https://doi.org/10.1016/j.hpb.2023.10.004 HPB

ORIGINAL ARTICLE

A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer

Lynn E. Nooijen[1,2], Lizzel van der Snee[2,3], Britte ten Haaft[2,3], Geert Kazemier[1,2], Heinz-Josef Klümpen[2,4], John Bridgewater[5], John Primrose[6] & Joris Erdmann[1,2]

[1]Amsterdam UMC, Location Vrije Universiteit Amsterdam, Department of Surgery, [2]Cancer Center Amsterdam, Cancer Treatment and Quality of Life, [3]Amsterdam UMC, Location University of Amsterdam, Department of Surgery, [4]Amsterdam UMC, Location University of Amsterdam, Department of Medical Oncology, Amsterdam, the Netherlands, [5]UCL Cancer Institute, Department of Medical Oncology, London, United Kingdom, and [6]University of Southampton, Department of Surgery, Southampton, United Kingdom

Abstract

Background: There is currently no evidence to support structured use of imaging or biomarkers during follow-up of patients after curative resection of biliary tract cancer (BTC). Besides, the influence of early detection of recurrence and subsequent start of palliative chemotherapy on overall survival remains unknown. The aim of this study is to describe and compare the results of two follow-up strategies.

Methods: This retrospective multicenter cohort study compared patients from the Amsterdam UMC undergoing pragmatic clinical follow-up, to patients from the observational cohort of the BILCAP study undergoing structured follow-up. Primary outcome was overall survival.

Results: A total of 315 patients were included n=91 pragmatic, n=224 structured follow-up). At median follow-up of 56.9 months, 189 (60%) patients were diagnosed with recurrence. After recurrence, more patients received palliative (chemo) therapy in the structured group (43% vs 75%, P<0.001). Median overall survival was lower in the pragmatic group (27.7 vs 39.1 months, P=0.003). Median overall survival of patients who actually received chemotherapy was comparable (27.2 vs 27.7 months, P=0.574).

Conclusion: This study describes the results of two follow-up strategies. Although these groups are biased, it is noted that after pragmatic follow-up fewer patients received palliative chemotherapy but that those who actually received chemotherapy had similar overall survival compared to patients undergoing structured follow-up.

Received 12 June 2023; accepted 1 October 2023

Correspondence

J.I. Erdmann, Department of surgery, Amsterdam UMC, Location VUMC, De Boelelaan 1118, 1118 HV Amsterdam, the Netherlands. E-mail: j.i.erdmann@amsterdamumc.nl

Introduction

Resection, sometimes in combination with adjuvant chemotherapy, is currently the only curative treatment option for biliary tract carcinoma (BTC). Techniques of resection depend on the primary site of BTC and usually entails pancreatoduodenectomy for distal cholangiocarcinoma (dCCA), (extended) hemihepatectomy for intrahepatic (iCCA) and perihilar cholangiocarcinoma (pCCA), and cholecystectomy including gallbladder bed resection for gallbladder cancer (GBC). These extensive resections frequently result in a 5-year overall survival (OS) rate of less than 50% (varying per primary site), mostly as a result of high recurrence rates.[1–8] Most common site of recurrence is local regional or in the liver.[3,6,9,10] Factors predicting recurrence include poor tumor differentiation, large tumor size, non-radical resection margin, positive lymph node involvement, high tumor stages, perineural growth, and lymph-angioinvasion.[3–5,7,11–15]

According to the ESMO and Medscape clinical practice guidelines, follow-up should include quarterly visits with biochemical analysis and radiological imaging for the first two years, not only to identify recurrence but also to detect post-

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

operative complications.[16,17] However, these guideline recommendations are not supported by clinical studies or other high level evidence.[13] For this reason the Dutch cholangio- and gallbladder carcinoma guideline committee recommends a pragmatic clinical follow-up strategy, and advises not to use radiological imaging or biochemical analysis, including tumor markers, during routine follow-up.[18]

It is justified to use a pragmatic clinical follow-up given the uncertainty of an improvement of outcome when using structured clinical, biochemical and radiological follow-up. However, most patients with recurrence are often asymptomatic.[3,13,19] In these cases structured follow-up may lead to early detection of recurrence and subsequently earlier start of palliative chemotherapy and potentially improve OS.

Structured follow-up has been investigated in studies concerning esophageal and colorectal cancer. These studies showed improved OS for patients receiving intensive follow-up, especially for patients with asymptomatic recurrences.[20–24] For colorectal metastasis this is probably due to the local treatment options available for metastatic disease. Unfortunately, clinical and biological features of this disease make extrapolation of these results to BTC impossible. Conversely, for esophageal cancer there are no local treatment options for recurrent or metastatic disease but it still appeared to benefit from structured follow-up with imaging. An important analogy compared to patients with BTC is that when these patients become symptomatic, often because of i.e. biliary or upper gastro-intestinal obstruction, the performance status often quickly deteriorates. This can delay the start of treatment or ultimately lead to the opportunity for palliative chemotherapy being missed completely.

This study aims to describe and compare the results of pragmatic clinical follow-up in a large Hepato-Pancreato-Biliary unit to structured follow-up, using imaging and biomarkers, in a clinical trial in patients with BTC following surgery with curative intent.

