ORIGINAL RESEARCH

The Implications of Treatment Delays in Adjuvant Therapy for Resected Cholangiocarcinoma Patients

Matthew Parsons[1] · Shane Lloyd[1] · Skyler Johnson[1] · Courtney Scaife[2] · Heloisa Soares[3] · Rebecca Kim[2] · Robin Kim[2] · Ignacio Garrido-Laguna[3] · Randa Tao[1]

Abstract

Purpose The purpose of this study is to understand factors associated with timing of adjuvant therapy for cholangiocarcinoma and the impact of delays on overall survival (OS).

Methods Data from the National Cancer Database (NCDB) for patients with non-metastatic bile duct cancer from 2004 to 2015 were analyzed. Patients were included only if they underwent surgery and adjuvant chemotherapy and/or radiotherapy (RT). Patients who underwent neoadjuvant or palliative treatments were excluded. Pearson's chi-squared test and multivariate logistic regression analyses were used to assess the distribution of demographic, clinical, and treatment factors. After propensity score matching with inverse probability of treatment weighting, OS was compared between patients initiating therapy past various time points using Kaplan Meier analyses and doubly robust estimation with multivariate Cox proportional hazards modeling.

Results In total, 7,733 of 17,363 (45%) patients underwent adjuvant treatment. The median time to adjuvant therapy initiation was 59 days (interquartile range 45–78 days). Age over 65, black and Hispanic race, and treatment with RT alone were associated with later initiation of adjuvant treatment. Patients with larger tumors and high-grade disease were more likely to initiate treatment early. After propensity score weighting, there was an OS decrement to initiation of treatment beyond the median of 59 days after surgery.

Conclusions We identified characteristics that are related to the timing of adjuvant therapy in patients with biliary cancers. There was an OS decrement associated with delays beyond the median time point of 59 days. This finding may be especially relevant given the treatment delays seen as a result of COVID-19.

Keywords Cholangiocarcinoma · Biliary · Radiation · Adjuvant · Treatment delay

Introduction

Cholangiocarcinoma (CCA) is comprised of a diverse set of epithelial tumors with features of cholangiocyte differentiation [1–3]. It is the most common biliary malignancy and the incidence has progressively increased over the last 40 years [3, 4]. These tumors are subdivided based on anatomical location as intrahepatic (iCCA), perihilar (pCCA), or extrahepatic/distal (dCCA) [3, 5]. Importantly, these subsets of CCA vary not only by location, but may also vary by molecular characteristics, biology, and treatment options [1, 6]. CCAs are aggressive tumors and the majority of patients have advanced disease at diagnosis [7]. As a result, prognosis for CCA is poor with a median survival of 24 months from diagnosis [7]. Surgery is considered the only curative therapy for patients with early stage, resectable disease [8].

The mainstay of therapy for all subtypes of early stage CCA is surgery, provided that patients are surgical candidates and have resectable disease [9]. The roles of adjuvant chemotherapy (CT) and radiation therapy (RT) are evolving and are dependent on the extent of surgical resection, lymph node status, and tumor location [10].

✉ Randa Tao
randa.tao@hci.utah.edu

1 Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, UT, Salt Lake City, USA

2 Department of Surgery, Huntsman Cancer Institute, University of Utah, UT, Salt Lake City, USA

3 Department of Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA

According to NCCN guidelines, adjuvant therapy is standard of care in patients with positive margins or lymph nodes and should be strongly considered in patients with negative margins or lymph nodes given the aggressive nature of the disease [11]. Support for the utilization of adjuvant treatment comes from two prospective trials, the SWOG 0809 and BILCAP studies. The SWOG study was a single arm phase II multi-center study that demonstrated promising efficacy and tolerable side effect profiles for adjuvant chemotherapy followed by chemoradiation therapy. The BILCAP study was a phase III randomized trial that evaluated the role of adjuvant capecitabine. The study primary endpoint was overall survival. The study showed a trend towards improved survival in the intention to treat analysis. The survival improvement was confirmed in a prespecified per-protocol analysis (53 vs 36 months, HR = 0.75, 95% CI 0.58–0.97) [12, 13].

The role of timing of adjuvant therapy in the setting of CCA has not yet been studied. The BILCAP study initially required patients to start adjuvant therapy within 8 weeks of surgery; however, the protocol was later adjusted to allow initiation within 12 weeks and later extended again to 16 weeks [13]. The SWOG trial required enrollment within 8 weeks. However, the impact of these time points has not been formally analyzed. With the emergence of COVID-19, delays in therapy have been seen for a number of oncology patients, including delays in screening, surgery, chemotherapy, and radiation therapy [14–16]. We set out to evaluate factors associated with delays in the initiation of adjuvant therapy for CCA as well as the impact of these delays on survival outcomes.

