype and independent prognostic variable in both colon and rectum cancer. *J Clin Oncol.* 2010;28:e358–e360. author reply e361–e362.

20.
Peng J, Sheng W, Huang D, et al. Perineural invasion in pT3N0 rectal cancer: the incidence and its prognostic effect. *Cancer* 2011;117:1415-1421.

21.
Peng SL, Thomas M, Ruszkiewicz A, Hunter A, Lawrence M, Moore J. Conventional adverse features do not predict response to adjuvant chemotherapy in stage II colon cancer. *ANZ J Surg.* 2014;84:837-841.

22.
Ozturk MA, Dane F, Karagoz S, et al. Is perineural invasion (PN) a determinant of disease free survival in early stage colorectal cancer? *Hepatogastroenterology.* 2015;62:59-64.



APPENDICES

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Journal of Surgical Research. 2018;232:595-604

SUMMARY AND FUTURE PERSPECTIVES

Despite significant improvements in diagnosis and treatment, colorectal cancer is still a major cause of morbidity and mortality worldwide. It affects nearly two million people each year with an estimated death rate of more than 800,000.[1] Advances in diagnosis and reduction in incidence are directly related to the introduction of population-based screening programs which identify and remove precancerous lesions and detect CRC at an early stage. This is then aided by advances in surgery and the advent of new and improved chemotherapeutic and biologic agents. Notwithstanding the increased interest and developments in adjuvant medicines, surgical resection remains the mainstay for curative treatment for malignant tumors in the large bowel. The objective of this thesis was to assess clinical and pathological issues encountered during the surgical treatment of colon and rectal cancer, to further optimize short- and long-term outcomes for these patients and contribute to determine a more targeted disease management.

This thesis begins by evaluating the implication of national screening programs. **Chapter 1** underlined the enormous impact of indication of colonoscopy and stressed the importance of screening compliance. Patients who were diagnosed with CRC through colonoscopy after developing symptoms presented far more often with advanced disease and consequently had significantly higher recurrence and mortality rates. This was true in both comparisons between screening patients and moderate to high-risk patients who underwent surveillance because of a history of adenomas, IBD or a positive family history. More notably, the impaired outcomes remained true after adjustment for patient characteristics, stage and (neo)adjuvant treatment (*Screening*: HR=0.46 (0.33-0.65), *Surveillance*: HR=0.73 (0.55-0.98)). This impact appeared even greater in patients who were diagnosed with colon cancer, which may be explained by the late onset of recognized symptoms since symptoms related to colon cancer are rather nonspecific compared to more profound symptoms usually seen in rectal cancer. Altogether, the results in this chapter emphasized the importance of screening before symptoms develop. To improve adherence to screening programs, in particular in the USA where programs are established on an opportunistic basis, a multifaceted approach tailored to patient, physician, and policy levels is required. Recent studies have demonstrated a tremendous effect of clinical recommendation [2] and outreach [3-4] on screening adherence. Moreover, varying screening rates by ethnicity, insurance status, education level, and age (45.3% of adults age 50-54 versus 71.8% of adults age 65-75) should be taken into account.[5] The latter is in particular important now that the recommendations from the American Cancer Society are changed and regular screening is advised from 45 years instead of the previous 50 years of age.[6] More awareness of the consequences of a delayed diagnosis, along with informative communication between the caregiver and patient, and the expansion of screening coverage might enhance adherence and further reduce the CRC burden.

In the previous chapter, a distinction between colon and rectal cancer in the screening population was discussed. This is only one of the many differences between these two tumor locations. Whereas previous literature led to modification in treatment patterns, recommendations in

early stage (stage I) and advanced disease (stage IV) do not differ considerably from each other. For stage I tumors, surgical resection without (neo)adjuvant is the gold standard. Since disease recurrence is rare in this early stage, little is known about risk factors for adverse outcomes other than method of resection. Current international guidelines are predominantly based on studies focusing on rectal cancer only, contributing to the increase use of less invasive resections for T1-T2 rectal cancer and subsequently the need to stratify risk factors for poor outcomes in this stage of disease.[7-11] **Chapter 2** focused on risk features after surgical resection for stage I colon and rectal cancer and found lymphatic invasion an independent predictor for disease recurrence (HR=4.26), in particular distant recurrence (HR=8.02). This was independent of tumor location, baseline characteristics and other histopathologic risk factors. Moreover, other than earlier detection of local recurrence (median time to detection: *Colon cancer*: 55.8 months versus *Rectal cancer*: 16.2 months), no differences were found between colon and rectal cancer patients. As the cause of disease recurrence in stage I cancer is either undetectable local residual tumor or the presence of micrometastasis, our results might suggest an association between the latter and lymphatic invasion. Whether or not to treat those patients with adjuvant therapy is questionable as the incremental benefit of postoperative treatment in lymph-node negative CRC in general is small and most likely even smaller for T1-T2 tumors. Considering the risk of overtreatment and the associated morbidity of adjuvant treatment, indiscriminate use of postoperative therapy in localized colon or rectal cancer is definitely not recommended. However, assessing high-risk patients in this early stage might help to determine which patients would benefit from a more intensive oncologic follow-up to prevent late detection of tumor recurrence.

On the other end of the spectrum, when the primary tumor has spread to other organs, the role of surgery is less significant and only advocated in patients with resectable metastasis or patients presenting with symptoms such as bowel obstruction, perforation or excessive bleeding. As the ultimate goal in patients with advanced disease is prolonging overall survival without negatively affecting quality of life, a surgical intervention - with its associated risks - remains controversial. **Chapter 3** evaluated the impact of postoperative complications on survival in metastatic colon and rectal cancer and demonstrated an independent relation to an impaired life expectancy after developing adverse outcomes in the palliative cohort only, in particular when patients developed respiratory (HR=7.53) or cardiac (HR=3.75) complications. This, however, underscored the feasibility of surgery in the group with resectable metastasis, but caution should be taken in palliative patients, in particular in patients with a poor performance status (ie respiratory or cardiac comorbidities). As chemotherapeutic agents keep improving, a trend toward less surgery in advanced disease is expected. Future randomized controlled trials are needed to confirm or contradict the benefit of primary tumor resection in stage IV colorectal cancer. Presently, all randomized controlled trials have failed to recruit enough patients and have not reached the required power to make definitive conclusions. Yet a number of trials evaluating this topic are ongoing.[12-14]

The second part of this thesis solely focused on colon cancer. The evolution of colon cancer management is ongoing, with improvements in systemic therapy, the introduction of immunotherapy and the continuous evolvement of surgical therapy. The benefit of a multidisciplinary team that is able to determine a personalized comprehensive treatment plan in oncologic patients is very clear. Nevertheless, an optimal surgical resection remains the cornerstone of improved long-term outcomes. Along with all the advancements in non-surgical treatment, oncologic colon surgery has experienced major improvements over the last decades. The introduction of laparoscopic surgery is without doubt the most significant improvement. Minimally invasive surgery has been adapted to a wide variety of abdominal diseases since the introduction in 1991, though many of the procedures remain technically difficult. **Chapter 4** started with pointing out the feasibility of a less extensive approach to mid-transverse colon cancer. Despite the ongoing trend toward less invasive surgery in general, an extended procedure (EC) for mid-transverse colon cancer remains the most common approach due to anatomic differences that makes a transverse colectomy (TC) a challenging procedure. In our study, a TC was indeed less frequently performed and demonstrated a decreasing trend over time. Simultaneously, the implementation of laparoscopic surgery increased over the study period, though mainly in the extended surgery group. The higher rate of laparoscopic procedures in the EC group did not result in better postoperative outcomes as morbidity was comparable between the two groups. Taking into consideration similar oncologic outcomes (*5-year estimate overall survival:* 78.8% versus 73.5% ; *disease-free survival*: 87.0% versus 90.1%), notwithstanding an obviously smaller specimen length (median: 25 versus 34 cm) and lymph node yield (median 17 versus 25), our study supported the oncological safety of a transverse colectomy for mid-transverse colon cancer.