Methods

Patients

A multicenter, retrospective cohort study was performed including patients with BTC after resection with curative intent. Patients were added from two cohorts, patients with pragmatic follow-up from the Amsterdam UMC and structured follow-up from the observational cohort of the BILCAP study.[19] The Institutional Medical Ethics committee of Amsterdam UMC, location VUmc and AMC waived the need for an ethical approval of this study (W21_010, 2021.0359).

The BILCAP study was a phase III study comparing adjuvant capecitabine with observation in patients with BTC following curative intent resection. All patients within the BILCAP study underwent follow-up according to the BILCAP study protocol, including CT scans every 3 months in year 1 and every 6 months in year 2 and annually thereafter. This also included biochemical analysis every 3 months in year 1 and every 6 months in year 2. Only patients from the observational cohort were included in this study.

The Amsterdam UMC cohort, comprises the former VUmc and AMC hospitals, consisted of patients who received a resection for BTC between January 2016 and February 2020 who were identified from the following prospective registries: Dutch Hepato Biliary Audit (DHBA) and the Dutch Pancreatic Cancer Audit (DPCA). Informed consent was obtained using the opt-out method. These patients received pragmatic clinical follow-up according to the Dutch guidelines without routine imaging or biochemical analysis.

Patients were excluded if they had R2 residual disease, died within the first 90 post-operative days, had benign disease, metastatic, or unresectable tumors, or had unknown recurrence status. Patients participating in other (prospective) studies including standardized biochemical and/or radiological surveillance, were excluded (e.g. ACTICCA-1 trial,[25] LEOPARD-2 trial,[26] SIRCCA trial [NCT02807181], ORANGE SEGMENTS trial [NCT03270917], and PREOPANC-2 trial[27]).

Outcomes

Primary outcome was overall survival (OS). Secondary outcome was recurrence free survival (RFS).

Statistical analysis

Data were presented as mean ± standard deviation (SD) or as median and interquartile range when appropriate. OS was defined as months after diagnosis to death or last follow-up using the Kaplan–Meier method. RFS was defined as months after diagnosis to recurrence or lost to follow-up using the Kaplan–Meier method. Survival curves were compared using the log-rank test. The reversed Kaplan–Meier based method was used to calculate median follow-up. Groups were compared using chi-square tests for proportions, Mann–Whitney U tests for medians, and independent sample T tests for means. Time dependent data from the BILCAP study was made comparable to Amsterdam UMC data by adding the time from diagnosis to randomization to all time dependent data points, which were only available in days. Conversion from days to months was based on an averaged conversion factor of 30.4167. Propensity score matching was used to balance baseline differences between the two groups. Variables were selected a priori and included age (<65 year/≥65 years, lymph node status (N+/N0) and resection margin (R1/R0). Nearest neighbor matching without replacement was performed, with a Caliper width of 0.1. A two-sided *P*-value of <0.05 was considered to indicate statistical significance. Data were analyzed using IBM SPSS statistics, version 25.0 (IBM Corp). Survival curves were

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

displayed using GraphPad Prism 8 (GraphPad Inc, La Jolla, California, USA).

Results

Baseline characteristics

Of the Amsterdam UMC cohort, a total of 314 patients with BTC met the inclusion criteria. From these, 223 patients were excluded because of study participation with structured follow-up, leaving 91 patients for inclusion. A flow diagram of the Amsterdam UMC patient selection is presented in Supplementary Fig. 1.

Of the BILCAP study cohort, a total of 224 patients from the observational arm were included. This resulted in a total group of 315 patients. Of these patients 162 (51%) were male. The median age at diagnosis was 65 (55–70) years. Distal cholangiocarcinoma was the most common type of BTC (n = 118, 38%) and pancreatoduodenectomy was the most performed type of surgery (n = 116, 37%). Time from diagnosis to surgery was 44 (32–68) days. In 198 (63%) patients the resection margin was negative at final pathology report. Lymph nodes were negative in 158 (50%) patients and the majority of the patients had a moderately differentiated tumor (n = 171, 54%). All baseline characteristic are displayed in Table 1.

Propensity score matching

After propensity score matching, two groups of 85 patients were obtained. After matching, age, differentiation grade, tumor size and first post-operative CA19.9 measurment were comparable between both groups. Only ECOG performance score, resection type and first post-operative bilirubin levels were significantly different between both groups. All baseline characteristic after matching are also displayed in Table 1.

Recurrence

In the total study cohort of 315 patients, 189 (60%) were diagnosed with recurrence during follow-up, 46 patients (51%) in the pragmatic follow-up group and 143 patients (64%) in the structured follow-up group, $P = 0.029$. In the propensity matched cohort, 95 (56%) out of the 170 patients developed recurrence, 45 patients (53%) in the pragmatic follow-up group and 50 patients (59%) in the structured follow-up group, $P = 0.440$.