Materials and Methods

Patient data was obtained from the National Cancer Database (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which includes data from approximately 1,500 hospitals and clinics in the USA and its territories. This database captures nearly 70% of new cancer diagnoses made in the USA [17]. The CoC NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used in this study; these data have not been verified, and the CoC is not responsible for the statistical validity of the data analysis or the conclusions of the authors.

The NCDB was queried for patients diagnosed with bile duct cancer between 2004 and 2015, which yielded 92,849 patients (Fig. 1). Patients were excluded if they had metastatic disease at diagnosis (55,335 remaining), had non-invasive disease (50,548 remaining), did not undergo surgery (21,773 remaining), underwent neoadjuvant therapy (20,013 remaining), were treated with palliative intent (19,510 remaining), and had an
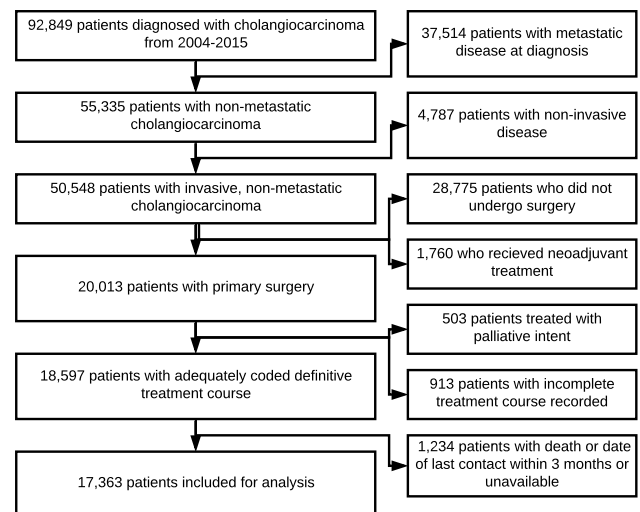
Fig. 1 Flow chart of patient selection. Patients with non-metastatic cholangiocarcinoma who underwent surgical resection were selected. Those who had metastatic disease, in situ lesions, received neoadjuvant or palliative treatments, or who did not undergo surgery were excluded

incompletely recorded treatment course (18,597 remaining), if death or date of the last contact occurred less than 3 months from diagnosis, and if survival time was unavailable (17,363 remaining).

Among patients who underwent adjuvant therapy, median and interquartile ranges (IQR) for time from surgical resection to adjuvant therapy were used to divide patients into quartiles of time to adjuvant therapy. Differences in the distribution of demographic, clinical, and treatment characteristics among groups were assessed using Pearson's chi-squared analysis. Propensity score matching with inverse probability of treatment weighting (IPTW) was employed to balance covariates between patients receiving adjuvant therapy at different time points. Characteristics matched by propensity score included age, sex, race, insurance status, income, education group, distance to care, Charlson-Deyo comorbidity score, tumor size, grade, margin status, presence of lymphovascular space invasion (LVSI), nodal status, stage, tumor location, and treatment modality. Univariate and multivariate logistic regression analyses were used to assess the predictive value for delay beyond various time points. Factors with P values < 0.05 on univariate analysis were included in multivariate logistic regression models. Significance was defined as any P value < 0.05.

The primary outcome variable was OS. Recurrence, progression-free survival, and toxicity were unable to be assessed as these data are not recorded within the NCDB. Survival was assessed using Kaplan–Meier analyses and Cox proportional hazards modeling. Doubly robust estimation was performed with multivariate Cox proportional

Table 1 Demographic, clinical, and management characteristics of the entire patient population by time to adjuvant therapy stratified by median time to initiation