Minimally invasive surgery is most appealing when it can substitute for primary open procedures. The increasing use of laparoscopy for colon cancer requires analysis of the impact of conversion on oncologic outcomes. Rates of conversion vary considerably but range up to 17% in most recent studies.[15-17] **Chapter 5** analyzed whether conversion was related to adverse short and long-term outcomes by comparing outcomes not only to patients who underwent successfully completed laparoscopy but also to patients undergoing a planned open procedure. Over the study period, ranging from 2004 through 2014, a decreasing conversion rate was observed, with an average of 11.6% in the first half to 7.7% in the latter. In line with previously reported risk factors, several patient- and tumor-related factors were detected including male gender, alcohol and/or nicotine abuse, left-sided tumors, advanced disease and pathologic risk features (eg. vascular and perineural invasion), as well as procedure-related factors (eg. adhesions, the need for a multivisceral resection). [18-20] Postoperative outcomes were significantly worse after conversion compared to a successful laparoscopic procedure, including a longer hospital admission, more complications during admission (21.2% versus 41.5%) and a higher readmission rate (3.4% versus 11.5%). This resulted in more disease recurrence (9.8% versus 21.4%) and impaired survival (*5-year estimate overall survival:* 86.2% versus 70.5%; *disease-specific survival:* 95.1% versus 87.7%). Long-term outcomes remained worse when analyzing survival stage-by-stage. Compared to primary open surgery, conversion was relat-

ed to a higher incidence of intra-abdominal abscesses/leaks (9.4% versus 2.7%) and surgical site infections (9.4% versus 3.2%). Multivariate analyses after adjustment for patient characteristics, stage, morbidity and the administration of adjuvant therapy, demonstrated that conversion was still an independent predictor for impaired survival compared to laparoscopic procedures (HR=2.04) with comparable ratios to primary open procedures (HR=0.84). With regards to disease-free survival, surgical approach did not withstand multivariate analysis and only pathological features remained independently related to worse outcomes. Our results are in line with previous literature demonstrating negative outcomes after conversion compared to successfully completed laparoscopic surgery. Nevertheless, to our understanding, only the comparison between conversion and primary open surgery will answer the question as to whether conversion could be considered a complication rather than a simple drawback. The latter statement is most likely true according to our findings. Other than a higher incidence of post-operative infections, both short- and long-term outcomes were comparable between conversion and planned open surgery. A reasonable explanation for the higher rate of infectious complications is the prolonged operative time in the conversion group.[21-22] An early verdict to convert the procedure might overcome those complications by simply reduce surgical time. Experience of the surgeon along with the capability of intra-operative clinical judgement may be favorable, as long as the need for conversion is not attributed to intra-operative complications.

Elaborating on other procedural difficulties in oncologic colon surgery, **Chapter 6** measured the impact of a local multivisceral resection (LMR) and adjuvant therapy in locally advanced colon cancer by comparing patients with pT4 tumors who did and did not undergo LMR and subsequently comparing them to patients with pT3 tumors. Despite the incremental benefit of LMR in locally advanced colon cancer, previous literature demonstrated that only 26-39% of patients with pT4 tumors actually underwent a multivisceral resection.[23] In our study, 66% of patients with pT4b underwent LMR compared to 21% of all pT4a tumors, with an increase of LMR in general over the study period. The main reason not to perform LMR in patients with pT4b tumors was a false discernment of oncological invasion as peri-tumorous inflammatory adhesions. As it is not yet possible to make this distinction through imaging, the judgment is based on a surgeon's perspective during surgery only. The reluctance to perform an LMR because of its associated morbidity is not fully justified by our findings as only the requirement for blood transfusion was significantly higher after LMR. More notably, oncological outcomes were significantly worse when LMR was not performed in pT4 tumors (*5-year estimate overall survival:* 46.3% versus 70.0%, *5-year disease-specific survival:* 67.2% versus 89.6%) but similar between patient who did undergo LMR compared to those with less advanced disease (78.6%, 92.8%, respectively). This remained true after adjustment for pTN-stage, adjuvant therapy and the achievement of R0 resection (*OS:* HR=1.72, *DSS:* HR=3.36). Taking into account the long-term benefits, LMR is safe and feasible and therefore highly recommended when tumor invasion is suspected.

The last part of this thesis shed light on issues encountered after receiving the results of the surgical pathology report. As mentioned earlier, the primary tool for clinical prediction of recurrence and survival is TNM-stag-

ing. Current guidelines are primarily based on this classification system and recommend adjuvant therapy in lymph-node positive disease only. Nevertheless, several histopathologic features have been incorporated as prognostic factors beyond TNM-staging. Predominantly in patients with node-negative disease, those factors might be important and updated guidelines recommend considering additional treatment in patients with features including positive margins, poorly differentiated tumors, lymph node sampling <12, lymphovascular invasion and pT4 tumors. Validation of those factors has often been done in cohorts grouping colon and rectal cancer together rather than separately even though treatment approaches and tumor biology are markedly different.[7-11, 24]

Chapter 7 reflected several clinicopathological dissimilarities between different tumor sides in colon cancer. Right-sided tumors were bigger and correlated with more advanced tumors, poorer histopathological outcomes and patient characteristics (higher age and ASA-score). The associated pathologic features in our study have been demonstrated earlier, including more poorly differentiated tumors, microsatellite-high and mismatch repair deficient tumors.[25-26] All those components led to worse survival outcomes as expected, though only to a higher overall survival (*estimated 5-year stage I-III:* right: 73.0%; transverse: 76.2%. left: 80.8%) as disease-specific survival was comparable (*estimated 5-year stage I-III:* right: 91.7%; transverse: 94.2%. left: 91.8%). In contrast to previous publications, tumor side did not persist as an independent prognostic factor when controlling for numerous variables.[27-29] The fact that we were able to adjust for factors including adjuvant therapy and more precise histopathological outcomes (eg perineural invasion, poor differentiation, (lympho) vascular invasion) most likely contributed to this discrepancy and emphasized once more the importance of pathologic features beyond TNM-stage.

Elaborating on new prognostic biomarkers in colon cancer, the impact of vascular invasion in colon cancer was investigated in **Chapter 8**. Vascular invasion, in particular extramural venous invasion (EMVI), is a pathologic characteristic that has been extensively studied in rectal cancer but rarely in colon cancer alone. In large part due to the potential finding of EMVI during preoperative magnetic resonance imaging (MRI), a diagnostic tool that is not routinely performed in patients with colon cancer. Vascular invasion was more often present in stage III patients (21.1% versus 40.0%) and showed an increasing detection rate over the study period (27.5% in the first half to 33.3% in the latter). Regardless of stage, EMVI was correlated with other risk factors including more advanced tumors and lymphatic and perineural invasion. Consequently, EMVI+ patients had higher rates of locoregional and distant recurrence subsequently leading to impaired overall and disease-specific survival. On the contrary, patients with only intramural vascular invasion (IMVI) had comparable outcomes to patients with no vascular invasion. In agreement with current guidelines, the administration of adjuvant chemotherapy was higher in stage II patients who did have EMVI on the pathology rapport (33.3% versus 16.3%). In multivariate Cox proportional hazard models, time to disease recurrence remained significantly shorter in patients who were EMVI+ compared to those who were EMVI- (HR=2.07) alongside earlier disease-specific mortality (HR=1.67). More notably, stage II EMVI+ patients had worse disease-specific survival than stage III patients without EMVI,

independent of adjuvant therapy (HR=2.02). This raised the question as to whether a different pre- or post-operative work-up is necessary for this subgroup of patients. In rectal cancer, improved disease-free survival has been demonstrated after the administration of neoadjuvant therapy to EMVI+ tumors.[30] Although neoadjuvant therapy for colon cancer is far from standard of care, the NCCN included pre-operative chemotherapy as a treatment option for patients with clinical T4b colon tumors in their updated version in 2016.[31] Considering the positive effect on EMVI in rectal cancer, it may give insights for therapy in EMVI+ colon cancer.