Local recurrence was found in 82 patients (43%). Distant recurrence was found in 102 patients (54%). An increase in CA19.9 level, with a median level of 126 U/ml (44–239) and a median accompanied low bilirubin level of 9 μmol/L (6–13.5), indicated the first sign of recurrence in 73 (39%) of the 189 patients. This included 4 patients (9%) in the pragmatic follow-up group and 69 patients (48%) in the structured follow-up group. In 61 patients (32%) recurrence was first suspected on imaging. This included 8 patients (17%) in the pragmatic follow-up group and 53 patients (37%) in the structured follow-up group. In 34 patients from the pragmatic follow-up group (18%), the first sign of recurrence were clinical complaints (e.g. pain, cholangitis, weight loss), Table 2.

In the group without recurrence (n = 126), 25 (20%) patients showed an increase of their CA19.9 levels at one point during follow-up. In one patient this was related to an increase of the bilirubin level. In 20 out of the 25 patients a CT scan was perfomed, which was negative for recurrent disease in all patients.

The median RFS was 21.5 months (95% CI 17.3–25.8). Median RFS was similar for both follow-up groups; 24.1 months (95% CI 20.0–28.2) pragmatic follow-up and 20.4 months (95% CI 14.9–25.8) structured follow-up ($P = 0.897$). In the propensity matched cohort, this remained similar; 22.7 months (95% CI 18.3–27.0) pragmatic follow-up and 25.1 months (95% CI 9.2–41.0) structured follow-up ($P = 0.393$). The accompanying Kaplan–Meier curves are displayed in Fig. 1.

Overall survival

Of the 315 patients, 186 had died within the follow-up period. Median follow-up of patients alive at last medical visit was 56.9 months (95% CI 48.2–65.6).

From the 189 patients with recurrence, 127 (67%) patients were treated with palliative (chemo) therapy. This included 20 patients (43%) in the pragmatic follow-up group and 107 patients (75%) in the structured follow-up group, $P < 0.001$. From the total group, 59 patients did not receive palliative (chemo) therapy. This included 23 patients (50%) in the pragmatic follow-up and 36 patients (25%) in the structured follow-up group. For three patients this information was unknown. Impaired performance status was the reason for not receiving palliative (chemo) therapy in 18 (78%) out of the 23 patients of the pragmatic follow-up group, for patients with structured follow-up this was unknown.

In the propensity matched cohort, 53 (56%) out of the 95 patients were treated with palliative (chemo) therapy. This included 19 patients (42%) in the pragmatic follow-up group and 34 (68%) patients in the structured follow-up group.

Overall, the median and 5 year OS was 34.6 months (95% CI 30.2–39.0) and 32%. The median and 5 year OS divided for follow-up method was 27.7 months (95% CI 22.0–33.4) and 14% for the pragmatic follow-up group and 39.1 months (95% CI 32.7–45.4) and 36% for the structured follow-up group ($P = 0.003$).

In the propensity matched cohort, this difference remained; the median and 5 year OS divided for follow-up method was 26.3 months (95% CI 21.9–30.6) and 13% pragmatic follow-up and 40.8 months (95% CI 27.1–54.5) and 43% structured follow-up ($P = 0.003$). The accompanying Kaplan–Meier curves are displayed in Fig. 2.

Palliative therapy after recurrence

For the patients who received palliative (chemo) therapy after recurrence (n = 127), the median and 5 year OS was 27.2 months (95% CI 23.0–31.3) and 7%. The median and 5 year OS was 27.7 months (95% CI 19.8–35.6) and 0% for the pragmatic follow-up group and 27.2 months (95% CI 22.6–31.7) and 8% for the structured follow-up group ($P = 0.574$).

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

Table 1 Baseline characteristics before and after matching.

