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ORIGINAL ARTICLE

Surgical Delay Is Associated with Improved Survival in Hepatocellular Carcinoma: Results of the National Cancer Database

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Abstract

Background Hepatocellular carcinoma (HCC) is one of the fastest growing causes of cancer-related death in the USA. Studies that investigated the impact of HCC therapeutic delays are limited to single centers, and no large-scale database research has been conducted. This study investigated the association of surgical delay and survival in HCC patients.

Methods Patients underwent local tumor destruction and hepatic resection for stages I–III HCC were identified from the 2004 to 2013 Commission on Cancer's National Cancer Database. Surgical delay was defined as > 60 days from the date of diagnosis to surgery. Generalized linear-mixed model assessed the demographic and clinical factors associated with delay, and frailty Cox proportional hazard analysis examined the prognostic factors for overall survival.

Results A total of 12,102 HCC patients met the eligibility criteria. Median wait time to surgery was 50 days (interquartile range, 29–86), and 4987 patients (41.2%) had surgical delay. Delayed patients demonstrated better 5-year survival for local tumor destruction (29.1 vs. 27.6%; $P = .001$) and resection (44.1 vs. 41.0%; $P = .007$). Risk-adjusted model indicated that delayed patients had a 7% decreased risk of death (HR, 0.93; 95% CI, 0.87–0.99; $P = .027$). Similar findings were also observed using other wait time cutoffs at 50, 70, 80, 90, and 100 days.

Conclusions A plausible explanation of this finding may be case prioritization, in which patients with more severe and advanced disease who were at higher risk of death received earlier surgery, while patients with less-aggressive tumors were operated on later and received more comprehensive preoperative evaluation.

Keywords Hepatocellular carcinoma · National Cancer Database · Surgical delay · Wait time · Cancer survival

Introduction

In the USA, hepatocellular carcinoma (HCC) is one of the fastest growing causes of cancer-related death, and death rates have doubled since the mid-1980s.[1] According to 2017 estimates, there were 40,710 newly diagnosed cases and 28,920 associated deaths of liver cancer in the USA.[2] The detrimental effect of HCC is indicated by its poor survival, with an estimated 5-year relative survival rate of just 17.7%.[3] Early-stage HCC patients can receive potentially curative options, such as liver transplantation, partial resection, and radiofrequency ablation (RFA).[4] Due to the shortage of liver donors with potential recipients outnumbering donors, and a lack of access to transplantation centers,[5] many surgeons perform resection and locoregional therapies as alternative treatments or as bridging therapy to prevent tumor progression.[6]

Due to the poor prognosis of HCC, it is necessary to initiate early active therapy once the disease is diagnosed. Furthermore, the natural course of untreated HCC is associated with

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advanced cancer staging.[7] The transition from diagnosis to treatment is complex and often requires multiple steps and many healthcare providers.[8] This transition involves decision-making on the optimal treatment, patient referral, appointment scheduling, preoperative clearance, and patient adherence in undertaking treatment.[9] These steps can occur in isolation or in combination, which often makes timely intervention difficult to accomplish. An obstacle that occurs in any stage could result in treatment delay. A systematic review consisting of 177 studies investigated the association between time to diagnosis, treatment, and clinical outcomes across different cancer types.[10] Although there are conflicting findings on the impact of delay from diagnosis to treatment in various malignancies, a large number of cancer studies have reported that prolonged wait time to surgery was associated with less-favorable outcomes.[10]

Currently, there are no established guidelines for defining delay in HCC-directed surgery or the optimal time interval from diagnosis to surgery. Several studies have investigated the clinical impact of HCC therapeutic delays or prolonged wait time on outcomes in patients who underwent locoregional therapies,[11–13] resection,[14, 15] and with different treatments analyzed altogether.[9, 16] Nevertheless, the findings produced inconsistent results and most were restricted to single centers with limited sample sizes. As of this date, no large-scale database analysis has been conducted on this matter. To address the aforementioned gap, we conducted a retrospective study utilizing data drawn from the Commission on Cancer's National Cancer Database (NCDB) 2004–2013 Participant User Data File for liver cancer. The main objectives of this study were to identify the demographic and clinical factors associated with delay in HCC surgical treatment and to evaluate the relationship between surgical delay and long-term survival in HCC patients.