Finally, **Chapter 9** evaluated the prognostic and predictive value of perineural invasion (PNI) in non-metastatic colon cancer. In 2009, the updated AJCC Cancer Staging Manual included PNI as an accessory factor after the publication of several studies demonstrating a prognostic impact of this feature in colorectal cancer. Moreover, the College of American Pathologists recommend reporting PNI in patients with primary carcinoma of the colon and rectum since that same year.[32] In our study, PNI was identified in 18.8% of all stage I-III primary colon cancer patients, with a stable detection rate over the study period and a significant increase over tumor staging. PNI was associated with left-sided tumors, which might be explained by the anatomic differences and therefore the more extensive tissue investigation as well as the autonomic nerve plexuses that surround the distal part of the colon in the pelvis. This underlined the necessity to evaluate the impact of PNI in colon and rectal cancer separately once more. Additionally, as with vascular invasion we found PNI to be related to more aggressive tumor markers (T4 tumors, node-positive disease, poor differentiation and (lympho)vascular invasion). Kaplan-Meier curves demonstrated worse outcomes, even when comparing PNI-positive node-negative patients to PNI-negative node-positive patients (*5-year estimate overall survival:* 55.0% vs. 71.0%). PNI withstood the multivariate analysis of overall survival (HR=1.75), as well as colon cancer specific survival (HR=1.52) and disease-free survival (HR=1.45). However, the impact of PNI was less evident than other well-established risk factors including T4 tumors, N+ disease, bowel obstruction and EMVI. This may be related to a limited predictive value of PNI with only a significant reduction of 77% on overall mortality after receiving adjuvant chemotherapy in stage III patients. In node-negative disease, a steeper incline of the Kaplan-Meier overall survival curve was observed in patients with PNI positive tumors in addition to higher hazard ratios of overall mortality (HR=2.10). Nonetheless, all outcomes were not significant. As disease-specific and disease-free survival were all comparable regardless of stage, the effect is seemingly best explained by a higher age and comorbidity rate in patients who did not receive adjuvant therapy. Incorporating the potential harm of postoperative chemotherapy, our results did not support adjuvant treatment in node-negative colon cancer when PNI is detected.

In conclusion, the debate on whether node-negative colon cancer patients should receive adjuvant chemotherapy is still ongoing. Most clinical trials were only able to demonstrate a marginal benefit in overall survival, not reaching over 5%.[33-34] Therefore, the advantage of treatment in high-risk node-negative patients should be weighed against the risk of overtreatment. Multiple studies concerning different clinical and histopathological aspects in colon cancer have been conducted which have led to remarkable differences in today's colon cancer practice compared to a

decade ago. The introduction of a multidisciplinary team, the incorporation of not only patient but also different pathologic factors and the introduction of new surgical and systemic therapy have contributed to the improved prognosis nowadays. With regards to pathologic high-risk factors, several features have been identified and subsequently incorporated in the current international guidelines. In this thesis, the prognostic impact of some of those features have been underlined for colon cancer patients specifically. Nevertheless, the predictive value is not fully understood and the decision to treat post-operatively should still be based on an individual basis. While up to now different genomic assays have been introduced to clinic that try to predict recurrence in node-negative patients (eg ColoPrint and Oncotype DX), the predictive outcome is limited. Hence the necessity to gain more knowledge concerning the impact of the current acknowledged high-risk features and to continue searching for other potential markers. We hopefully can expect more specific tools in the near future that would allow further progress in today's colon cancer practice.

REFERENCES

1.
Ferlay J, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8): 1941-1953.

2.
Peterson EB, et al. Impact of provider-patient communication on cancer screening adherence: a systematic review. *Prev Med*. 2016;93:96-105.

3.
Gupta S, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. *JAMA Intern Med*. 2013;173(18):1725-1732.

4.
Singal AG, et al. Outreach invitations for FIT and colonoscopy improve colorectal cancer screening rates: a randomized controlled trial in a safety-net health system. *Cancer* 2016;122(3):456-463.

5.
White A, et al. Cancer Screening Test Use – United States, 2015. *MMWR Morb Mortal Wkly Rep* 2017;66(8): 201-206.

6.
Wolf AMD, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2018;68(4):250-281.

7.
Benson AB III, et al; National Comprehensive Cancer Network. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(7):874-901.

8.
Benson AB III, et al; National Comprehensive Cancer Network. NCCN Guidelines Insight: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw*. 2018;16(4):359-369.

9.
Labianca R, et al; ESMO Guidelines Working Group. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24_suppl6:vi64-vi72.

10.
Glynne-Jones R, et al; ESMO Guidelines Working Group. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017; 28_suppl4:iv22-iv40.

11.
Watanabe T, et al; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol.* 2018;23(1):1-34.

12.
't Lam-Boer J, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer–a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014;14:741.

13.
Biondo S, et al. Impact of resection versus no resection of the primary tumor on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4). *Int J Colorectal Dis* 2017;32:1085-1090.

14.
Rahbari NN, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS–a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012;12:142.

15.
Allaix ME, et al. Laparoscopic versus open resection for colon cancer: 10-year outcomes of a prospective clinical trial. *Surg Endosc.* 2015;29(4): 916-924.

16.
Yerokun BA, et al. Does conversion in laparoscopic colectomy portend an inferior oncologic outcome? Results from 104,400 patients. *J Gastrointest Surg.* 2016;20(5):1042-1048.

17.
Li J, et al. The impact of laparoscopic converted to open colectomy on short-term and oncologic outcomes for colon cancer. *J Gastrointest Surg.* 2015;19(2):335-343.

18.
Thorpe H, et al; Medical research council conventional versus laparoscopic-assisted surgery in colorectal cancer trial group. Patient factors influencing conversion from laparoscopically assisted to open surgery for colorectal cancer. *Br J Surg.* 2008;95(2):199–205.

19.
Bhama AR, et al. Factors associated with conversion from laparoscopic to open colectomy using the National Surgical Quality Improvement Program (NSQIP) database. *Colorectal Dis.* 2015;17(3):257-264.

20.
Masoomi H, et al. Risk factors for conversion of laparoscopic colorectal surgery to open surgery: does conversion worsen outcome? *World J Surg.* 2015;39(5):1240-1247.

21.
Jackson TD, et al. Does speed matter? The impact of operative time on outcome in laparoscopic surgery. *Surg Endosc.* 2011;25(7):2288-1895.

22.
Bailey MB, et al. Longer operative time: deterioration of clinical outcomes of laparoscopic colectomy versus open colectomy. *Dis Colon Rectum.* 2014;57(5):616-622.

23.
Govindarajan A, et al. Population-based assessment of the surgical management of locally advanced colorectal cancer. *J Natl Cancer Inst.* 2006;98(20):1474-1481.

24.
Li M, et al. Colorectal cancer or colon and rectal cancer? Clinicopathological comparison between colonic and rectal carcinomas. *Oncology*. 2007; 73(1-2):52-57.

25.
Hugen N, et al. Advances in the care of patients with mucinous colorectal cancer. *Nat Rev Clin Oncol.* 2016; 13(6):361-369.

26.
Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer.* 2002;101(5):403-408.

27.
Benedix F, et al; Colon/Rectum Carcinomas (Primary Tumor) Study Group. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum.* 2010;53 (1):57-64.