	Total	Before matching		*P* value[a]	After matching		*P* value[a]
		Amsterdam UMC Pragmatic follow-up	BILCAP Structured follow-up		Amsterdam UMC Pragmatic follow-up	BILCAP Structured follow-up	
	n = 315	n = 91	n = 224		n = 85	n = 85	
Age (median)	65 (55–70)	70 (61–75)	64 (55–69)	**<0.001**	70 (61–74.5)	69 (64–72)	0.787
Male (%)	162 (51%)	49 (54%)	113 (50%)	0.584	46 (54%)	40 (47%)	0.357
Primary tumor site				0.135			0.500
Gallbladder cancer	47 (15%)	7 (8%)	40 (18%)		6 (7%)	12 (14%)	
Intrahepatic cholangiocarcinoma	61 (19%)	20 (22%)	41 (18%)		15 (18%)	13 (15%)	
Perihilar cholangiocarcinoma	89 (28%)	26 (29%)	63 (28%)		26 (31%)	26 (31%)	
Distal cholangiocarcinoma	118 (38%)	38 (42%)	80 (36%)		38 (45%)	34 (40%)	
ECOG				**<0.001**			**<0.001**
0	134 (43%)	33 (36%)	101 (45%)		29 (52%)	34 (40%)	
1	138 (44%)	22 (24%)	116 (52%)		20 (36%)	51 (60%)	
2	14 (4%)	7 (8%)	7 (3%)		7 (13%)	0	
unknown	29 (9%)	29 (32%)	0		0	0	
Baseline Bilirubin µmol/L[b]	8 (5–11)	9 (6–22)	8 (5–11)	0.116	9 (6–22)	7 (5–10)	**0.023**
Baseline CA19.9 U/ml[b]	18 (11–41)	23 (11–178)	17 (10–35)	**0.040**	25 (11–240)	20 (10–37)	0.114
Tumorsize (mm)	26 (20–50)	34 (20–68)	25 (20–44)	**0.006**	30 (20–69)	26 (18–49)	0.052
Time to surgery (days)[c]	44 (32–68)	44 (29–68)	45 (33–68)	0.786	45 (31–69)	46 (35–65)	0.688
Resection type				**<0.001**			**<0.001**
Right (extended) hemihepatectomy	50 (16%)	22 (24%)	28 (13%)		22 (26%)	12 (14%)	
Left (extended) hemihepatectomy	44 (14%)	16 (18%)	28 (13%)		13 (15%)	8 (9%)	
Minor liverresection	47 (15%)	7 (8%)	40 (18%)		5 (6%)	12 (14%)	
External bile duct resection only	1 (<1%)	1 (1%)	0		1 (1%)	0	
Hepatic bed (including cholecystectomy)	28 (9%)	8 (9%)	20 (9%)		7 (8%)	9 (11%)	
Pancreatoduodenectomy	116 (37%)	37 (41%)	79 (35%)		37 (44%)	30 (35%)	
Unknown	29 (9%)	0	29 (13%)		0	14 (17%)	
Resection margin				0.837			1.000
R0	198 (63%)	58 (64%)	140 (62.5%)		53 (62%)	53 (62%)	
R1	117 (37%)	33 (36%)	84 (37.5%)		32 (38%)	32 (38%)	
T stage (extent of the tumor)				0.428			0.754
T1	27 (9%)	11 (12%)	16 (7%)		9 (11%)	7 (8%)	
T2	109 (35%)	27 (30%)	82 (37%)		27 32%)	33 (39%)	
T3	156 (50%)	44 (48%)	112 (50%)		44 (52%)	39 (46%)	
T4	13 (4%)	4 (4%)	9 (4%)		4 (5%)	4 (5%)	
Unknown	10 (3%)	5 (6%)	5 (2%)		1 (1%)	2 (2%)	
Lymph nodes				0.511			1.000
N0	158 (50%)	50 (55%)	108 (48%)		50 (59%)	50 (59%)	
N+	137 (44%)	35 (39%)	102 (46%)		35 (41%)	35 (41%)	
Unknown	20 (6%)	6 (7%)	14 (6%)		0	0	
Differentiation grade				**0.032**			0.977
G1: well differentiated	47 (15%)	11 (12%)	36 (16%)		11 (13%)	11 (13%)	
G2: moderately differentiated	171 (54%)	51 (56%)	120 (54%)		47 (55%)	51 (60%)	

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

Table 1 (*continued*)

	Total	Before matching		*P* value[a]	After matching		*P* value[a]
		Amsterdam UMC Pragmatic follow-up	BILCAP Structured follow-up		Amsterdam UMC Pragmatic follow-up	BILCAP Structured follow-up	
	n = 315	n = 91	n = 224		n = 85	n = 85	
G3: poorly differentiated	72 (23%)	16 (18%)	56 (25%)		16 (19%)	18 (21%)	
Unknown	25 (8%)	13 (14%)	12 (5%)		11 (13%)	5 (6%)	

Bold values: statistically significant.
[a] *P*-values based on complete case analysis unless unknown is displayed
[b] First measurement post-operative.
[c] Only available in 74/224 patients of the BILCAP data.

This was similar in the propensity matched cohort (n = 53), the median and 5 year OS was 26.3 months (95% CI 18.7–33.8) and 0% pragmatic follow-up and 25.8 months (95% CI 20.2–31.5) and 11% structured follow-up, (P = 0.705). The accompanying Kaplan–Meier curves are displayed in Fig. 3.

Discussion

This study is the first retrospective cohort study comparing two follow-up strategies in patients with resected BTC and found that patients undergoing structured follow-up have a favorable OS compared to patients with pragmatic follow-up (39.1 months

Table 2 Follow-up characteristics

	Total	Amsterdam UMC Pragmatic follow-up	BILCAP Structured follow-up	*P* value[a]
	n = 315	n = 91	n = 224	
Number of follow-up visits (median)	8 (4–13)	9 (5–15)	7 (3–13)	**0.032**
Number of follow-up visits (excluding non-regular visits)	6 (3–11)	4 (3–7)	7 (3–13)	**<0.001**
Number of follow-up scans (median)	3 (1–5)	2 (1–4)	3 (1–5)	0.058
Number of follow-up CA19.9 determinations (median)	2 (1–5)	1 (0–2)	3 (1–6)	**<0.001**
Recurrence	189 (60%)	46 (51%)	143 (64%)	**0.029**
First sign of recurrence				**<0.001**
Complaints	34 (18%)	34 (74%)	0	
CA19.9 (U/mL)	73 (39%)	4 (9%)	69 (48%)	
Imaging	61 (32%)	8 (17%)	53 (37%)	
Unknown	21 (11%)	0	21 (15%)	
CA19.9 level at recurrence[c] (U/mL)	126 (44–239)	272 (77–1086)	126 (42–235)	0.445
Location of recurrence				**0.002**
Local recurrence	82 (43%)	10 (22%)	72 (50%)	
Distant	102 (54%)	34 (74%)	68 (48%)	
unknown	5 (3%)	2 (4%)	3 (2%)	
Palliative (chemo) therapy	127 (67%)	20 (43%)	107 (75%)	**<0.001**
Type of therapy				**0.020**
Chemotherapy	87 (69%)	13 (65%)	74 (69%)	
Radiotherapy	5 (4%)	3 (15%)	2 (2%)	
Surgery	1 (<1%)	1 (5%)	0	
Multiple[b]	32 (25%)	3 (15%)	29 (27%)	
Other	2 (2%)	0	2 (2%)	

Bold values: statistically significant.
[a] *P*-values based on complete case analysis unless unknown is displayed.
[b] Combination of surgery/radiotherapy/chemotherapy.
[c] If CA19.9 was the first sign of recurrence.