	≤ 59 days n=3,939		> 59 days n=3,794		
	No	%	No	%	
Age					**P < 0.01**
≤ 65 years	2,256	57	1,972	52	
> 65 years	1,683	43	1,822	48	
Sex					P=0.90
Male	2,287	58	2,208	58	
Female	1,652	42	1,586	42	
Charlson group					P=0.13
0	2,981	77	2,802	75	
1+	903	23	920	25	
Grade					P=0.29
Well differentiated	347	10	385	11	
Moderately differentiated	1,862	52	1,814	52	
Poorly Differentiated	1,350	38	1,277	36	
Undifferentiated	30	1	32	1	
LVSI					P=0.13
Negative	935	24	976	26	
Positive	1,058	27	996	26	
Unknown	1,946	49	1,822	48	
Margin status					P=0.27
Negative margins	2,876	84	2,875	85	
Positive microscopic margins	492	14	461	14	
Positive macroscopic margins	44	1	32	1	
Tumor size					**P < 0.01**
2 cm or Less	1,386	35	1,433	38	
2.1 cm to 5 cm	1,667	42	1,627	43	
5 cm or greater	438	11	337	9	
Unknown	448	11	397	10	
Nodal status					P=0.31
Node negative	1,324	48	1,304	49	
Node positive	1,447	52	1,349	51	
Race					**P=0.03**
White	3,039	78	2,845	75	
Black	312	8	338	9	
Hispanic	293	7	340	9	
Others	269	7	251	7	
Insurance status					**P < 0.01**
Private insurance	1,866	48	1,617	43	
No Insurance	107	3	121	3	
Medicaid	253	7	267	7	
Medicare	1,649	43	1,737	46	
Income ($)					P=0.56
Less than 30,000	407	11	411	12	
30,000–34,999	568	16	537	16	
35,000–45,999	923	26	923	27	
46,000+	1,677	47	1,563	46	
Percent of residents without a high school degree					P=0.28

Table 1 (continued)

	≤ 59 days n=3,939		> 59 days n=3,794		
	No	%	No	%	
29%+	542	15	572	17	
20–28.9%	754	21	736	21	
14–19.9%	825	23	786	23	
< 14%	1,453	41	1,337	39	
Distance from treatment facility					P=0.79
Less than 50 miles	3,044	82	2,934	83	
50 to 200 miles	545	15	512	14	
Greater than 200 miles	103	3	91	3	
Stage at diagnosis					P=0.12
Stage 1	628	16	637	17	
Stage 2	1,952	50	1,927	51	
Stage 3	1,025	26	911	24	
Unknown	304	8	301	8	
Treatment modality					
Radiation alone	108	3	175	5	**P < 0.01**
Chemotherapy alone	1,625	41	1,632	43	
Chemoradiation	2,206	56	1,987	52	
Tumor location					**P=0.02**
Intrahepatic	570	14	469	12	
Extrahepatic	3,325	84	3,277	86	
Unknown	44	1	48	1	

hazards modeling on propensity score-matched cohorts to account for imperfect balancing of covariates. All matched variables were included within these doubly robust multivariate models. All analyses were performed using the STATA 14.2 statistical package [18].

Results

Patient demographic information is shown in Table 1. Among the 17,363 patients with non-metastatic, surgically resected CCA included in our analysis, 7,733 (45%) underwent adjuvant therapy. This included 283 patients (4%) treated with RT alone, 3,257 patients (42%) treated with CT alone, and 4,193 patients (54%) treated with combination chemoradiation therapy (CRT). Among patients treated with adjuvant therapy, the median time to initiation of therapy was 59 days (IQR 45–78 days).

Patients who were among the first quartile to initiate adjuvant treatment were compared to those who were not on multivariable analysis (Table 2). Patients in the first quartile to be treated were more likely to have intrahepatic tumors, less likely to be over the age of 65 and less likely to be treated with RT alone than those treated beyond this time point. Similar multivariable analyses were performed for those among

Table 2 Predictors of initiation of adjuvant therapy beyond the first quartile of patients (> 45 days) assessed by multivariable analysis