28.
Meguid RA, et al. Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol.* 2008;15(9):2388-2394.

29.
Petrelli F, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2017;3(2):211-219.

30.
Chand M, et al. Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br J Cancer*. 2014;110(1):19-25.

31.
Benson AB III, et al; National Comprehensive Cancer Network. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(3):370-398.

32.
Washington MK, et al; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med.* 2009;133(10):1539-1551.

33.
Quasar Collaborative Group, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet.* 2007; 370(9604):2020-2029.

34.
Wilkinson NM, et al. Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. *Ann Surg Oncol.* 2010;17(4):959-966

NEDERLANDSE SAMENVATTING

Dikke darmkanker is wereldwijd een van de meest voorkomende kwaadaardige aandoeningen. Jaarlijks worden bijna twee miljoen mensen gediagnosticeerd met deze vorm van kanker, met een geschat sterftecijfer van meer dan 800.000 mensen. De afgelopen decennia is er veel veranderd op het gebied van diagnostiek en behandeling van darmkanker. Allereerst door de introductie van het bevolkingsonderzoek, bedoeld om de ziekte in een eerder stadium te detecteren en zo het sterftecijfer te verlagen. Daarnaast is verbetering van de klassieke behandelvormen (chirurgie, radiotherapie en chemotherapie) en de ontwikkeling van immunotherapie in volle gang. Desalniettemin blijft tot op heden een chirurgische resectie de gouden standaard voor kwaadaardige tumoren in de dikke darm.

Het onderzoek dat wordt gepresenteerd in dit proefschrift focust zich op verschillende factoren rondom de chirurgische behandeling van patiënten met dikke darmkanker die de zorg en overlevingskans kunnen verbeteren. Het eerste deel van het proefschrift richt zich op de verschillen tussen dikke darmkanker (colon) en endeldarmkanker (rectum). Ondanks reeds bekende grote verschillen in anatomie, epidemiologie en tumorbiologie worden deze twee type kanker vaak als één entiteit beschouwd en omschreven als “dikke darmkanker” (colorectaal carcinoom). In het tweede en derde deel van het proefschrift ligt de focus uitsluitend op colontumoren. Deel twee richt zich op de chirurgische behandeling en brengt verschillende ingrepen in kaart. Tot slot worden pathologische uitkomsten en hun voorspellende waarden op een (ziektevrije) overleving besproken in deel drie.

Het eerste deel begint met de evaluatie van de indicatie van een coloscopie, een inwendig darmonderzoek dat ingezet wordt als screeningsmethode bij het bevolkingsonderzoek. In **hoofdstuk 1** worden patiënten die een coloscopie ondergingen nadat zij zich met klachten presenteerden in het ziekenhuis vergeleken met patiënten die voor screening of surveillance kwamen. De laatste groep wordt gezien als een hoog-risicogroep, omdat zij bekend zijn met chronische darmziekten, darmpoliepen in het verleden hebben gehad of een positieve familieanamnese voor darmkanker hebben. Bij de patiënten met klachten werd vaker een verder gevorderd stadium darmkanker gevonden wat resulteerde in 50% meer kans op het ontwikkelen van uitzaaiingen op de lange termijn en ook een twee keer hoger sterftecijfer. Het risico op overlijden bleef na correctie voor covariabelen (patiëntkarakteristieken, stadiëring en behandeling met chemotherapie) significant hoger voor de symptoom-groep (*Screening*: HR = 0,46 (0,33-0,65), *Surveillance*: HR = 0,73 (0,55-0,98)). De impact leek zelfs groter bij patiënten met colontumoren. Een mogelijke verklaring hiervoor is de relatief late herkenning van symptomen die gerelateerd zijn aan de dikke darm (buikpijn, veranderd ontlastingspatroon, vermoeidheid) in vergelijking met de endeldarm (zichtbaar bloed en/of slijm bij de ontlasting, tenesmus). Samenvattend wordt in deze studie het belang van screening voordat symptomen zich ontwikkelen benadrukt. In tegenstelling tot de meeste Europese landen zijn bevolkingsonderzoeken in de Verenigde Staten niet landelijk georganiseerd, maar op een individuele (opportunistische) basis. Om deelname in zo’n setting te verbeteren is een optimale benadering naar patiënten, en samenwerking tussen artsen en beleidsma-

kers vereist. Daarbij dient rekening gehouden te worden met het verschil in screeningsdeelname tussen verschillende etniciteiten, mate van verzekering, opleidingsniveau en leeftijd. Meer onderkenning van de gevolgen van een verlate diagnose, bij zowel medici als de patiëntpopulatie, in combinatie met een verbeterde kostendekking voor screeningprogramma's zal de deelname verbeteren en vervolgens de impact van darmkanker op de populatie verminderen.

Ondanks vele overeenkomsten zijn er grote verschillen tussen het colon en het rectum, die tot aanpassingen in het therapeutisch beleid hebben geleid. De richtlijnen voor vroeg (stadium I) en laat stadium (stadium IV) colon en rectum carcinomen verschillen daarentegen nauwelijks van elkaar. Stadium I tumoren worden in principe chirurgisch verwijderd, zonder bestraling of chemotherapie. Omdat de prognose voor patiënten met dit stadium tumoren heel gunstig is, is er weinig bekend over risico's op een recidief of uitzaaiingen. Door de opkomst van lokale resecties voor T1-T2 tumoren komt er steeds meer aandacht voor potentieel ongunstige factoren in dit stadium. Echter, tot op heden wordt een lokale excisie vooral in het rectum uitgevoerd en is er dus nog weinig bekend over risicofactoren in stadium I colontumoren. **Hoofdstuk 2** bespreekt factoren die een prognostische rol spelen in dit vroege stadium. Ondanks het volledig verwijderen van de tumor en het ontbreken van aanwijzingen voor lymfeklier-uitzaaiingen vonden we bij 2.7% van de patiënten een lokaal recidief of metastasen op langere termijn. De aanwezigheid van lymfovasculaire invasie bleek een belangrijke en onafhankelijke rol te spelen in de kans op terugkeer van de ziekte (HR=4.26), met name op afstandsmetastasen (HR=8.02). Dit suggereert een relatie tussen lymfovasculaire invasie en micrometastasen, die tot op heden nog niet gedetecteerd kunnen worden. Echter, het al dan niet behandelen van hoog-risico T1-T2 patiënten met adjuvante therapie is zeer twijfelachtig. Gezien het risico van overbehandeling en de daarmee samenhangende morbiditeit is postoperatieve therapie niet aan te bevelen. Wel zou gedacht kunnen worden aan een frequentere follow-up voor hoog-risico stadium I patiënten om late detectie van een recidief te voorkomen. Volgens deze studie geldt dit voor colon- en rectumtumoren. Het enige verschil tussen de twee tumor locaties waar men beducht op kan zijn is het eerder detecteren van een lokaal recidief bij rectum tumoren (mediane tijd: *Colontumoren:* 55.8 maanden versus *Rectumtumoren:* 16.2 maanden), wat het belang aantoont van een goede en volledige surveillance.

Aan de andere kant van het spectrum, wanneer de primaire tumor zich heeft verspreid naar andere organen, is de rol van chirurgie minder significant en adviseren de richtlijnen alleen een operatie bij patiënten met resectabele metastasen of patiënten met symptomen zoals darmobstructie, perforatie of bloedingen. Het uiteindelijke doel bij patiënten met laat stadium darmkanker is het verlengen van de overleving zonder de kwaliteit van leven daarbij te schaden. Een chirurgische interventie – met in dit stadium een hoge kans op complicaties – is daarom controversieel. **Hoofdstuk 3** beschrijft de impact van postoperatieve complicaties op overleving bij patiënten met gemetastaseerd colon- en rectumtumoren. In de groep waarbij de uitzaaiingen niet resectabel waren was een duidelijk negatief effect te zien van complicaties na de operatie, in het bijzonder bij respiratoire (HR=7.53) en cardiale klachten (HR=3.75). Bij patiënten met resectabele afstandsmetastasen werd de overleving niet beïnvloed door

postoperatieve complicaties, wat de indicatie voor een operatieve ingreep bij deze groep bekrachtigt. Omdat de verwachting is dat chemotherapeutische behandelingen blijven verbeteren, is een trend naar minder operatieve ingrepen bij stadium IV colorectaal carcinomen zeer waarschijnlijk. Om het voordeel van primaire tumorresectie in dit stadium te bevestigen of te weerleggen zijn meer gerandomiseerde studies nodig.