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

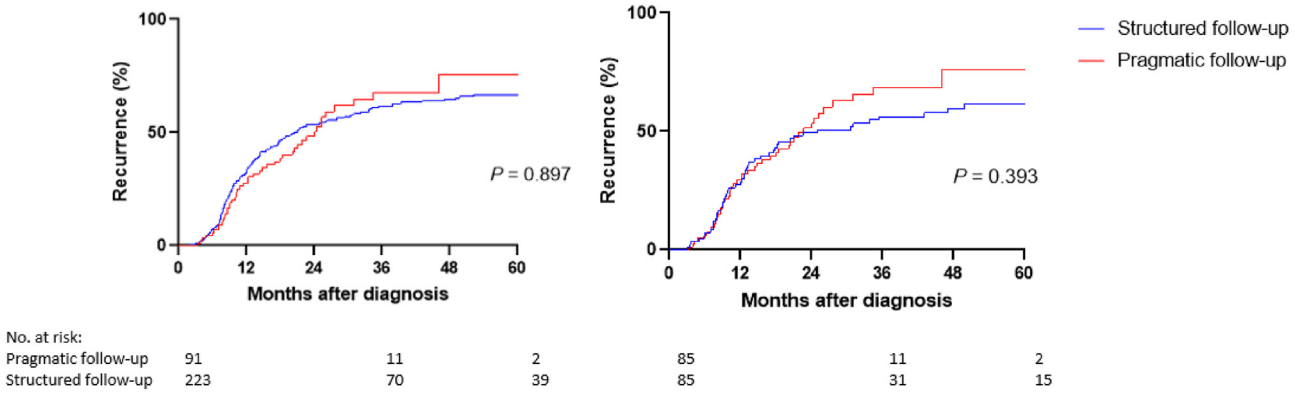

Figure 1 (Left): recurrence free survival displayed for both groups. The median RFS for the pragmatic follow-up group was 24.1 months (95% CI 20.0–28.2) and 20.4 months (95% CI 14.9–25.8) for the structured follow-up group (P = 0.897). (right): Recurrence free survival of the propensity matched cohort. The median RFS for the pragmatic follow-up group was 22.7 months (95% CI 18.3–27.0) and 25.1 months (95% CI 9.2–41.0) for the structured follow-up group (P = 0.393)

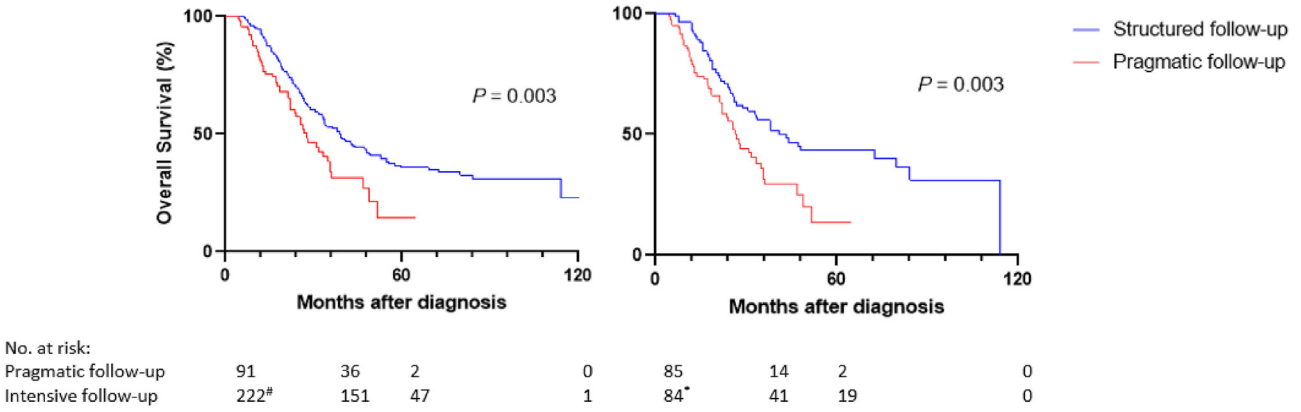

Figure 2 (Left): overall survival displayed for both groups. The median and 5 year OS divided for follow-up method was 27.7 months (95% CI 22.0–33.4) and 14% for the pragmatic follow-up group and 39.1 months (95% CI 32.7–45.4) and 36% for the structured follow-up group (P = 0.003). #For two patients time to diagnosis and therefore total time from diagnosis to death or last follow-up was not available. (right): Overall survival of the propensity matched cohort. The median and 5 year OS divided for follow-up method was 6.3 months (95% CI 21.9–30.6) and 13% for the pragmatic follow-up group and 40.8 months (95% CI 27.1–54.5) and 43% for the structured follow-up group (P = 0.003). *For one patient time to diagnosis and therefore total time from diagnosis to death or last follow-up was not available

structured vs 27.7 months pragmatic). After propensity score matching, this observation persisted. Although this comparison is not perfect, given the obvious bias and selection issues, the findings provide some interesting observations.