	Odds ratio	Standard error	z-score	P > z	95% confidence interval	
Margin status						
Negative margins	Reference					
Positive microscopic margins	0.99	0.08	− 0.15	0.88	0.84	1.16
Positive macroscopic margins	0.66	0.17	− 1.64	0.10	0.40	1.09
LVSI						
Negative	Reference					
Positive	1.02	0.08	0.28	0.78	0.87	1.20
Unknown	0.95	0.07	− 0.74	0.46	0.82	1.09
Tumor size						
2 cm or Less						
2.1 cm to 5 cm	0.95	0.06	-0.79	0.43	0.84	1.08
5 cm or greater	0.99	0.11	-0.12	0.90	0.79	1.24
Unknown	0.82	0.09	-1.81	0.07	0.66	1.02
Stage at diagnosis						
Stage 1	Reference					
Stage 2	1.08	0.09	0.97	0.33	0.92	1.28
Stage 3	0.96	0.09	− 0.45	0.65	0.80	1.15
Unknown	1.03	0.14	0.20	0.84	0.79	1.34
Age						
≤ 65 years	Reference					
> 65 years	1.20	0.10	2.27	**0.02**	1.03	1.41
Treatment modality						
Radiation alone	Reference					
Chemotherapy alone	0.56	0.11	− 2.88	**0.00**	0.38	0.83
Chemoradiation	0.53	0.10	− 3.22	**0.00**	0.36	0.78
Insurance status						
Private insurance	Reference					
No insurance	1.23	0.22	1.17	0.24	0.87	1.73
Medicaid	1.25	0.15	1.84	0.07	0.99	1.59
Medicare	1.14	0.10	1.60	0.11	0.97	1.34
Race						
White	Reference					
Black	1.11	0.12	0.95	0.34	0.90	1.37
Hispanic	1.25	0.14	1.91	0.06	0.99	1.56
Others	0.98	0.11	− 0.17	0.87	0.78	1.23
Tumor location						
Intrahepatic	Reference					
Extrahepatic	1.39	0.14	3.30	**0.00**	1.14	1.70
Unknown	1.85	0.60	1.92	0.06	0.99	3.48

the first half of patients to initiate treatment and those in the final quartile (Tables 3 and 4, respectively). Those who initiated treatment in the first half of patients were more likely to have tumors larger than 5 cm than those who started later. They were less likely to be older than 65, black or Hispanic, and treated with RT alone. Patients in the final quartile to initiate adjuvant treatment were more likely to be over 65, Hispanic, have Medicaid, have Charlson comorbidity scores of 1 and above, and were more likely to be treated with RT alone. These patients were less likely to have high-grade disease than those treated in the first three quartiles.

After propensity score matching and doubly robust estimation (Supplemental Table 1), Charlson scores of 1 or higher, positive LVSI, positive margins, lymph node positivity, tumors larger than 2 cm, age > 65, high-grade disease, and node positivity were prognostic for significantly decreased

Table 3 Predictors of initiation of adjuvant therapy among the second half of patients (> 59 days) assessed by multivariable analysis

	Odds ratio	Standard error	z-score	P > z	95% confidence interval	
Treatment modality						
Radiation alone	Reference					
Chemotherapy alone	0.64	0.08	− 3.38	**0.00**	0.50	0.83
Chemoradiation	0.57	0.07	− 4.28	**0.00**	0.44	0.74
Insurance status						
Private insurance	Reference					
No insurance	1.19	0.17	1.22	0.22	0.90	1.56
Medicaid	1.16	0.11	1.52	0.13	0.96	1.40
Medicare	1.05	0.07	0.68	0.50	0.92	1.19
Tumor size						
2 cm or less	Reference					
2.1 cm to 5 cm	0.96	0.05	− 0.80	0.42	0.87	1.06
5 cm or greater	0.81	0.08	− 2.27	**0.02**	0.68	0.97
Unknown	0.86	0.07	− 1.83	0.07	0.74	1.01
Race						
White	Reference					
Black	1.19	0.10	2.06	**0.04**	1.01	1.40
Hispanic	1.23	0.11	2.34	**0.02**	1.03	1.46
Others	0.99	0.09	− 0.12	0.90	0.82	1.19
Age						
≤ 65 years	Reference					
> 65 years	1.23	0.08	3.18	**0.00**	1.08	1.40
Tumor location						
Intrahepatic	Reference					
Extrahepatic	1.12	0.09	1.53	0.13	0.97	1.30
Unknown	1.27	0.28	1.07	0.28	0.82	1.96

overall survival in the entire cohort. Income > \$46,000 and extrahepatic disease site were prognostic for improved survival. There was no association between treatment modality and survival outcomes (Supplemental Tables 2 and 3). Comparing initiation of treatment at various time points, there was no OS difference between patients in the first quartile to initiate adjuvant treatment (≤ 45 days) and those treated later (HR 0.97, 95%, CI 0.87–1.08, P = 0.55) (Fig. 2a). However, there was a survival decrement to initiating treatment beyond the median time point of 59 days (HR 1.14, 95% CI 1.04–1.24 P < 0.01) (Fig. 2b). There was also a survival decrement associated with being amongst the final quartile of patients to initiate treatment (> 78 days) (HR 1.15, 95% CI 1.04–1.27, P = 0.01) (Fig. 2c).