Het tweede deel van dit proefschrift focust zich uitsluitend op colontumoren. De diagnostische en therapeutische behandelingen voor dikke darmkanker blijven zich ontwikkelen. Daarnaast zijn we door een multidisciplinaire werkwijze nu beter in staat een gepersonaliseerd behandelplan op te stellen. Desalniettemin blijft een optimale chirurgische resectie de basis voor verbeterde langetermijnresultaten. Een van de belangrijkste veranderingen binnen de oncologische darmchirurgie is de ontwikkeling van de laparoscopische chirurgie. Tegenwoordig gaat de voorkeur dan ook uit naar een minimaal invasieve procedure, mits dat technisch haalbaar is en niet ten koste gaat van de oncologische uitkomsten. Voor de resectie van tumoren in het colon transversum (het horizontale deel van de dikke darm) wordt nog vaak gekozen voor een hemicolectomie, waarbij naast een deel van het horizontaal gelegen transversum ook het rechter of linker deel van de dikke darm wordt verwijderd. Het feit dat minimaal invasieve chirurgie tot op heden nog niet zo frequent wordt toegepast voor deze tumoren komt met name door de anatomische ligging van het transversum wat het een moeilijke ingreep maakt. Ook in deze studie, beschreven in **Hoofdstuk 4**, bleek een transversum colectomie (TC) minder vaak uitgevoerd dan de hemicolectomie, waarbij zelfs een dalende trend over de studieperiode werd waargenomen. Dit laatste ging hand in hand met de invoer van de laparoscopische benadering, die bij een hemicolectomie veel frequenter werd uitgevoerd. Dit resulteerde echter niet in betere postoperatieve uitkomsten in de hemicolectomie groep, wat wel de verwachting was bij meer laparoscopische procedures. De oncologische uitkomsten waren daarnaast vergelijkbaar (*geschatte 5-jaars overleving*: 78.8% versus 73.5%; *ziektevrije overleving*: 87.0% versus 90.1%). Een transversum colectomie lijkt dus een veilige oncologische ingreep voor de behandeling van kanker in het mid-transversum, met mogelijk zelfs betere uitkomsten dan een hemicolectomie mits er meer ingrepen laparoscopisch verricht kunnen worden.

Voor een succesvolle laparoscopische ingreep is ervaring nodig en moet het klinisch ook een haalbare ingreep zijn. In de loop der jaren is de ervaring gegroeid, wat resulteert in meer succesvol verlopen laparoscopieën. Desalniettemin blijft conversie naar een open procedure een probleem, wat blijkt uit recente studies waarin 17% van de oncologische laparoscopieën geconverteerd moeten worden. **Hoofstuk 5** analyseert de impact van conversie op het postoperatieve beloop en lange termijn uitkomsten door niet alleen te vergelijken met patiënten die een succesvolle laparoscopische ingreep ondergingen maar ook met patiënten waarbij een primaire open procedure werd uitgevoerd. De noodzaak tot conversie daalde van 11.6% in de eerste helft van de studie naar 7.7% in de tweede helft. Verschillende patiënt- en tumorgerelateerde factoren waren geassocieerd met conversie, waaronder het mannelijk geslacht, alcohol- en/of nicotinemisbruik, linkszijdige tumoren, verder gevorderd stadium van de darmkanker en pathologische risicofactoren (o.a. angio-invasie en peri-

neural invasie), maar daarnaast ook procedure-gerelateerde factoren (o.a. verklevingen en een multiviscerale resectie). Postoperatieve uitkomsten waren significant slechter na conversie in vergelijking met een succesvolle laparoscopische procedure, waaronder een langere ziekenhuisopname, meer complicaties tijdens opname (21.2% versus 41.5%) en meer heropnames (3.4% versus 11.5%). Op de langere termijn werden meer recidieven gezien (9.8% versus 21.4%) en een kortere overleving (*geschatte 5-jaars overleving*: 86.2% versus 70.5%). De uitkomsten bleven slechter na het corrigeren voor het stadium van de ziekte. Vergeleken met primaire open chirurgie ontwikkelden geconverteerde patiënten vaker intra-abdominale abcessen/naadlekkages (9.4% versus 2.7%) en postoperatieve wondinfecties (9.4% versus 3.2%). Onafhankelijk van patiëntkarakteristieken, stadium van de ziekte, postoperatieve complicaties en behandeling middels adjuvante therapie bleef conversie een voorspeller voor een slechtere overleving in vergelijking met laparoscopische chirurgie (HR=2.04). De uitkomsten waren daarentegen vergelijkbaar met primair open procedures (HR=0.84). In de multivariate analyse van ziektevrije overleving was chirurgische benadering geen onafhankelijke factor meer en waren enkel pathologische uitkomsten gerelateerd aan slechtere uitkomsten. Deze bevindingen zijn een aanvulling op de reeds bekende resultaten uit de literatuur. In deze studie wordt namelijk niet alleen vergeleken met een succesvol verlopen laparoscopische procedure maar ook met een geplande open ingreep. Dit laatste is van essentieel belang om te kunnen beoordelen of conversie daadwerkelijk gedefinieerd moet worden als een complicatie of slechts als een nadelige uitkomst zonder consequenties. Deze studie suggereert het laatste omdat behoudens een hogere incidentie van postoperatieve infecties zowel korte- als langetermijnresultaten vergelijkbaar waren tussen de conversie en de geplande open operatie. De langere operatieduur speelt naar alle waarschijnlijkheid een belangrijke rol in het ontwikkelen van infectieuze complicaties. Idealiter wordt dan ook het besluit tot converteren zo vroeg mogelijk gemaakt, om de operatieve duur te bekorten. Om dit te bewerkstelligen is ervaring van de chirurg noodzakelijk, zowel op technisch niveau als het vermogen om intra-operatief een (vroegtijdig) oordeel te vellen over de haalbaarheid van een laparoscopische ingreep.

Een andere factor die oncologische darmchirurgie ingewikkeld maakt is de noodzaak voor een multiviscerale resectie (LMR). LMR is geïndiceerd bij T4 tumoren om volledige tumorresectie te bewerkstelligen. Uit bestaande literatuur blijkt echter dat slechts 26-39% van de patiënten met pT4-tumoren een multiviscerale resectie ondergaan. In deze studie, beschreven in **hoofdstuk 6**, onderging 66% van de patiënten met pT4b (betrokkenheid van andere organen) een multiviscerale resectie en 21% van alle pT4a-tumoren (betrokkenheid van enkel het viscerale peritoneum). Gedurende de onderzoeksperiode was een duidelijke toename van LMR te zien. De belangrijkste reden om geen LMR uit te voeren bij patiënten met pT4b-tumoren was het bekende en moeilijke onderscheid tussen oncologische invasie en benigne reactieve verklevingen. Omdat het nog niet mogelijk is om dit onderscheid preoperatief te maken door middel van beeldvorming, is het enkel gebaseerd op het intra-operatieve oordeel van een chirurg. Eerder werd LMR geassocieerd met een hogere morbiditeit, wat enige terughoudendheid van de chirurg in de hand zou kunnen werken. In deze studie was het postoperatieve beloop echter gelijk, met uitzondering van meer bloedtransfusies bij patiënten die LMR ondergingen. De oncologische uitkomsten waren

daarnaast significant slechter wanneer LMR niet werd uitgevoerd in pT4-tumoren (*geschatte 5-jaars overleving*: 46.7% versus 70.0%, *5-jaars darmkanker-gerelateerde overleving*: 67,2% versus 89,6%) en bleek de overleving van T4-patienten die wel LMR hadden ondergaan vergelijkbaar met patiënten met een lager stadium darmkanker (T3-tumoren: 78.6%, 92.8%, respectievelijk). Ook na correctie voor pTN-stadium, adjuvante therapie en het behalen van complete tumorresectie (R0) was de prognose slechter voor T4-patienten die geen multiviscerale resectie hadden ondergaan (*totale overleving*: HR = 1.72, *darmkanker-gerelateerde overleving*: HR = 3.36). Een multiviscerale resectie lijkt dus een veilige ingreep met verbeterde langetermijnresultaten en is daarom ten zeerste aanbevolen bij twijfel over tumorinvasie.

