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

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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].
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 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
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 1 | Demographic, clinical, and management characteristics of the entire patient population by time to adjuvant therapy stratified by median time to initiation |
|---------|-------------------------------------------------|
|         | ≤ 59 days | ≥ 59 days |
|         | n = 3,939 | n = 3,794 |
| 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 |

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 | P < 0.01

Radiation alone | 108  | 3   | 175    | 5   |
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   |

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

| Margin status                | Odds ratio | Standard error | z-score | P > z 95% confidence interval |
|-----------------------------|------------|----------------|---------|-----------------------------|
| 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 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 Reference       |            |                |         |                             |
| 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           | -1.12   | 0.90 0.79 1.24              |
| Unknown                      | 0.82       | 0.09           | -1.81   | 0.07 0.66 1.02              |
| Stage at diagnosis Reference |            |                |         |                             |
| Stage 1                      |            |                |         |                             |
| 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 Reference                |            |                |         |                             |
| ≤ 65 years Reference         |            |                |         |                             |
| > 65 years                   | 1.20       | 0.10           | 2.27    | **0.02** 1.03 1.41          |
| Treatment modality Reference |            |                |         |                             |
| 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 Reference               |            |                |         |                             |
| 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              |
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.

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

| Treatment modality       | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| 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         | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| 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               | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| 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                     | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| 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                      | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| ≤ 65 years               | Reference  |                |         |       |                        |
| > 65 years               | 1.23       | 0.08           | 3.18    | 0.00  | 1.08–1.40              |

| Tumor location           | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|--------------------------|------------|----------------|---------|-------|------------------------|
| Intrahepatic             | Reference  |                |         |       |                        |
| Extranhepatic            | 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              |
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.

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

| Predictor                                | Odds ratio | Standard error | z-score | P > z | 95% confidence interval |
|------------------------------------------|------------|----------------|---------|-------|-------------------------|
| **Charlson group**                       |            |                |         |       |                         |
| 0 Reference                              | 1.00       | 0.10           | 0.00    | 1.00  | 1.00 1.00               |
| 1 Reference                              | 1.19       | 0.10           | 2.09    | 0.04  | 1.01 1.40               |
| **Grade**                                |            |                |         |       |                         |
| Well differentiated Reference            | 1.00       | 0.10           | 0.00    | 1.00  | 1.00 1.00               |
| Moderately differentiated Reference      | 0.75       | 0.09           | -2.39   | 0.02  | 0.60 0.95               |
| Poorly differentiated Reference          | 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                | 0.62       | 0.13           | -2.22   | 0.03  | 0.41 0.95               |
| Chemotherapy alone                       | 0.54       | 0.12           | -2.86   | < 0.01 | 0.35 0.82               |
| Chemoradiation                           | 0.54       | 0.12           | -2.86   | < 0.01 | 0.35 0.82               |
| **Percent of residents without a high school degree** |            |                |         |       |                         |
| 29% Reference                            | 0.93       | 0.11           | -0.57   | 0.57  | 0.74 1.18               |
| 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%                                      | 0.91       | 0.10           | -0.59   | 0.56  | 0.75 1.17               |
| **Race**                                 |            |                |         |       |                         |
| White Reference                          | 1.26       | 0.16           | 1.75    | 0.08  | 0.97 1.62               |
| 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                  | 0.90       | 0.07           | -1.46   | 0.14  | 0.78 1.04               |
| Node positive                            | 0.90       | 0.07           | -1.46   | 0.14  | 0.78 1.04               |
| **Insurance status**                     |            |                |         |       |                         |
| Private insurance                        | 1.04       | 0.23           | 0.18    | 0.86  | 0.68 1.60               |
| 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                               | 1.40       | 0.14           | 3.3     | < 0.01 | 1.15 1.71               |
| > 65 years                               | 1.40       | 0.14           | 3.3     | < 0.01 | 1.15 1.71               |
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 initiation 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 patients 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)

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)
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 healthcare 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.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12029-022-00820-4.

Author Contribution

MP and RT conceived and designed the research. MP conducted the data analysis and wrote the manuscript. All authors read, edited, and approved the manuscript.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability

The custom code created for analysis of the data is available from the corresponding author on reasonable request.

Declarations

Conflict of Interest

The authors declare no competing interests.

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