The American Journal of Surgery 218 (2019) 145–150

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

The role of preoperative therapy prior to pancreatoduodenectomy for distal cholangiocarcinoma

Jordan M. Cloyd*, Laura Prakash, Jean-Nicolas Vauthey, Thomas A. Aloia, Yun Shin Chun, Ching-Wei Tzeng, Michel P. Kim, Jeffrey E. Lee, Matthew H.G. Katz

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, USA

ARTICLE INFO

Article history:
Received 6 June 2018
Received in revised form
31 July 2018
Accepted 31 August 2018

Keywords:
Whipple
Neoadjuvant therapy
Pancreatic ductal adenocarcinoma
Chemoradiation
Chemotherapy

ABSTRACT

Background: Although increasingly administered to patients with pancreatic ductal adenocarcinoma, the role of preoperative therapy for patients with distal cholangiocarcinoma is undefined.
Methods: All patients with distal cholangiocarcinoma who underwent pancreatoduodenectomy between 1999 and 2014 were retrospectively reviewed. Differences in clinicopathologic characteristics and overall survival (OS) were compared between patients who underwent surgery *de novo* and those who received preoperative therapy.
Results: Twenty-one patients (46.7%) received preoperative therapy and 24 (53.3%) did not. Five-year OS rates were not statistically significantly different between patients who received preoperative therapy and those who did not (46.6% vs 49.1%, $p > 0.05$). On multivariate cox proportional hazards analysis, lymph node positivity was the strongest predictor of OS (HR 4.68 (95%CI 1.52–14.42)). Whereas preoperative therapy was not associated with improved OS (HR 1.06 (95%CI 0.42–2.66)), the receipt of either pre- or post-operative therapy was (HR 0.40 (95%CI 0.16–1.00)).
Conclusion: While these results do not support the routine administration of preoperative therapy to patients with distal cholangiocarcinoma, it may be an alternative treatment strategy appropriate for a subset of patients with high risk clinical or pathologic features.

Introduction

Periampullary cancers are a heterogeneous group of neoplasms that include pancreatic ductal adenocarcinoma (PDAC), adenocarcinoma of the ampulla of Vater, duodenal adenocarcinoma and distal common bile duct (CBD) cancer. Of these, distal cholangiocarcinoma is the least common.[1] The standard of care for patients with radiographically resectable distal cholangiocarcinoma is removal of the primary tumor and regional lymph nodes with pancreatoduodenectomy (PD), which results in an overall 5-year survival rate of approximately 30%.[2]

Patients with PDAC who undergo PD benefit from the administration of postoperative chemotherapy and possibly chemoradiation.[3,4] Alternatively, the delivery of nonoperative therapies prior to, instead of following PD may allow for earlier treatment of micrometastatic disease, may be used to select patients with appropriate tumor biology and physiology for surgery, and may help achieve optimal locoregional control - all important considerations for a disease which will likely recur.[5] The administration of preoperative therapy to patients with potentially curable PDAC is now recognized as an acceptable sequencing of multimodality therapy.[6] Within this context, some have proposed a similar treatment paradigm be adopted for patients with localized distal cholangiocarcinoma.[7] However, while systemic chemotherapy is regularly recommended to patients who undergo resection of PDAC, the routine administration of postoperative therapies to patients with distal cholangiocarcinoma is not supported by randomized controlled trials and remains controversial.[8,9] Not surprisingly, therefore, evidence to support the use of preoperative therapy for distal cholangiocarcinoma is limited.

At the University of Texas MD Anderson Cancer Center, we have preferentially treated patients with PDAC with preoperative chemotherapy and/or chemoradiation prior to pancreatectomy for the past three decades[10] and this treatment sequencing strategy has occasionally been utilized for patients with other

* Corresponding author. Division of Surgical Oncology, The Ohio State University Wexner Medical Center, 410 W 10th Ave, N-907 Doan Hall Columbus, OH, 43210, USA.
E-mail address: jordan.cloyd@osumc.edu (J.M. Cloyd).

https://doi.org/10.1016/j.amjsurg.2018.08.024
0002-9610/

periampullary neoplasms.[11] Using this experience, and in direct response to a previously published call for additional data regarding the efficacy of preoperative therapy for patients with distal cholangiocarcinoma,[7] we sought to evaluate the effects of preoperative therapy in this clinical setting.