Het laatste deel van dit proefschrift belicht de uitkomsten van het pathologisch onderzoek op het chirurgisch verwijderd weefsel. Stadiëring van de kanker vindt hoofdzakelijk plaats aan de hand van de TNM (Tumor, Node, Metastasis) classificatie. Huidige richtlijnen adviseren postoperatieve chemotherapie bij stadium III patiënten (als de lymfeklieren zijn aangedaan). Desalniettemin krijgen ongeveer 30% van patiënten zonder positieve lymfeklieren een recidief, wat de tekortkoming van de TNM-classificatie laat zien. Meerdere histopathologische risicofactoren buiten de TNM-stadiëring om zijn tot op heden beschreven. De huidige richtlijnen adviseren dan ook adjuvante therapie te overwegen bij patiënten met stadium II darmkanker en positieve snijranden, slecht gedifferentieerde tumoren, bij een presentatie met obstructie of perforatie, T4 tumoren of lymfangio-invasie. Echter is validatie van deze factoren vaak gedaan in cohorten waar zowel colon- als rectumpatiënten in zaten ondanks de bekende verschillen tussen beide tumoren.

Verschillen in klinische presentatie en pathologische kenmerken tussen verscheidene locaties binnen het colon worden beschreven in **hoofdstuk 7**. Rechtszijdige tumoren bleken groter en gecorreleerd met slechtere karakteristieken, waaronder een verder gevorderd stadium van de kanker, ongunstigere histopathologische resultaten (slechte differentiatie, microsatelliet instabiliteit en deficiënties in de mismatch repair eiwitten) en patiëntkenmerken (hogere leeftijd en ASA-score). Al deze componenten leidden, zoals verwacht, tot een slechtere prognose (*geschatte 5-jaars overleving stadium I-III*: rechtszijdig: 73,0%; transversum: 76,2%; linkszijdig: 80,8%). De darmkanker-gerelateerde overleving was echter vergelijkbaar (91,7%, 94,2%, 91,8%, respectievelijk). In tegenstelling tot resultaten van eerder gepubliceerde onderzoeken bleek tumorlocatie geen onafhankelijke prognostische waarde te hebben. Het grootste verschil met voorgaande studies was de mogelijkheid te corrigeren voor relevante covariabelen, zoals adjuvante therapie en pathologische factoren (slechte differentiatie, lymfangio-invasie en perineurale invasie). Deze studie benadrukt dus nogmaals het belang histopathologische factoren te integreren in de bestaande TNM-classificatie.

Een van de eerder genoemde prognostische biomarkers is angio-invasie. Angio-invasie, en in het bijzonder extramuraal (EMVI), is een histopathologisch kenmerk dat uitgebreid is onderzocht in rectumkanker maar zelden in colontumoren alleen. Dit is met name te wijten aan het feit dat bij rectumtumoren preoperatief een MRI wordt verricht waarop betrokkenheid van de omliggende bloedvaten goed te beoordelen is. Dit beeldvormend onderzoek wordt echter niet routinematig gebruikt voor de stadiëring van colontumoren. In **hoofdstuk 8** wordt de impact van an-

gio-invasie in colontumoren onderzocht. Bij het stijgen van het stadium van de ziekte werd ook meer angio-invasie gezien (21.1% in stadium II, 40.0% in stadium III). Daarnaast nam de detectie in haar geheel toe gedurende de studieperiode (gemiddeld 27.5% in de eerste helft naar 33.3% in de laatste). Ongeacht het stadium van de ziekte was EMVI gecorreleerd met andere risicofactoren, waaronder lymfovasculaire en perineurale invasie. Daarnaast zagen we een hoger percentage locoregionale recidieven en afstandsmetastasen met vervolgens een slechtere overleving bij EMVI positieve patiënten. Bij patiënten met enkel intramurale angio-invasie werden vergelijkbare resultaten gezien als bij patiënten met helemaal geen invasie. In lijn met de huidige richtlijnen kregen stadium II patiënten met EMVI positieve tumoren vaker adjuvante therapie (33.3% versus 16.3%). Na multivariate analyse bleef de ziektevrije periode en tijd tot overlijden korter bij patiënten met EMVI positieve tumoren. Daarnaast bleken stadium II patiënten met EMVI een slechtere prognose te hebben dan stadium III patiënten zonder EMVI, onafhankelijk van adjuvante therapie (HR=2.02). Als postoperatieve chemotherapie niet afdoende werkt is de vraag of een andere pre-of postoperatieve benadering nodig is voor patiënten met colontumoren en angio-invasie. De rol van neoadjuvante behandeling bij colontumoren lijkt tot op heden beperkt. Gezien het gunstige effect van deze therapie op EMVI positieve tumoren in het rectum, zou dit mogelijk vertaald kunnen worden naar EMVI positieve tumoren in het colon. Meer onderzoek is uiteraard nodig om hier een definitieve uitspraak over te kunnen doen.

Tot slot wordt in **hoofdstuk 9** de prognostische waarde van perineurale invasie (PNI) bij stadium I-III colontumoren bestudeerd. PNI werd gevonden in 18.8% van de patiënten, waarbij de incidentie hoger was in een later stadium van de ziekte. Daarnaast werd meer PNI in linkszijdige tumoren gevonden, wat mogelijk te verklaren is door het verschil in anatomie en het daarmee samenhangende uitgebreider weefselonderzoek bij distale tumoren en tevens de uitgebreide zenuwinnervatie in het kleine bekken. Dit bevestigt nogmaals het belang van het scheiden van colon- en rectumtumoren in prognostische onderzoek. Net als bij angio-invasie vonden we bij perineurale invasie ook een relatie met andere risicofactoren (T4 tumoren, positieve lymfeklieren, slecht gedifferentieerde tumoren en ook (lymf)angio-invasie). Kaplan-Meier curves toonden slechtere uitkomsten voor PNI positieve tumoren, zelfs wanneer PNI positieve stadium II tumoren vergeleken werden met PNI negatieve stadium III tumoren (*geschatte 5-jaars overleving:* 55.0% versus 71.0%). PNI bleek, onafhankelijk van andere risicofactoren, een 45% hoger risico op een ziektevrije overleving en een 52% hogere kans op darmkanker-gerelateerde sterfte te geven. De impact was echter minder groot dan de eerder beschreven risicofactoren, waaronder T4 tumoren, lymfeklier metastasen, darmobstructie en extramurale angio-invasie. Bij stadium III patiënten werd een evidente reductie van 77% op de totale mortaliteit gezien na behandeling met adjuvante chemotherapie. In stadium II patiënten was dit minder duidelijk. De kans op overlijden was twee keer zo groot bij PNI patiënten die geen postoperatieve behandeling kregen, maar de ziektevrije overleving en de kans op darmkanker-gerelateerde mortaliteit veranderde niet. Hoogstwaarschijnlijk is de hogere totale mortaliteit bij stadium II PNI patiënten niet direct toe te schrijven aan de perineural invasie, maar aan de groep patiënten die vanwege een hogere leeftijd en meer comorbiditeit niet in aanmerking

kwamen voor adjuvante behandeling. Onze resultaten steunen het advies om postoperatief te behandelen in lymfeklier negatieve, maar PNI positieve tumoren dus onvoldoende.