Discussion

This is a retrospective analysis of the adjuvant treatment of individuals with CCA using a large population database (NCDB). Although CCA is the most common biliary malignancy, it remains rare overall, and the data on adjuvant therapy is evolving. Our analysis of a nationwide longitudinal dataset allows for description of care patterns across the USA and its territories. This allows for a patterns of care analysis that would not be feasible using single institution or prospective data. We found that a large number of patients did not receive any adjuvant therapy after surgery. Among patients who did receive adjuvant therapy, CRT was the most commonly utilized modality followed by CT alone and RT alone.

The median time to initiation of adjuvant therapy was 59 days, which is largely consistent with the timing requirements on the SWOG and BILCAP studies [12, 13]. It is important to note that the NCDB only contains the first course of planned therapy so that early salvage treatments or unplanned treatments for residual disease are not included. We identified a number of patient characteristics that were associated with timing of initiation of adjuvant therapy. Many of these characteristics are consistent with expectation. Age over 65, for example, was associated with delay in initiation of adjuvant therapy, and increased comorbidity score

Table 4 Predictors of initiation of adjuvant therapy within the final quartile of patients (> 78 days) assessed by multivariable analysis

	Odds ratio	Standard error	z-score	P > z	95% confidence interval	
Charlson group						
0	Reference					
1+	1.19	0.10	2.09	**0.04**	1.01	1.40
Grade						
Well differentiated	Reference					
Moderately differentiated	0.75	0.09	− 2.39	**0.02**	0.60	0.95
Poorly differentiated	0.75	0.09	− 2.36	**0.02**	0.59	0.95
Undifferentiated	0.72	0.28	− 0.82	0.41	0.34	1.57
Treatment modality						
Radiation alone	Reference					
Chemotherapy alone	0.62	0.13	− 2.22	**0.03**	0.41	0.95
Chemoradiation	0.54	0.12	− 2.86	**< 0.01**	0.35	0.82
Percent of residents without a high school degree						
29%+	Reference					
20–28.9%	0.93	0.11	− 0.57	0.57	0.74	1.18
14–19.9%	0.85	0.10	− 1.33	0.18	0.67	1.08
< 14%	0.94	0.10	− 0.59	0.56	0.75	1.17
Race						
White	Reference					
Black	1.26	0.16	1.75	**0.08**	0.97	1.62
Hispanic	1.56	0.20	3.39	**< 0.01**	1.21	2.01
Others	0.85	0.13	− 1.07	0.28	0.64	1.14
Nodal status						
Node negative	Reference					
Node positive	0.90	0.07	− 1.46	0.14	0.78	1.04
Insurance status						
Private insurance	Reference					
No insurance	1.04	0.23	0.18	0.86	0.68	1.60
Medicaid	1.39	0.20	2.3	**0.02**	1.05	1.85
Medicare	1.02	0.11	0.21	0.83	0.83	1.26
Age						
≤ 65 years	Reference					
> 65 years	1.40	0.14	3.3	**< 0.01**	1.15	1.71

was associated with initiating treatment among the final quartile of patients. Surgical approaches for cholangiocarcinoma vary with location and tumor size; however, for most patients, it often requires hemi-hepatectomy and bile duct resection [19]. This is a major surgery with risks of both peri-operative morbidity and mortality [20, 21]. Outcomes have been previously shown to be worse in elderly patients with increased comorbidity; therefore, it is unsurprising these patients would be afforded a longer post-operative recovery period [22]. Larger tumors and higher-grade disease were associated with less likelihood of treatment delay; both of these factors have previously been shown to have negative impact on outcomes, which may influence providers to be more aggressive initiating adjuvant therapy in these patients [23, 24]. Extrahepatic tumors were more likely to be treated among the first quartile of patients, which may be a result of differences in surgical techniques and associated recovery times between tumor locations [25–27].