Materials & methods

Patients

The Institutional Review Board at the University of Texas MD Anderson Cancer Center approved data collection and analysis for this retrospective study on protocol number PA16-0560. We used our institution's prospectively maintained multidisciplinary database to identify all patients diagnosed with adenocarcinoma of the distal bile duct who underwent PD between 1999 and 2014.[12] The clinicopathologic features and long-term outcomes of patients who underwent PD either *de novo* or following the administration of preoperative chemotherapy and/or chemoradiation were compared.

Staging

Prior to the initiation of any therapy, all patients underwent a comprehensive staging evaluation that included a history and physical examination, a pancreatic-protocol CT scan, a chest CT or radiograph, and standard laboratory studies. Endoscopic ultrasound and endoscopic retrograde cholangiopancreatography were used selectively. Comorbidity was measured using the Adult Comorbidity Evaluation 27 index, which quantifies the extent of comorbidity on the basis of 27 ailments in 12 different systems; the severity of each patient's comorbidity profile was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).[13] Performance status was categorized according to the Eastern Cooperative Group (ECOG) scoring system.[14]

Preoperative therapy

The decision to perform resection primarily or to administer preoperative therapy prior to anticipated resection was made in a multidisciplinary setting with the consensus of medical, surgical and radiation oncologists. For the purposes of this study, the primary rationale for selecting preoperative therapy was retrospectively determined by chart review. In general, patients with localized cancers and a preserved physiologic status were offered PD *de novo*.

When administered, systemic chemotherapy was typically gemcitabine or 5-fluorouracil (5 FU) based. Chemoradiation was typically administered following systemic chemotherapy and consisted of either a hypofractionated (30Gy) or standard fractionated (45–63Gy) regimen with concomitant 5 FU, capecitabine or gemcitabine.[15] Following receipt of preoperative therapy, all patients underwent comprehensive re-staging. Those patients without evidence of disease progression and with optimal physiologic status were considered for surgical resection.

Surgical technique and histopathologic analysis

PD was performed using a standardized technique as previously described, although unlike the standard method in PDAC resections, a periadventitial dissection of the superior mesenteric artery was not routinely performed.[16] All surgical specimens were evaluated using a standardized protocol by dedicated gastrointestinal pathologists.[17] An R1 margin status was assigned to the resection if cancer cells were identified at any final inked margin.[18] American Joint Committee on Cancer 7th edition was used for TNM staging.

Postoperative therapy and follow-up

Following PD, postoperative chemotherapy and/or chemoradiation were administered selectively. In general, postoperative therapies were recommended to patients who had high-risk histopathologic features associated with their cancer, such as positive lymph nodes, advanced T stage, R1 margin status, poor tumor differentiation or lymphovascular/perineural invasion. Patients underwent postoperative evaluation every 4–6 months with cross-sectional imaging, physical examination and standard laboratory analysis in order to monitor for locoregional (LR) or distant recurrence. LR was defined as a new low density mass in the region of the resected pancreas or new lymphadenopathy localized to the root of the mesentery as a component of first failure.

Statistical analysis

Clinicopathological variables and long-term outcomes were compared between patients who received preoperative therapy followed by surgery versus those who underwent surgery first. Categorical variables were compared using the Fisher exact test while continuous variables were compared using the two-tailed student's t-test. Overall survival (OS) was compared using the Kaplan-Meier method. Statistical significance was assessed using the Mantel-Cox log rank test. Univariate and multivariate Cox proportional hazards regression models were created to identify factors associated with OS. Two separate multivariate models were created: the first forced preoperative therapy into the model and the second forced any adjuvant (pre- or post-operative) therapy into the model. In both, non-collinear variables with $p < 0.2$ on univariate regression were also included. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) with significance established at $p < 0.05$.