Het gebruik van adjuvante chemotherapie in stadium II darmkanker blijft controversieel. Tot nog toe is er slechts een marginaal voordeel van maximaal 5% op de totale overleving aangetoond. Ondanks de vele veranderingen en verbeteringen in diagnostiek en behandeling valt er zonder twijfel nog veel winst te behalen. Een van de factoren waar winst te behalen is, is het achterhalen van de exacte implicatie van de klinische en pathologische karakteristieken die in de huidige richtlijnen zijn opgenomen als risicofactoren. In dit proefschrift is de prognostische waarde van een aantal van deze factoren in het colon onderzocht, maar wordt de toegevoegde waarde van adjuvante behandeling niet bevestigd voor alle risicogroepen. De keuze om postoperatief aanvullende therapie te geven blijft tot op heden dus gebaseerd op de voorkeur van arts en patiënt. Dit benadrukt de behoefte aan een gedetailleerder risicoprofiel waarbij duidelijker wordt welke hoog-risico patiënten baat zullen hebben bij aanvullende therapie.

LIST OF PUBLICATIONS

PUBLICATIONS IN THIS THESIS, IN CHRONOLOGICAL ORDER OF ACCEPTANCE:

The Impact Of Postoperative Morbidity On Survival In Patients With Metastatic Colon And Rectal Cancer
Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL
Journal of Surgical Oncology 2019 Sep;120(3):460-472

Detrimental Impact Of Symptom-Detected Colorectal Cancer
Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL
Surgical Endoscopy 2019 April [Epub ahead of print]

Perineural Invasion Is A Prognostic But Not A Predictive Factor In Non-Metastatic Colon Cancer
Leijssen LGJ, Dinaux AM, Amri R, Taylor MS, Deshpande V, Bordeianou LG, Kunitake H, Berger DL
Diseases of the Colon & Rectum. 2019; 62(10): 1212-1221

Impact Of Intramural And Extramural Vascular Invasion On Stage II-III Colon Cancer Outcomes
Leijssen LGJ, Dinaux AM, Amri R, Taylor MS, Deshpande V, Bordeianou LG, Kunitake H, Berger DL
Journal of Surgical Oncology 2019 May;119(6):749-757

Do Stage I Colorectal Cancers With Lymphatic Invasion Require A Different Postoperative Approach?
Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL
Journal of Gastrointestinal Surgery. 2018;23(9):1884-1892

Is There A Drawback Of Converting A Laparoscopic Colectomy In Colon Cancer?
Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL
Journal of Surgical Research 2018 Dec;232:595-604

The Impact Of A Multivisceral Resection And Adjuvant Therapy In Locally Advanced Colon Cancer
Leijssen LGJ, Dinaux AM, Amri R, Kunitake H, Bordeianou LG, Berger DL
Journal of Gastrointestinal Surgery 2019 Feb;23(2):357-366

A Transverse Colectomy Is As Safe As An Extended Right Or Left Colectomy For Mid-Transverse Colon Cancer
Leijssen LGJ, Dinaux AM, Amri R, Kunitake H, Bordeianou LG, Berger DL
World Journal of Surgery 2018 Oct;42(10):3381-3389

Pathologic Factors Are More Important Than Tumor Location In Long-Term Survival In Colon Cancer
Leijssen LGJ, Dinaux AM, Kunitake H, Bordeianou LG, Berger DL
International Journal of Colorectal Disease 2018 Jun;33(6):709-717

PUBLICATIONS NOT FEATURED IN THIS THESIS:

Presence of Agrin in the Muscularis Mucosa Distinguishes Hyperplastic Polyps from Sessile Serrated Adenomas/Polyps
Rickelt S*, Condon C, Mana M, Whittaker CA, Pfirschke C, Roper J, Patil DT, Brown I, Mattia AR, Zukerberg L, Zhao Q, Chetty R, Lauwers G, Neyaz A, *Leijssen LGJ*, Boylan K, Yilmaz OH, Deshpande V* and Hynes RO*
Submitted

The influence of screening on outcomes of clinically locally advanced rectal cancer
Dinaux AM, *Leijssen LGJ*, Bordeianou LG, Kunitake H, Berger DL
Journal of Gastrointestinal Surgery 2018 Jun;22(6):1052-1058

Outcomes Of Persistent Lymph Node Involvement After Neoadjuvant Therapy For Stage Iii Rectal Cancer
Dinaux AM, *Leijssen LGJ*, Bordeianou LG, Kunitake H, Amri R, Berger DL
Surgery 2018 Apr;163(4):784-788

Effect Of Local Multivisceral Resection For Clinically Locally Advanced Rectal Cancer On Long-Term Outcomes
Dinaux AM, *Leijssen LGJ*, Bordeianou LG, Kunitake H, Berger DL
Journal of Surgical Oncology 2018 May;117(6):1323-1329

The Negative Impact Of Understaging Rectal Cancer Patients
Dinaux AM, *Leijssen LGJ*, Bordeianou LG, Kunitake H, Amri R, Berger DL
The American Journal of Surgery 2018 Jul;216(1):93-98

Rectal Cancer In Patients Under 50 Years Of Age
Dinaux AM, *Leijssen LGJ*, Bordeianou LG, Kunitake H, Berger DL
Journal of Gastrointestinal Surgery 2017 Nov;21(11):1898-1905

Colorectal Anastomotic Leak: Delay In Reintervention After False-Negative Computed Tomography Scan Is A Reason For Concern
Marres CCM, van de Ven AWH, *Leijssen LGJ*, Verbeek PCM, Bemelman WA, Buskens CJ
Techniques in Coloproctology 2017 Sep;21(9):709-714

Do packed red blood cell transfusions really worsen oncologic outcomes in colon cancer?
Amri R, Dinaux AM, *Leijssen LGJ*, Kunitake H, Bordeianou LG, Berger DL
Surgery 2017 Sep;162(3):586-591

PHD PORTFOLIO

1. PHD TRAINING

	YEAR	WORKLOAD (Hours/ECTS)
COURSES		
· Searching for Systematic Review, *AMC Amsterdam*	2016	0.1
· Practical Biostatistics, *AMC Amsterdam*	2016	1.0
· T3/T4: Translating Effective Interventions into Practice	2016	0.2
· Medical Device Development	2016	0.2
· Basic Biostatistics Course	2017	1.0
· Managing Yourself before Managing others	2017	0.1
· Comparative Effectiveness Research	2017	0.2
· Leadership Strategies for the Researcher	2017	0.2
· Introduction to Bioinformatics	2017	0.1
· Fundamentals of Clinical and Translational Research (FaCToR)	2017	1.0
· Certificate in Applied Biostatistics	2017-2018	6.0
SEMINARS, WORKSHOPS AND MASTER CLASSES		
· Biweekly Gastrointestinal Surgery meeting	2016-2018	2.0
· Weekly Journal Club, General Surgery	2016-2018	2.0
· Gut-Club meetings, *the Netherlands*	2016-2019	1.0
PRESENTATIONS		
ORAL PRESENTATIONS	2017	1.0
· American Society of Colon and Rectal Surgeons (2)	2017	0.5
· American College of Surgeons (1)	2018	1.0
· American Surgical Congress (2)	2018	0.5
· Digestive Disease Week (1)		
POSTER PRESENTATIONS	2017	0.5
· Digestive Disease Week (2)	2017	0.5
· American Society of Colon and Rectal Surgeons (1)	2017	1.0
· New England Surgical Society (2)	2018	1.0
· Digestive Disease Week (2)		
(INTER)NATIONAL CONFERENCES		
· New England Surgical Society *Boston, Bretton Woods*	2016	1.5
· Digestive Disease Week *Chicago, San Diego*	2017-2018	2.0
· American Society of Colon and Rectal Surgeons *Seattle*	2017	1.25
· American College of Surgeons *San Diego*	2017	1.25
· American Surgical Congress *Las Vegas, Jacksonville*	2017-2018	1.5
· NESS, Resident and Fellow Research Day *Waltham*	2017	0.25