We also identified some predictors of delay that were less expected, including treatment with RT alone as well as black and Hispanic race. As RT alone is not a guideline-supported option for adjuvant therapy, patients treated with RT alone may represent a cohort that is unable to recover adequately from surgery to be treated with CT or CRT [11]. The finding of black and Hispanic patients having an increased likelihood of treatment delay is a concerning one.
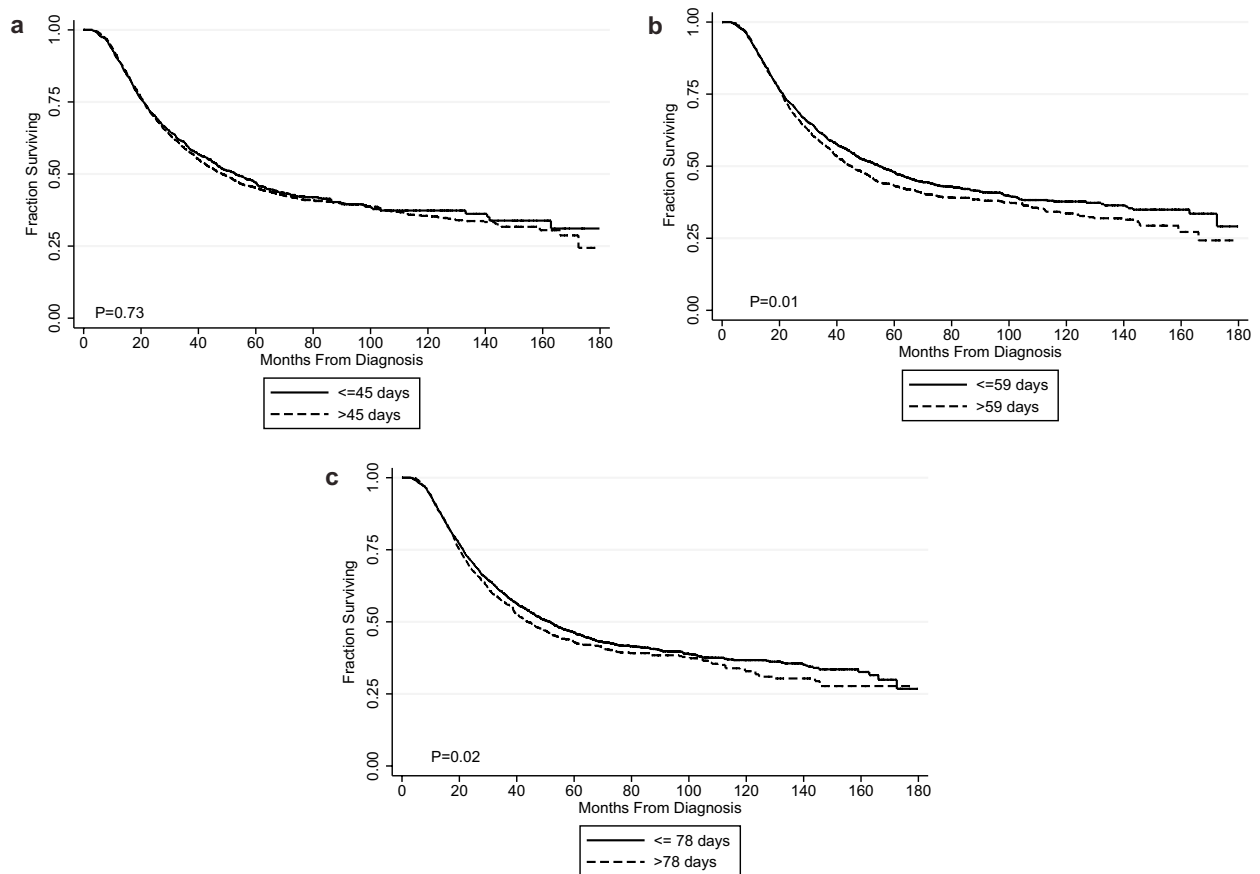
Fig. 2 Fifteen-year overall survival for patients who were treated before and after various time points. Propensity score matched data are shown for **a** patients treated before and after 45 days (the first quartile), **b** patients treated before and after 59 days (the median), **c** patients treated before and after 78 days (the final quartile)

While this has not been previously documented in patients with CCA, numerous studies in other malignancies have shown an increased likelihood in therapy delay for minority patients [28, 29]. The explanation for this is complex and multifactorial, with previously explored contributors including decreased access to healthcare resources, distrust in the medical system, language barriers, health literacy, and biases from the medical system [30–32]. Our findings underscore the continued need for improvements in the equitability of access to timely care for black and Hispanic patients in our medical system.

We identified a number of factors that were associated with decreased OS after propensity score weighting and doubly robust estimation. The majority of these, such as Charlson scores of 1 or higher, positive LVSI, positive margins, lymph node positivity, tumors larger than 2 cm, age > 65, high-grade disease, and node positivity, are consistent with previously known prognostic factors in CCA [2, 33, 34]. Perhaps surprisingly, there was not an association of treatment modality

with overall survival; however, this may be a result of insufficient power to detect a difference with only a small number of patients treated with radiation therapy alone.