Results

Of the 45 patients for whom PD was performed for distal cholangiocarcinoma between 1999 and 2014, 21 (46.7%) received preoperative therapy and 24 (53.3%) did not. Preoperative therapy consisted of systemic chemotherapy alone (n = 5, 23.8%), chemoradiation alone (n = 10, 47.6%) or both (n = 6, 28.6%). The most common reason cited for the delivery of preoperative therapy was concern for advanced disease (n = 9, 42.9%) defined as radiographic evidence of regional adenopathy (n = 6), locally advanced vascular anatomy (n = 1), a markedly elevated serum CA 19-9 level (n = 1), or the presence of an indeterminate liver lesion (n = 1). Other reasons given for administering preoperative therapy included concern for patient performance status and/or comorbidities (n = 7, 33.3%) or because the patient was believed to have PDAC (n = 3, 14.3%). A reason could not be precisely determined by review of the medical record in 2 cases (9.5%).

The demographic, clinical, and histopathologic profile of patients who underwent PD *de novo* was similar to those of patients who completed preoperative therapy prior to PD (Table 1). The preoperative chemotherapy and chemoradiation regimens used are listed in Table 2. The majority of resected specimens were pathologic T3 tumors (68.9%) and node-positive (53.3%). Although the proportion of viable tumor cells in the pathologic specimen was not recorded in the majority (68.9%) of cases, one (4.8%) patient who received preoperative therapy experienced a complete pathologic response. 37.5% of patients who underwent surgery *de novo* and 19.0% of patients who received preoperative therapy received

Table 1
Demographic, clinical, and pathologic profile of patients who underwent surgery *de novo* and patients who received preoperative chemotherapy and/or chemoradiation (N = 45).

	Surgery First (n = 24)	Preoperative Therapy (n = 21)	p-Value
Baseline Demographic/Clinical			
Age, Mean (SD)	63.0 (11.3)	63.1 (10.8)	0.98
Male Gender	18 (75.0)	12 (57.1)	0.21
Median serum CA 19-9 (1st/3rd Quartile), U/mL	35 (15, 115)	61 (29, 109)	0.28
Performance Status[†], mean (SD)			0.81
0	3 (12.5)	4 (19.0)	
1	18 (75.0)	15 (71.4)	
≥2	3 (12.5)	2 (9.5)	
Comorbidity Index[$], mean (SD)			0.10
0 (None)	14 (58.3)	7 (33.3)	
1 (Mild)	6 (25.0)	5 (23.8)	
≥2 (Moderate or severe)	4 (16.7)	9 (42.9)	
Preoperative Biopsy			<0.001
Adenocarcinoma	12 (50.0)	21 (100.0)	
Suspicious	4 (16.7)	0	
None/Negative	8[a] (33.3)	0	
Clinical Lymph Node Staging			0.65
Normal	9 (37.5)	7 (33.3)	
Suspicious	5[b] (20.8)	7[c] (33.3)	
Indeterminate/Nonspecific	10 (41.7)	7 (33.3)	
Surgery			
Year of Surgery			
1999–2007	16 (66.7)	10 (47.6)	0.24
2008–2014	8 (33.3)	11 (52.4)	
EBL			0.44
<500	5 (20.8)	8 (38.1)	
500-1000	16 (66.7)	11 (52.4)	
>1000	3 (12.5)	2 (9.5)	
Lymph nodes Excised			0.51
<15	6 (26.1)	3 (14.3)	
15-30	13 (56.5)	12 (57.1)	
>30	4 (17.4)	6 (28.6)	
Pathology			
Tumor size, mean (SD)	1.8 (1.3)	1.8 (1.5)	0.95
Differentiation			0.58
Well	2 (8.3)	1 (4.8)	
Moderate	18 (75.0)	14 (66.7)	
Poor	4 (16.7)	4 (19.0)	
Unknown	0	2 (9.5)	
Margin Status			0.37
R0	20 (83.3)	19 (95.0)	
R1	4 (16.7)	1 (5.0)	
T Stage			0.20
T0/1	2 (8.3)	3 (14.3)	
T2	7 (29.2)	2 (9.5)	
T3	15 (62.5)	16 (76.2)	
N Stage			0.19
N0	9 (37.5)	12 (57.1)	
N1	15 (62.5)	9 (42.9)	
LNR			0.28
0	9 (37.5)	12 (57.1)	
≤0.2	7 (53.8)	6 (28.6)	
>0.2	8 (33.3)	3 (14.3)	
Lymphovascular Invasion			0.25
Yes	14 (58.3)	7 (33.3)	
No	7 (29.2)	10 (47.6)	
Unknown	3 (12.5)	4 (19.0)	
Perineural Invasion			0.57
Yes	16 (66.7)	11 (52.4)	
No	4 (16.7)	6 (28.6)	
Unknown	4 (16.7)	4 (19.0)	
Outcomes			
Distant Recurrence	10 (55.6)	8 (44.4)	0.81
Local Recurrence	0	3 (14.3)	0.06