Methods

Data Source and Study Population

The NCDB is a nationwide, facility-based, comprehensive clinical oncology dataset that consists of 70% of newly diagnosed malignancies in the USA.[17] The NCDB is a jointly sponsored program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is sourced from hospital registry data that are collected prospectively from more than 1500 commission-accredited cancer programs in the USA and Puerto Rico and contains more than 34 million historical records of adult patients 18 years old or older.[17]

Cases selected for analysis were composed of cancers reported with International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), topographical code C22.0 (liver), and histopathologic types 8170–8175 (hepatocellular carcinoma) ($n = 118,800$). The study solely consisted of cases with a malignant primary tumor site, and cases were staged in accordance with the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging system. Based on the eligibility criteria (Fig. 1 summarizes the patient selection process), we included HCC patients surgically treated with local tumor destruction (LTD) and hepatic resection. For disease stage, the analysis was limited to cases with stages I to III disease. Clinical stage was given priority, and pathologic stage was used when clinical stage was not reported. Patients with a sequence number other than "00" or "01" were excluded. Sequence code "00" indicates that the patient had only one lifetime cancer diagnosis and "01" represents that the reported tumor was the first of multiple diagnoses. Since wait time to surgery was based on the number of days between date of diagnosis to date of the most definitive surgery, patients who received cancer-directed surgery prior to undergoing definitive surgery were excluded. We further excluded patients whose wait time between diagnosis and definitive surgery was unavailable, as well as patients with definitive surgery performed past 2 years after diagnosis to eliminate for possible outliers. Cases were excluded if the diagnosis date was the same as date of definitive surgery, which indicated an emergent procedure or coding error. The final study population consisted of 12,102 patient-level observations. Survival data were available for patients diagnosed between 2004 and 2012 ($n = 10,285$), and those diagnosed in 2013 were not included in survival analysis ($n = 1817$).

Definitions and Coding

Wait time to surgery was classified as a dichotomous outcome of "non-delayed" and "delayed" groups. The date of diagnosis was coded as that of the most definitive method of diagnostic confirmation, and diagnosis was primarily based on histologic or cytologic confirmation of biopsy specimens (77.1%) and imaging techniques (20.1%). Based on the data distribution and proportionality, and a review of similar studies that defined delay in patients who underwent locoregional therapies or resection,[11, 16, 18] delay in surgery was defined as an interval of longer than 60 days.

For the variables used in this study, facility type was classified as comprehensive community cancer program, community cancer program, academic research cancer program, and integrated network cancer program. Patient demographic data included age at diagnosis, gender, race/ethnicity, insurance status, travel distance to treatment facility, and Charlson-Deyo comorbidity score, which is a comorbidity index based on ICD diagnosis codes. Clinical data consisted of AJCC TNM stage, preoperative serum alpha-fetoprotein (AFP), size of primary tumor, tumor grade (collected at pathologic diagnosis), Model for End-Stage Liver Disease (MELD) score,