An important novel finding of our study is the finding that delays in initiation beyond the median time point of 59 days were associated with decrements in OS. While this has not been previously described in CCA, there are a number of malignancies in which delay to adjuvant therapy has been shown to be associated with worse outcomes [28, 35, 36]. However, in pancreatic ductal adenocarcinoma, the EPSAC-3 showed that completion of chemotherapy rather than early initiation was prognostic, and there was no survival decrement with delay of inititiation up to 12 weeks [37]. While there are likely a number of patients in whom early initiation of adjuvant therapy is not feasible due to the significant potential morbidity associated with surgery for this disease, these results suggest that timely initiation of adjuvant therapy should be the goal when possible. These findings are especially pertinent in the era of COVID-19 as many cancer

therapy patients experience treatment delays. While there may be some patients in whom treatment delay is a reasonable approach for decreasing exposure risk, CCA patients may not be an appropriate group for this mitigation strategy.

This study has several limitations, many of which are present in all large retrospective database analysis. The NCDB does not include information on symptomatology, comorbidities, or palliation which may allow for the introduction of confounding bias into our data. We performed propensity score-matching by IPTW and doubly robust estimation, in an attempt to reduce the possibility of selection bias [38, 39]. However, we are limited by the NCDB in the factors available to include in the matching, and it is difficult to control for all possible confounders. It is possible, therefore, that factors unavailable to include in the matching process may be associated with delays in therapy and influence our results. Additionally, we are unable to evaluate the impact of delays in therapy on local recurrence or disease-specific survival as these endpoints are not available in the NCDB. Finally, we did not have any information regarding the morbidity associated with surgery which may contribute to both timing of adjuvant therapy survival outcomes. Due to these limitations, these findings are hypothesis generating and require further study to confirm the findings.

Conclusions

This is the first study to evaluate the impact of timing of adjuvant therapy in patients with resected CCA. We identified characteristics that are related to the timing of adjuvant therapy in these patients. Black and Hispanic patients were more likely to experience a delay in adjuvant therapy, and there is a need for improved equitable access to heathcare resources for these CCA patients. There was an OS decrement associated with delays beyond the median time point of 59 days. Our findings may be especially relevant given the treatment delays seen for cancer patients as a result of COVID-19 and to heighten awareness on treatment delays for vulnerable populations.

Declarations

References

1. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145(6):1215–29. https://doi.org/10.1053/j.gastro.2013.10.013.

2. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15(2):95–111. https://doi.org/10.1038/nrclinonc.2017.157.

3. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557–88. https://doi.org/10.1038/s41575-020-0310-z.

4. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist*. May 2016;21(5):594–9. https://doi.org/10.1634/theoncologist.2015-0446

5. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(9):512–22. https://doi.org/10.1038/nrgastro.2011.131.

6. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New horizons for precision medicine in biliary tract cancers. Cancer Discov. 2017;7(9):943–62. https://doi.org/10.1158/2159-8290.CD-17-0245.

7. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg*. Oct 2001;234(4):507–17; discussion 517–9. https://doi.org/10.1097/00000658-200110000-00010

8. Blechacz B. Tumors of the bile ducts, gallbladder, and ampulla. *Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Saunders; 2010:1171–1176.

9. Doherty B, Nambudiri VE, Palmer WC. Update on the diagnosis and treatment of cholangiocarcinoma. Curr Gastroenterol Rep. 2017;19(1):2. https://doi.org/10.1007/s11894-017-0542-4.

10. Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines insights: hepatobiliary cancers, version 2.2019. *J Natl Compr Canc Netw*. Apr 1 2019;17(4):302–310. https://doi.org/10.6004/jnccn.2019.0019

11. (NCCN) NCCN. Hepatobiliary cancers version 5.2020. Updated August 4, 2020. Accessed 2/9/21, 2021. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

12. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extra-hepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol. 2015;33(24):2617–22. https://doi.org/10.1200/JCO.2014.60.2219.

13. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019;20(5):663–73. https://doi.org/10.1016/S1470-2045(18)30915-X.

14. Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. JCO Clin Cancer Inform. 2020;4:1059–71. https://doi.org/10.1200/CCI.20.00134.

15. Akula SM, Abrams SL, Steelman LS, et al. Cancer therapy and treatments during COVID-19 era. Adv Biol Regul. 2020;77:100739. https://doi.org/10.1016/j.jbior.2020.100739.

16. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. Ann Intern Med. 2020;172(11):756–8. https://doi.org/10.7326/M20-1133.

17. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol. 2008;15(3):683–90. https://doi.org/10.1245/s10434-007-9747-3.