Values are number (%) unless otherwise stated.
SD, standard deviation; † Eastern Cooperative Group; $ Adult Comorbidity Evaluation 27 index.
[a] 6 patients had biopsy with no malignant cells identified.
[b] 2 patients had biopsies and were negative for malignancy.
[c] 2 patients had biopsies and were positive for malignancy.

Table 2
Preoperative therapy regimens.

Preoperative Chemotherapy (n=11)	
Gemcitabine Alone	3 (27.3)
Gemcitabine Combination	6 (54.5)
5-Fu Based	2 (18.2)
Preoperative Chemoradiation (n=16)	
Radiation Dose	
Hypofractionated (30Gy)	5 (31.3)
Standard Fractionated (45–63 Gy)	11 (68.8)
Chemoradiation Sensitizer	
5-Flourouracil/Capecitabine	14 (87.5)
Gemcitabine	2 (12.5)

systemic chemotherapy following PD ($p > 0.05$).

The median follow-up duration of all patients was 38.1 months. The median OS duration and 5-year OS rate of patients with distal cholangiocarcinoma who underwent PD *de novo* (50.3 [95% CI 0–101.8] months, 49.1%) and following preoperative therapy (40.3 [95% CI 0–111.5] months, 46.6%) were similar ($p > 0.05$, Fig. 1). The rate of LR, as a component of first recurrence, was 14.3% in patients who received preoperative therapy and 0% in those who underwent surgery first, though this did not reach statistical significance ($p = 0.06$). On univariate (OR 3.54 (95% CI 1.51–8.30)) and multivariable (OR 4.68 (95% CI 1.52–14.42)) cox proportional hazards analysis, lymph node positivity was the strongest predictor of survival. Whereas preoperative therapy was not associated with improved OS after controlling for other covariates, the receipt of either pre- or post-operative therapy was (HR 0.40 (95% CI 0.16–1.00)) (Table 3).

Discussion

This is the first study to directly evaluate the potential impact of preoperative therapy on the oncologic outcomes of patients with distal cholangiocarcinoma. Using a relatively large, single institution series of patients who underwent PD for extrahepatic cholangiocarcinoma, we found that patients who received chemotherapy and/or chemoradiation prior to PD had a median OS similar to that of patients who underwent PD *de novo*. Although its findings may not support the *routine* administration of preoperative therapy to patients with known periampullary cholangiocarcinoma, they do demonstrate that delivery of chemotherapy and/or radiation in the preoperative setting is associated with acceptable clinical results. Further, they suggest