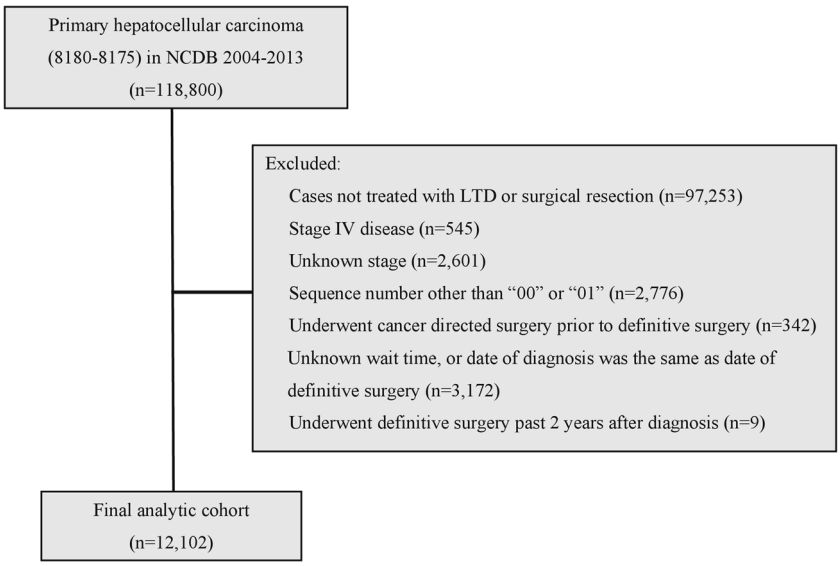


Fig. 1 Diagram for patient selection. Abbreviations: NCDB, National Cancer Database; LTD, local tumor destruction

and surgical intervention of primary site (LTD and resection). Treatment surgery was defined as cancer-directed surgical intervention, excluding incisional biopsy. In the database, LTD included but was not limited to RFA, electrocautery ablation, laser ablation, photodynamic therapy, cryosurgery, percutaneous ethanol injection, and acetic acid injection. Partial or simple removal of the primary tumor site, which consisted of wedge resection, segmental resection, lobectomy, and extended lobectomy were considered surgical resection.

Statistical Analysis

All data analyses were conducted using SAS 9.4 (*SAS Institute*, Inc., Cary, NC). Descriptive statistics were performed on patient demographics and clinical characteristics. Chi-square test was utilized to examine the association of categorical variables, and Mann-Whitney *U* non-parametric test reported mean and standard deviation for the continuous variable. To identify factors associated with surgical delay, all demographic and clinical factors with the exception of MELD score were first assessed in univariate analysis. The candidate variables with statistical significance (inclusion $P < 0.10$) were then entered into a multivariate generalized linear-mixed model accounting for clustering of outcomes within hospitals. Patient survival was determined in months from the date of diagnosis to the date of last contact or death as a result of any cause, and patients were censored at the time of lost to follow-up. The 5-year unadjusted survival based on time from diagnosis to surgery was examined using Kaplan-Meier plots stratified by surgical intervention, and significance was evaluated by log-rank test. A Cox proportional hazards frailty model adjusting for all factors (except for MELD score) was built to determine the predictors of overall survival and adjusted risk ratios. Since components of the MELD score were included in the database starting 2010, we were not able to adjust for this variable in survival analysis due to insufficient years of follow-up. In addition to using 60 days as the main cutoff point to define surgical delay, survival was further evaluated using wait time cutoffs at 50, 70, 80, 90, and 100 days, adjusting for demographic and clinical factors. For all tests, a two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Patient Demographics

The median follow-up time of the entire cohort was 25.9 months (range, 0–130.0 months), and median wait time from diagnosis to definitive surgery was 50 days (interquartile range, 29–86 days). Figure 2 illustrates the distribution of wait time to surgery by month intervals. A total of 4987 patients (41.2%) had a wait time > 60 days after date of HCC diagnosis. Within the delayed group, 85 patients (1.7%) underwent surgery after a year since diagnosis. Among all patients, 52.5% underwent LTD and 47.5% received resection. The mean age of diagnosis was 62.5 years, and most patients were male (72.5%). Based on patient demographic characteristics (Table 1), delayed patents were more likely be male (74.5 vs. 71.1%), African American race (16.2 vs. 13.1%), Medicaid holder (16.6 vs. 12.3%), and traveling for > 100 miles to treatment facilities (12.3 vs. 10.6%). There was also a greater proportion of delayed patients treated in academic research cancer centers (71.5 vs. 66.5%). In terms of clinical characteristics, there was a greater proportion of non-delayed patients who had stage III disease (18.6 vs. 13.9%), with primary tumor > 5 cm (36.3 vs. 25.5%) and having poorly differentiated/undifferentiated tumor (14.9 vs. 9.2%). Furthermore, in