2. TEACHING

	YEAR	WORKLOAD (Hours/ECTS)
TUTORING, MENTORING		
Mentoring new research students and new PhD students, introducing them to MGH	2017-2018	0.5
SUPERVISING		
Research fellow in Surgery: Yasmeen Qwaider	2019	1.0

3. PARAMETERS OF ESTEEM

	YEAR
Grants	
Prins Bernhard Cultuurfonds	2016-2018
Hendrik Muller's Fonds	2017
McKinsey Grant Amsterdam	2018

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Geachte leden van de promotiecommissie, geachte prof. dr. P.J. Tanis, prof. dr. E. Dekker, dr. J.B. Tuynman, prof. dr. F.P. Vleggaar, prof. dr. M.J. van de Vijver en prof. dr. C.J.A. Punt, hartelijk dank voor uw bereidheid om zitting te nemen in mijn promotiecommissie en om mijn proefschrift op haar wetenschappelijke waarde te beoordelen.

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Lieve Quirina, roommate! En de leukste uit de Honours-groep! Wat een geluk dat we van het begin tot het einde samenwoonden in Boston. Naast al het harde werk was jij gelukkig ook altijd in voor mooie trips en afleiding. Hiken, langlaufen en zelfs op de racefiets door Texas. Samen lachen en af en toe huilen om de gemiddelde Amerikaan. Wat een tijd. Casa Rossmore. You can't survive. But we did it.

Alexandra, I am so grateful that we ran into each other. Sunday mornings along the Charles, weekdays at the MIT track and always time for some proper pancakes or Tatte, as the perfect distraction from research. You are a gem of a friend. And I still think Europe would suit you well.

MIJN PARANIMFEN

Lieve Kiek, in de zomer van 2011 was het meteen raak. Sindsdien zijn er vrij weinig dagen geweest dat we geen contact hebben gehad, ook toen ik in Boston zat was je nooit te beroerd om te pas en te onpas te bellen. Jouw eerlijkheid, betrouwbaarheid, neurotische trekjes en ontzettend aanstekelijke lach zijn een zegen. Je bent een keiharde werker die uitdagingen niet uit de weg gaat. Ik ben benieuwd waar we op terug kunnen kijken als we later samen giechelend in het bejaardentehuis zitten.

Lieve Ka. Er zijn maar weinig mensen die zo ijzersterk zijn als jij. De afgelopen jaren heb je nog meer dan ooit laten zien waar je allemaal toe in staat bent, en we weten allemaal dat we nog veel meer kunnen verwachten. Je bent er altijd, in goede en minder goede tijden. En altijd even trots.

Fellows. Sophie, Lau, Ka en Ari. Ietwat bescheiden kwam ik in de derde klas toch nog op het Barlaeus terecht, waar de Cornelis Vrij-clan zich vrij duidelijk had gevestigd. Toch klikte het meteen en accepteerden jullie "het ghetto-kind uit Oost". Ik had me echt geen betere vriendinnen kunnen wensen, en nog steeds niet. Kogels vangen voor m'n matties. Ook nu in Zuid zou ik het blijven doen.

De Boys. Rik, Mau, Len en Just, goed dat jullie er zijn! Zo ver van Damsko af was het fijn om te weten dat er goed gezorgd wordt voor mijn vriendinnen. En ondertussen ook voor elkaar. Het Kwartier… Zolang het maar geen eigen leven gaat leiden.

Lieve Jaap en Marloes. De WP voelde vanaf het begin al meteen als een tweede thuis, en dat is alleen maar sterker geworden. Grootse plannen, ideeën en ambities kan ik altijd met jullie bespreken. En of het nu slaagt of niet, alles mag gevierd worden. Jullie hebben me laten zien dat er meer is dan een scalpel en een scoop, zonder mijn ambities in het ziekenhuis te veranderen. Wat een geluk om zulke lieve schoonouders te hebben!

Katrien, Beckett en Dorothy. Na een aantal jaren zijn we dan nu eindelijk allemaal in Amsterdam. En dan ook nog op loopafstand van elkaar. Ik heb ontzettend veel bewondering voor hoe jullie het allemaal doen. Tijdrovende banen, reizen, en ondertussen het allerliefste nichtje van de wereld grootbrengen. Ik ben ontzettend blij dat we nu zo dichtbij elkaar zijn, want het is altijd fijn om bij jullie te zijn.

Zusjes, lieve zusjes. Hoe is het toch mogelijk dat pap en mam drie totaal verschillende dochters op de wereld hebben gezet? Soms geeft dat wat wrijving, maar het is vooral keihard lachen met jullie. Juulz, lieve Juul, wat gaat het worden? Hou je de stethoscoop om, of ga je voor het hoge torentje? Welke plek je ook kiest, overal zullen ze blij zijn dat je voor hen hebt gekozen. En Pollewop, lieve Paola, de wereld ligt aan je voeten. Met zo'n groot hart en ijzersterk doorzettingsvermogen kom je overal. Ik ben apetrots op jullie. Het is ook maar goed dat jullie niet meer zoveel naar je oudste zus luisteren. Want ik moet eerlijk toegeven dat ik misschien niet altijd gelijk heb. Misschien, niet altijd, maar meestal wel.

Lieve pap en mam, waar moet ik beginnen. Jullie hebben ons altijd in alles gesteund, lieten ons altijd doen waar wij zelf in geloofden. En keken dan, ongeacht het resultaat, vol trots toe. Jullie hebben mij geleerd mijn grenzen op te zoeken en laten me zien wanneer het mooi is geweest. Ik kan niet vaak genoeg zeggen dat ik me geen betere en lievere ouders had durven wensen.

ABOUT THE AUTHOR

Lisa Godelieve Josephine was born on August 21st 1990 in Amsterdam, the Netherlands. In 2008, she graduated from high school at the Barlaeus Gymnasium and started medical school at the University of Amsterdam the next year. At the same time, she continued her former rowing career at the Amsterdam Rowing Club Nereus, winning a silver medal at the World Championships under 23 in 2012. A new adventure awaited and in 2013 she started with her clinical internships. Her enthusiasm for colorectal cancer evolved over her rotations and after her final rotation in Gastroenterology and Hepatology in the OLVG West Hospital she got connected to a colorectal cancer research group in Boston, Massachusetts. After obtaining her medical degree (*cum laude*) in 2016 Lieve started her PhD project in Boston. The research presented in this thesis was conducted under the supervision of Dr. D.L. Berger and encouraged by Prof. dr. W.A. Bemelman and Prof. dr. P. Fockens. After two years in the United States, Lieve returned to the Netherlands to gain more clinical experiences. In October 2018, she started as a resident not in training in Internal Medicine at the Onze Lieve Vrouwe Gasthuis West (dr. Y.F.C. Smets and dr. M.C. Weijmer) in Amsterdam. From January 2020 on, she will start her training in Gastroenterology and Hepatology at the Academic Medical Center Amsterdam (Prof. dr. K.M.A.J. Tytgat and Prof. dr. G.R.A.M. D'Haens). Lieve lives together with her boyfriend Philip in Amsterdam.