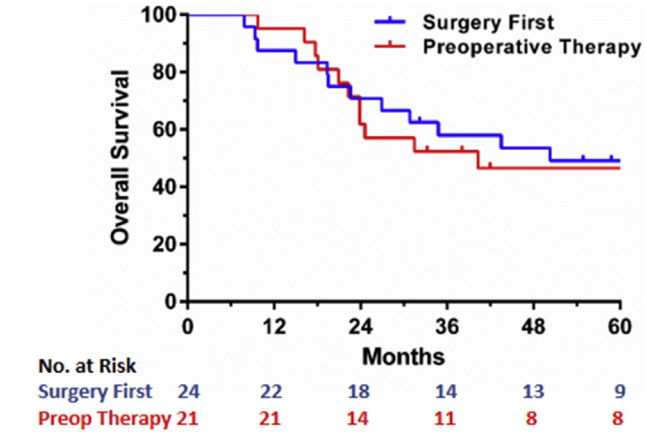

Fig. 1. Overall survival of patients receiving preoperative therapy prior to pancreatoduodenectomy versus surgery *de novo*.

that this sequencing strategy may be appropriate for certain patients, such as those in whom a clinical concern for advanced disease exists, or those in whom a depressed physiologic status prohibits immediate surgery.

A sound rationale exists for the delivery of preoperative therapy to patients with PDAC. Indeed, recommendations for this therapeutic sequence have been established in national guidelines for both borderline resectable[19] and resectable[6] cancers. However, all patients with PDAC benefit from systemic chemotherapy in the perioperative setting based on high level evidence that it prolongs survival when administered following surgery.[3,4] In contrast, distal cholangiocarcinoma is a distinct entity from PDAC[20] and whether patients should receive either chemotherapy or radiation in the postoperative setting is controversial.[9] It therefore might not be surprising that the preoperative administration of chemotherapy and/or chemoradiation in this study was not independently associated with a longer duration of survival. These findings are similar to those of our recent analysis of preoperative therapy for adenocarcinoma of the ampulla of Vater.[11]

Most authors support the selective delivery of postoperative therapy to patients with high-risk extrahepatic cholangiocarcinoma, such as those with positive resection margins, advanced T stage or positive lymph nodes. These recommendations are largely based on retrospective analyses of administrative datasets.[21–24] However, the largest randomized controlled trial of periampullary cancers (22.4% distal cholangiocarcinomas) suggested that postoperative chemotherapy was associated with a survival benefit after controlling for high-risk prognostic factors. In addition, the recently reported BILCAP trial found improved survival among patients with resected biliary tract cancers (34.9% extrahepatic cholangiocarcinoma) who received postoperative capecitabine, especially after adjusting for high risk features.[25] Our study demonstrated similar findings in that the receipt of either pre- or post-operative therapy was associated with improved survival after controlling for lymph node status. Therefore, the selective delivery of chemo- and/or radiotherapy to patients with recognized high risk clinical features in the preoperative setting could be advantageous given the large proportion of patients who are unable to receive these treatments following PD due to postoperative complications or poor performance status.[26]

This strategy also has appeal in cases of locally advanced anatomy, where downstaging might be necessary to facilitate a successful margin-negative resection. This strategy has been most often employed in cases of intrahepatic or hilar cholangiocarcinoma and gallbladder cancer. However, the administration of preoperative chemotherapy to unresectable biliary tract cancers rarely seems to result in sufficient downstaging to allow for surgical resection.[27,28] It is also notable that, although complete pathologic responses (pCR) have been reported in the explants of livers of patients with perihilar cholangiocarcinoma treated with preoperative chemoradiation and liver transplantation, only case reports and small series of pCR in patients with resected extrahepatic cholangiocarcinoma have been published.[29,30] Whether pCR in extrahepatic cholangiocarcinoma is associated with long term survival, as it is for PDAC,[31] is unknown (the patient with pCR in our study is alive with no evidence of disease at 72 months).

Taken in the context of available literature on multimodality therapy for periampullary cancers, the data presented herein suggest a selective approach for the use of preoperative therapy may be most appropriate for patients with distal cholangiocarcinoma. For example, if the diagnosis of distal cholangiocarcinoma is made preoperatively and high-risk features (e.g. advanced T stage or lymph node positivity) are clinically apparent such that postoperative chemotherapy and/or chemoradiation will likely be recommended, then delivery of nonoperative therapies prior to

Table 3
Results of cox proportional hazards analysis for overall survival.