18. STATA/IC-14. Version Version Release 14. StataCorp, LP; 2015.

19. Cillo U, Fondevila C, Donadon M, et al. Surgery for cholangiocarcinoma. Liver Int. 2019;39(Suppl 1):143–55. https://doi.org/10.1111/liv.14089.

20. Nuzzo G, Giuliante F, Ardito F, et al. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients. Arch Surg. 2012;147(1):26–34. https://doi.org/10.1001/archsurg.2011.771.

21. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative mortality after liver resection for perihilar cholangiocarcinoma: development of a risk score and importance of biliary drainage of the future liver remnant. *J Am Coll Surg*. Aug 2016;223(2):321–331 e1. https://doi.org/10.1016/j.jamcollsurg.2016.03.035

22. Tzeng CW, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford). 2014;16(5):459–68. https://doi.org/10.1111/hpb.12155.

23. Martin SP, Ruff S, Diggs LP, et al. Tumor grade and sex should influence the utilization of portal lymphadenectomy for early stage intrahepatic cholangiocarcinoma. HPB (Oxford). 2019;21(4):419–24. https://doi.org/10.1016/j.hpb.2018.07.026.

24. Bagante F, Spolverato G, Merath K, et al. Intrahepatic cholangiocarcinoma tumor burden: a classification and regression tree model to define prognostic groups after resection. Surgery. 2019;166(6):983–90. https://doi.org/10.1016/j.surg.2019.06.005.

25. Beal EW, Cloyd JM, Pawlik TM. Surgical treatment of intrahepatic cholangiocarcinoma: current and emerging principles. *J Clin Med*. Dec 30 2020;10(1). https://doi.org/10.3390/jcm10010104

26. Cipriani F, Ratti F, Fiorentini G, Reineke R, Aldrighetti L. Systematic review of perioperative and oncologic outcomes of minimally-invasive surgery for hilar cholangiocarcinoma. *Updates Surg*. Feb 22 2021; https://doi.org/10.1007/s13304-021-01006-6

27. Jikei K, Ebata T, Mizuno T, et al. Oncologic reappraisal of bile duct resection for middle-third cholangiocarcinoma. *Ann Surg Oncol*. Sep 22 2020; https://doi.org/10.1245/s10434-020-09157-3

28. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2(3):322–9. https://doi.org/10.1001/jamaoncol.2015.3856.

29. Fedewa SA, Edge SB, Stewart AK, Halpern MT, Marlow NM, Ward EM. Race and ethnicity are associated with delays in breast cancer treatment (2003–2006). J Health Care Poor Underserved. 2011;22(1):128–41. https://doi.org/10.1353/hpu.2011.0006.

30. Levy H, Janke A. Health literacy and access to care. J Health Commun. 2016;21(Suppl 1):43–50. https://doi.org/10.1080/10810730.2015.1131776.

31. Halbert CH, Armstrong K, Gandy OH Jr, Shaker L. Racial differences in trust in health care providers. Arch Intern Med. 2006;166(8):896–901. https://doi.org/10.1001/archinte.166.8.896.

32. Davis TC, Williams MV, Marin E, Parker RM, Glass J. Health literacy and cancer communication. CA Cancer J Clin May-Jun. 2002;52(3):134–49. https://doi.org/10.3322/canjclin.52.3.134.

33. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31(9):1188–95. https://doi.org/10.1200/JCO.2012.41.5984.

34. Aktas G, Kus T, Balkan A, Metin T, Gulsen MT, Abali H. Prognostic factors in patients with advanced extrahepatic cholangiocarcinoma: a single center experience. Medicine (Baltimore). 2019;98(8): e14556. https://doi.org/10.1097/MD.0000000000014556.

35. Thong DW, Kim J, Naik A, Lu CT, Nolan GJ, Von Papen M. Delay to adjuvant chemotherapy: survival and recurrence in patients of rectal cancer treated with neo-adjuvant chemoradiotherapy and surgery. J Gastrointest Cancer. 2020;51(3):877–86. https://doi.org/10.1007/s12029-019-00312-y.

36. McMillan MT, Ojerholm E, Roses RE, et al. Adjuvant radiation therapy treatment time impacts overall survival in gastric cancer. Int J Radiat Oncol Biol Phys. 2015;93(2):326–36. https://doi.org/10.1016/j.ijrobp.2015.05.025.

37. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32(6):504–12. https://doi.org/10.1200/JCO.2013.50.7657.

38. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. Am J Epidemiol. 2011;173(7):761–7. https://doi.org/10.1093/aje/kwq439.

39. Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399–424. https://doi.org/10.1080/00273171.2011.568786.