In total, 189 (60%) patients were diagnosed with recurrence of whom 127 where treated with palliative (chemo) therapy. Interestingly, this included 107 (75%) patients from the structured and only 20 (43%) patients from the pragmatic follow-up group. Median OS of patients who actually received palliative (chemo) therapy was comparable in both groups, this remained after propensity score matching. These findings could lead to the question if perhaps early detection of recurrence is important for the OS in patients with BTC. Early detection of recurrence could result in a timely start of chemotherapy maybe resulting in increased OS. Clinical detection of recurrence often includes jaundice, cholangitis and peritoneal dissemination with ascites and/or bowel obstruction. These challenging clinical situations frequently occur in individuals who are already vulnerable. Perhaps structured follow-up leads to early detection and start of palliative (chemo) therapy before clinical performance deteriorates.

Recently, an international multicenter study exploring the impact of intensive structured follow-up after esophageal cancer surgery on oncological and quality of life outcomes was

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

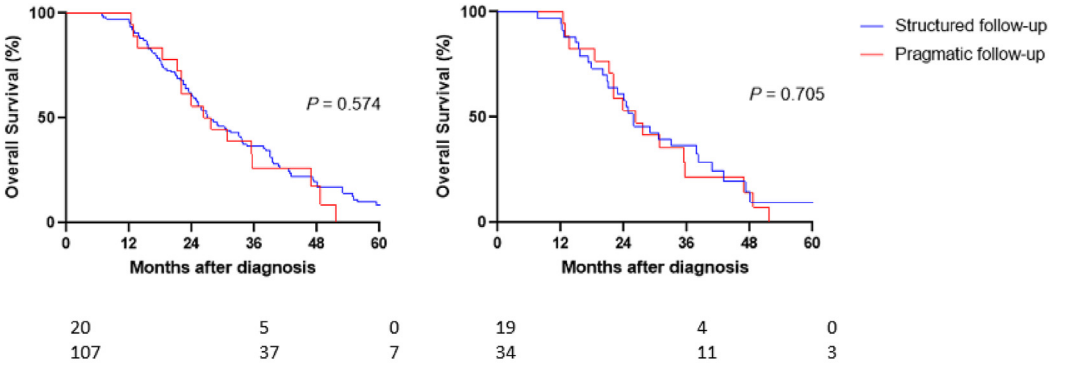

Figure 3 (Left): overall survival of patients who received palliative (chemo) therapy after recurrence displayed for both groups. The median and 5 year OS was 27.7 months (95% CI 19.8–35.6) and 0% for the pragmatic follow-up group and 27.2 months (95% CI 22.6–31.7) and 8% for the structured follow-up group (P = 0.574). (Right): overall survival for the propensity matched cohort (n = 53), the median and 5 year OS was 26.3 months (95% CI 18.7–33.8) and 0% for the pragmatic follow-up group and 25.8 months (95% CI 20.2–31.5) and 11% for the structured follow-up group (P = 0.705)

published. Results of the ENSURE study (NCT03461341), showed that structured follow-up was associated with reduced symptomatic recurrence and increased tumor-directed therapy, with a clear OS benefit.[20]

The difference in OS between both groups in the current study cannot easily be explained by differences in tumor biology, as the tumor stage (T), lymph node stage (N), and differentiation grade are comparable between groups and in the propensity matched cohorts. The only difference between groups was the high ECOG score in the pragmatic follow-up group which may have had an effect on the outcome. Besides it is known that participation in a clinical trial improves patient outcomes, which can mostly be attributed to indirect positive effects.[28,29]

It can be argued that pragmatic follow-up has several clear advantages compared to structured follow-up. As mentioned before, patients with recurrence are most often asymptomatic.[3,13,19] Many oncologists will be reluctant to give palliative chemotherapy to asymptomatic patients, simply because there are no complaints to palliate and chemotherapy will merely decrease quality of life (QOL) with only a modest benefit for OS.[30] This makes structured follow-up futile as long as there are no complaints amenable to palliative chemotherapy or any proof that starting early may improve OS or QOL.

Currently, imaging using Computed Tomography (CT) may be the most reliable follow-up method as biochemical follow-up using Carbohydrate Antigen 19.9 (CA19.9), a serum tumor marker,[31] is subjected to several limitations. Patients may experience elevated CA19.9 levels without signs of recurrence and about 10% of patients are unable to synthesize CA19.9 resulting in potential false negative outcomes.[32] Results can also be false positive for other reasons, for example an increase of CA19.9 can be the result of cholestasis.[1,33–35] Additionally, due to low disease activity and difficult reachable locations, histological confirmation of recurrence can be challanging. This causes a delay in confirmation of recurrence and consequently start of palliative chemotherapy.