	Univariate	Multivariate[b]	Multivariate[c]
Demographic/Clinical			
Age ≥65	1.75 (0.82–3.72), 0.15[a]	1.56 (0.68–3.63), 0.30	1.35 (0.58–3.18), 0.49
Male Gender	0.60 (0.28–1.29), 0.19[a]	0.32 (0.12–0.88), 0.03	0.40 (0.15–1.04), 0.06
CA 19-9 ≥200, U/mL	0.91 (0.34–2.44), 0.85		
Performance Status			
0	–		
1	2.33 (0.54–10.00), 0.25		
≥2	2.82 (0.51–15.52), 0.23		
Comorbidity Index			
0 (None)	–		
1 (Mild)	0.96 (0.36–2.53), 0.93		
≥2 (Moderate or severe)	1.18 (0.49–2.85), 0.72		
Therapy			
Any Preoperative Therapy[1]	0.99 (0.46–2.11), 0.97[a]	0.96 (0.39–2.32), 0.92	
Preoperative Chemotherapy	1.22 (0.51–2.93), 0.65		
Preoperative Chemoradiation	1.10 (0.50–2.41), 0.81		
EBL, mL			
<500	–	–	
500-1000	0.80 (0.34–1.89), 0.60[a]	0.98 (0.35–2.72), 0.97	0.87 (0.32–2.34), 0.78
>1000	2.35 (0.74–7.46), 0.15[a]	2.92 (0.78–10.88), 0.11	3.05 (0.83–11.25), 0.09
Lymph nodes Excised			
<15	–		
15-30	0.93 (0.36–2.39), 0.88		
>30	0.67 (0.20–2.20), 0.51		
Postoperative Therapy	0.62 (0.25–1.56), 0.31		
Preoperative or Postoperative Therapy[2]	0.66 (0.30–1.42), 0.28[a]		0.40 (0.16–1.00), <0.05
Pathology			
Tumor size	1.08 (0.82–1.42), 0.60		
Differentiation			
Well/Moderate	–		
Poor	1.37 (0.54–3.44), 0.51		
R1 Margin Status	0.55 (0.13–2.33), 0.42		
T Stage			
T0/T1	–	–	
T2	2.58 (0.30–22.16), 0.39[a]	1.12 (0.11–11.76), 0.91	1.25 (0.13–12.4), 0.85
T3	5.44 (0.73–40.61), 0.10[a]	1.80 (0.20–15.93), 0.60	2.37 (0.25–22.53), 0.45
N1 Stage	3.54 (1.51–8.30), 0.004[a]	4.61 (1.48–14.43), 0.009	4.73 (1.59–14.10), 0.005
LNR			
0	–		
≤0.2	2.75 (1.07–7.08), 0.04		
>0.2	5.83 (2.09–16.27), 0.001		
Lymphovascular Invasion	1.17 (0.49–2.82), 0.72		
Perineural Invasion	1.20 (0.44–3.29), 0.72		

Values are OR (95% CI), p-value.
SD, standard deviation; EBL, estimated blood loss; LNR, lymph node ratio.
[a] Included in multivariate model.
[b] multivariate model with preoperative therapy.
[c] multivariate model with any perioperative therapy.

surgical resection is an appropriate strategy given the proportion of patients who are unable to receive adjuvant therapy following PD secondary to complications of surgery or poor performance status. Similarly, if a major vascular resection is anticipated during PD for a distal cholangiocarcinoma, particularly in the setting of comorbidities or a depressed performance status, then nonoperative therapy may be considered preoperatively in order to ensure acceptable tumor biology before a potentially morbid operation. On the other hand, for patients in good physiological condition with no high-risk clinicopathologic features, or if the diagnosis is in question (e.g. suspicious bile duct stricture without definitive biopsy), then a surgery first approach with final pathology determining the need for adjuvant therapy is still most appropriate.