This study was not able to point to the best method of follow-up. Frequent measuring of CA19.9 seems straightforward and inexpensive. However, as shown in this study, high CA19.9 levels do not always accurately indicate recurrence. In the group without recurrence, 25 patients showed an increased CA19.9 level at one point during follow-up. This led to a negative CT scan in 20 patients. It is unknown why some patients have elevated levels without other signs of recurrence.[34]

The findings of this study should be interpreted with caution due to the fact that this is a retrospective cohort study including patients from a clinical trial and patients who are treated with pragmatic clinical practice. In an attempt to compensate for bias and selection, a propensity score matched analysis was performed. Nevertheless, selection bias has probably influenced the composition of the included groups. For the Amsterdam UMC group for example, only 91 patients could be included. Most of the excluded patients participated in the ACTICCA-1 trial. Patients who were not included in the ACTICCA-1 study either waived the study or may have been excluded because of to an impaired post-operative functional status. On the other hand, this study is based on the only available data simply because there have been no trials or prospective studies on this subject for BTC.

This study shows several interesting observations which can be used in a future randomized controlled trial comparing pragmatic and structured follow-up. Looking slightly further, it could be interesting to stratify patients in this future trial for positive lymph nodes. It is known from earlier studies that patients with positive lymph nodes more often show early recurrence.[10,36] This might lead to a different strategy for those patients. Besides, as mentioned earlier, CA19.9 is not always the best marker indicating recurrence. Currently there is a growing interest in

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

Circulating Tumor DNA, which could offer an interesting addition to the clinical pathway for detecting recurrence.[37]

In conclusion, this study describes two commonly used strategies for follow-up of patients with BTC following resection with curative intent. Conclusions whether one strategy is superior to the other cannot be drawn as result of the bias in the selected groups. Nevertheless several interesting observations are made which may help to set up a future randomized controlled trial comparing pragmatic and structured follow-up.

Conflict of interest

None to declare.

References

1. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ *et al*. (2019) Surgery for cholangiocarcinoma. *Liver Int* 39(Suppl. 1): 143–155.
2. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen HJ *et al*. (2022) Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. *J Hepatol* 76(5):1109–1121. https://doi.org/10.1016/j.jhep.2021.12.010. Epub 2022 Feb 12. PMID: 35167909.
3. Groot Koerkamp B, Wiggers JK, Allen PJ, Besselink MG, Blumgart LH, Busch OR *et al*. (2015) Recurrence rate and pattern of perihilar cholangiocarcinoma after curative intent resection. *J Am Coll Surg* 221: 1041–1049.
4. Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L *et al*. (2016) Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. *Ann Surg Oncol* 23:235–243.
5. Hyder O, Hatzaras I, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H *et al*. (2013) Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 153:811–818.
6. Nakanishi Y, Okamura K, Tsuchikawa T, Nakamura T, Noji T, Asano T *et al*. (2020) Time to recurrence after surgical resection and survival after recurrence among patients with perihilar and distal cholangiocarcinomas. *Ann Surg Oncol* 27:4171–4180.
7. Zhang XF, Beal EW, Chakedis J, Chen Q, Lv Y, Ethun CG *et al*. (2018) Defining early recurrence of hilar cholangiocarcinoma after curative-intent surgery: a multi-institutional study from the US Extrahepatic Biliary Malignancy Consortium. *World J Surg* 42:2919–2929.
8. Sallinen V, Sirén J, Mäkisalo H, Lehtimäki TE, Lantto E, Kokkola A *et al*. (2020) Differences in prognostic factors and recurrence patterns after curative-intent resection of perihilar and distal cholangiocarcinomas. *Scand J Surg* 109:219–227.
9. Miyazaki Y, Kokudo T, Amikura K, Kageyama Y, Takahashi A, Ohkohchi N *et al*. (2017) Survival of surgery for recurrent biliary tract cancer: a single-center experience and systematic review of literature. *Jpn J Clin Oncol* 47:206–212.
10. Bridgewater J, Fletcher P, Palmer DH, Malik HZ, Prasad R, Mirza D *et al*. (2022) Long-term outcomes and exploratory analyses of the randomized phase III BILCAP study. *J Clin Oncol*, Jco2102568.
11. Komaya K, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T *et al*. (2018) Recurrence after curative-intent resection of perihilar cholangiocarcinoma: analysis of a large cohort with a close postoperative follow-up approach. *Surgery* 163:732–738.
12. Choi WJ, Williams PJ, Claasen M, Ivanics T, Englesakis M, Gallinger S *et al*. (2022) Systematic review and meta-analysis of prognostic factors for early recurrence in intrahepatic cholangiocarcinoma after curative-intent resection. *Ann Surg Oncol*. https://doi.org/10.1245/s10434-022-11463-x. Epub ahead of print. PMID: 35181812.
13. Nakahashi K, Ebata T, Yokoyama Y, Igami T, Mizuno T, Yamaguchi J *et al*. (2020) How long should follow-up be continued after R0 resection of perihilar cholangiocarcinoma? *Surgery* 168:617–624.
14. Sahara K, Tsilimigras DI, Kikuchi Y, Ethun CG, Maithel SK, Abbott DE *et al*. (2021) Defining and predicting early recurrence after resection for gallbladder cancer. *Ann Surg Oncol* 28:417–425.
15. Margonis GA, Gani F, Buettner S, Amini N, Sasaki K, Andreatos N *et al*. (2016) Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium. *HPB* 18:872–878.
16. Medscape. (2022) Cholangiocarcinoma follow-up. Available from: https://emedicine.medscape.com/article/277393-followup#e1.
17. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D *et al*. (2023) Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 34:127–140.
18. IKNL. (2013) Richtlijn Galweg en Galblaascarcinoom. Available from: https://richtlijnendatabase.nl/gerelateerde_documenten/f/1801/Galweg-%20en%20Galblaascarcinoom%20-%20Detectie%20nieuwe%20kankermanifestaties.pdf.
19. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D *et al*. (2019) Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 20:663–673.
20. Elliott JA, Markar SR, Klevebro F, Johar A, Goense L, Lagergren P *et al*. (2022) An international multicenter study exploring whether surveillance after esophageal cancer surgery impacts oncological and quality of life outcomes (ENSURE). *Ann Surg* 277(5):e1035–e1044. https://doi.org/10.1097/SLA.0000000000005378. Epub ahead of print. PMID: 35129466; PMCID: PMC10082056.
21. Pita-Fernández S, Alhayek-Aí M, González-Martín C, López-Calviño B, Seoane-Pillado T, Pértega-Díaz S. (2015) Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol* 26: 644–656.
22. Verberne CJ, Zhan Z, van den Heuvel E, Grossmann I, Doornbos PM, Havenga K *et al*. (2015) Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: results of the randomized "CEAwatch" trial. *Eur J Surg Oncol* 41:1188–1196.
23. Egenvall M, Martling A, Veres K, Horváth-Puhó E, Wille-Jørgensen P, Høirup Petersen S *et al*. (2021) No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels – an analysis within the COLOFOL randomized clinical trial. *Eur J Surg Oncol* 47:2053–2059.
24. Sisic L, Strowitzki MJ, Blank S, Nienhueser H, Dorr S, Haag GM *et al*. (2018) Postoperative follow-up programs improve survival in curatively resected gastric and junctional cancer patients: a propensity score matched analysis. *Gastric Cancer* 21:552–568.
25. Stein A, Arnold D, Bridgewater J, Goldstein D, Jensen LH, Klümpen HJ *et al*. (2015) Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004