We acknowledge several important limitations in this study. First, this is a retrospective study of a single institution experience in which treatment decisions were not made randomly. We attempted to ascertain the reasons for which decisions regarding preoperative therapy were made, but the accuracy of medical chart review is inherently limited. Furthermore, given the relative rarity for which resectable distal cholangiocarcinoma occurs, as well as the challenges recently observed enrolling patients with PDAC which is much more common, a prospective randomized controlled trial comparing preoperative therapy and surgery first strategies is unlikely to occur in the near future. Second, since we could not clearly distinguish patients treated definitively with nonoperative therapy from those who received intended neoadjuvant therapy but did not ultimately undergo PD, only patients who underwent surgery were included. Third, a variety of preoperative regimens were used throughout the study period but a standardized regimen has only been recently proposed for distal cholangiocarcinoma and only in the adjuvant setting.[25] Recent evidence has suggested that even some distal cholangiocarcinomas may have an intestinal type histopathologic phenotype[32]; future studies therefore may benefit from incorporating immunohistochemistry results into their analyses. Fourth, while postoperative morbidity data was not reported in this study, previous research at our institution has demonstrated

that the use of preoperative therapies for other periampullary neoplasms does not influence postoperative complication rates[11,33]. Finally, and perhaps most importantly, the small sample size of the current study limits the power to detect small but potentially meaningful differences in oncologic outcomes. Future studies should utilize multi-institutional databases paired with statistical matching processes to confirm these findings.

Conclusions

In conclusion, the outcomes of patients with distal cholangiocarcinoma who underwent preoperative therapy followed by PD were similar to those of patients who underwent surgery *de novo*. While these results do not support the routine administration of preoperative therapy to patients with this disease, it may be an alternative treatment strategy appropriate for a subset of patients, particularly those with high risk clinicopathologic features or poor performance status that may limit a patient's ability to receive postoperative adjuvant therapy.

Acknowledgement

The authors would like to thank the many courageous patients and families who have formed the basis of our experience. We also thank our numerous colleagues in medical oncology, radiation oncology, gastroenterology, radiology, nutritional services, and nursing who reinforce the importance of multidisciplinary care of these patients.

References

1. Sarmiento JM, Nagorney DM, Sarr MG, et al. PERIAMPULLARY CANCERS: are there differences? *Surg Clin North Am*. 2001;81:543–555.
2. Veillette G, Castillo CF-D. Distal biliary malignancy. *Surg Clin North Am*. 2008;88:1429–1447. xi.
3. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *J Am Med Assoc*. 2007;297:267–277.
4. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–1210.
5. Youngwirth LM, Nussbaum DP, Thomas S, et al. Nationwide trends and outcomes associated with neoadjuvant therapy in pancreatic cancer: an analysis of 18 243 patients. *J Surg Oncol*. 2017. https://doi.org/10.1002/jso.24630. Epub ahead of print April 13.
6. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: american society of clinical oncology clinical practice guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34:2541–2556.
7. Turaga KK, Tsai S, Wiebe LA, et al. Novel multimodality treatment sequencing for extrahepatic (mid and distal) cholangiocarcinoma. *Ann Surg Oncol*. 2013;20:1230–1239.
8. Erdmann JI, Eskens F a LM, Vollmer CM, et al. Histological and molecular subclassification of pancreatic and nonpancreatic periampullary cancers: implications for (neo) adjuvant systemic treatment. *Ann Surg Oncol*. 2015;22:2401–2407.
9. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *J Am Med Assoc*. 2012;308:147–156.
10. Cloyd JM, Katz MHG, Prakash L, et al. Preoperative therapy and pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a 25-year single-institution experience. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2017;21:164–174.
11. Cloyd JM, Wang H, Overman M, et al. Influence of preoperative therapy on short- and long-term outcomes of patients with adenocarcinoma of the ampulla of vater. *Ann Surg Oncol*. 2017;24:2031–2039.
12. Hwang RF, Wang H, Lara A, et al. Development of an integrated biospecimen bank and multidisciplinary clinical database for pancreatic cancer. *Ann Surg Oncol*. 2008;15:1356–1366.
13. Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *J Am Med Assoc*. 2004;291:2441–2447.
14. West H, Jin JO. PErformance status in patients with cancer. *JAMA Oncol*. 2015;1,998–998.
15. Cloyd JM, Crane CH, Koay EJ, et al. Impact of hypofractionated and standard fractionated chemoradiation before pancreatoduodenectomy for pancreatic ductal adenocarcinoma. *Cancer*. 2016;122:2671–2679.
16. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2004;8:935–949. discussion 949-950.
17. 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.
18. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg*. 2007;246:52–60.
19. National Comprehensive Cancer Network. NCCN practice guidelines for pancreatic cancer Available from: http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed March 1, 2016.
20. Ethun CG, Lopez-Aguiar AG, Pawlik TM, et al. Distal cholangiocarcinoma and pancreas adenocarcinoma: are they really the same disease? A 13-institution study from the US extrahepatic biliary malignancy consortium and the central pancreas consortium. *J Am Coll Surg*. 2017;224:406–413.
21. Fuller CD, Wang SJ, Choi M, et al. Multimodality therapy for locoregional extrahepatic cholangiocarcinoma: a population-based analysis. *Cancer*. 2009;115:5175–5183.
22. Im JH, Seong J, Lee IJ, et al. Surgery alone versus surgery followed by chemotherapy and radiotherapy in resected extrahepatic bile duct cancer: treatment outcome analysis of 336 patients. *Cancer Res Treat Off J Korean Cancer Assoc*. 2016;48:583–595.
23. Yang H, Zhou J, Wei X, et al. Survival outcomes and progonostic factors of extrahepatic cholangiocarcinoma patients following surgical resection: adjuvant therapy is a favorable prognostic factor. *Mol Clin Oncol*. 2014;2:1069–1075.
24. Dover LL, Oster RA, McDonald AM, et al. Impact of adjuvant chemoradiation on survival in patients with resectable cholangiocarcinoma. *HPB*. 2016;18:843–850.
25. Primrose JN, Fox R, Palmer DH, et al. Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study. *J Clin Oncol*. 2017;35, 4006–4006.
26. Tzeng C-WD, Tran Cao HS, Lee JE, et al. Treatment sequencing for resectable pancreatic cancer: influence of early metastases and surgical complications on multimodality therapy completion and survival. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2014;18:16–24. discussion 24-25.
27. Kato A, Shimizu H, Ohtsuka M, et al. Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. *Ann Surg Oncol*. 2013;20:318–324.
28. Grendar J, Grendarova P, Sinha R, et al. Neoadjuvant therapy for downstaging of locally advanced hilar cholangiocarcinoma: a systematic review. *HPB*. 2014;16:297–303.
29. McMasters KM, Tuttle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. *Am J Surg*. 1997;174:605–608. discussion 608-609.
30. Walker EJ, Simko JP, Nakakura EK, et al. A patient with cholangiocarcinoma demonstrating pathologic complete response to chemotherapy: exploring the role of neoadjuvant therapy in biliary tract cancer. *J Gastrointest Oncol*. 2014;5:E88–E95.
31. Cloyd JM, Wang H, Egger ME, et al. Association of clinical factors with a major pathologic response following preoperative therapy for pancreatic ductal adenocarcinoma. *JAMA Surg*. 2017;152:1048–1056.
32. Williams JL, Chan CK, Toste PA, et al. Association of histopathologic phenotype of periampullary adenocarcinomas with survival. *JAMA Surg*. 2017;152:82–88.
33. Denbo J, Bruno M, Cloyd JM, et al. Preoperative chemoradiation for pancreatic adenocarcinoma does not increase 90-day postoperative morbidity or mortality. *J Gastrointest Surg*. 2016 Dec;20(12):1975–1985.