1 trial) – a randomized, multidisciplinary, multinational phase III trial. *BMC Cancer* 15:564.

26. van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG *et al*. (2019) Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterol Hepatol* 4:199–207.

27. Janssen QP, van Dam JL, Bonsing BA, Bos H, Bosscha KP, Coene P *et al*. (2021) Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial. *BMC Cancer* 21:300.

28. Peppercorn JM, Weeks JC, Cook EF, Joffe S. (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 363:263–270.

29. Engelbak Nielsen Z, Eriksson S, Schram Harsløf LB, Petri S, Helgesson G, Mangset M *et al*. (2020) Are cancer patients better off if they participate in clinical trials? A mixed methods study. *BMC Cancer* 20:401.

30. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A *et al*. (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362:1273–1281.

31. Yoo T, Park SJ, Han SS, Kim SH, Lee SD, Kim YK *et al*. (2015) Postoperative CA19-9 change is a useful predictor of intrahepatic cholangiocarcinoma survival following liver resection. *Dis Markers* 2015:298985.

32. Parra-Robert M, Santos VM, Canis SM, Pla XF, Fradera JMA, Porto RM. (2018) Relationship between CA 19.9 and the Lewis phenotype: options to improve diagnostic efficiency. *Anticancer Res* 38:5883–5888.

33. Gundín-Menéndez S, Santos VM, Parra-Robert M, Pla XF, Fradera JMA, Porto RM. (2019) Serum CA 19.9 levels in patients with benign and malignant disease: correlation with the serum protein electrophoretic pattern. *Anticancer Res* 39:1079–1083.

34. Kim S, Park BK, Seo JH, Choi J, Choi JW, Lee CK *et al*. (2020) Carbohydrate antigen 19-9 elevation without evidence of malignant or pancreatobiliary diseases. *Sci Rep* 10:8820.

35. Liu W, Liu Q, Wang W, Wang P, Chen J, Hong T *et al*. (2018) Differential diagnostic roles of the serum CA19-9, total bilirubin (TBIL) and the ratio of CA19-9 to TBIL for benign and malignant. *J Cancer* 9:1804–1812.

36. Nooijen LE, Banales JM, de Boer MT, Braconi C, Folseraas T, Forner A *et al*. (2022) Impact of positive lymph nodes and resection margin status on the overall survival of patients with resected perihilar cholangiocarcinoma: the ENSCCA registry. *Cancers* 14.

37. Labiano I, Huerta AE, Arrazubi V, Hernandez-Garcia I, Mata E, Gomez D *et al*. (2023) State of the art: ctDNA in upper gastrointestinal malignancies. *Cancers* 15.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.10.004.

Please cite this article as: Nooijen LE et al., A critical appraisal of the potential benefit of post-operative structured follow-up after resection for biliary tract cancer, HPB, https://doi.org/10.1016/j.hpb.2023.10.004