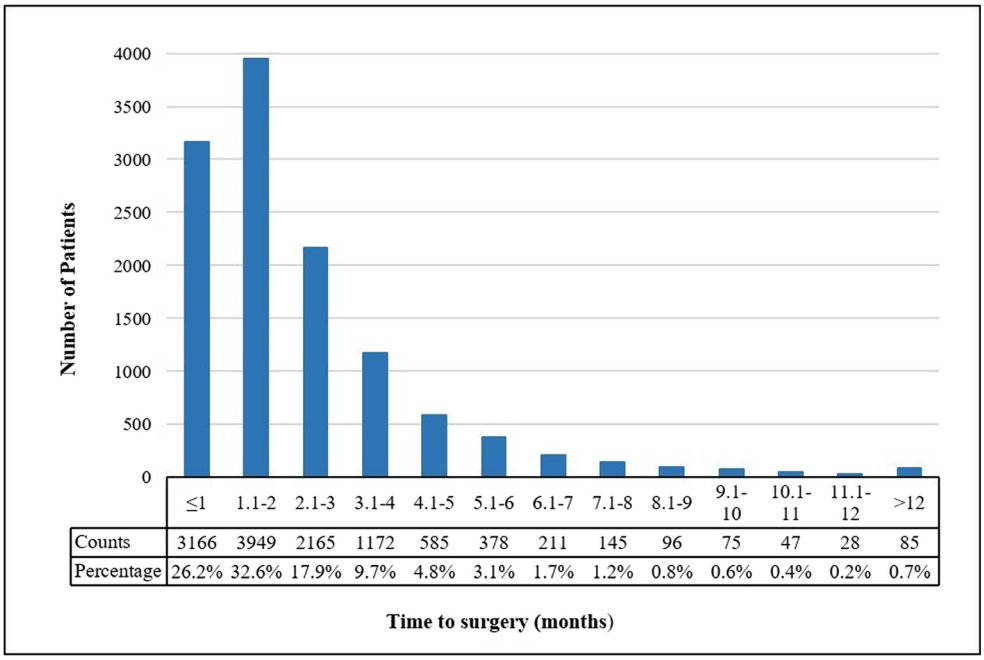


Fig. 2 Patient distribution of wait time from diagnosis to surgery by month intervals. Excluded definitive surgeries performed past 2 years after diagnosis date

comparison, delayed patients tended to have underwent surgical resection (53.8 vs. 38.7%).

Independent Factors Associated with Surgical Delay

Supplemental Table 1 outlines the results from multivariate analysis and presents the demographic and clinical factors that were significantly associated with wait time to surgery. As shown, travel distance to treatment facility of > 100 versus ≤ 10 miles increased odds of delay by 25% (OR, 1.25; 95% CI, 1.08–1.46). Female patients had lower odds for experiencing delay (OR, 0.85; 95% CI, 0.78–0.94), and African Americans had higher odds for having delayed surgery compared with non-Hispanic Caucasian patients (OR, 1.32; 95% CI, 1.17–1.49). Likewise, the odds for delay was higher among Medicaid beneficiaries compared with private insurance holders (OR, 1.28; 95% CI, 1.13–1.45). Clinically, patients with poorly differentiated or undifferentiated tumor had lower odds for delayed surgery compared with those with well-differentiated tumor (OR, 0.70; 95% CI, 0.60–0.83), and this was also the trend for larger tumor versus tumor < 2 cm (2–5 vs. < 2 cm (OR, 0.87; 95% CI, 0.77–0.99); > 5 vs. < 2 cm (OR, 0.70; 95% CI, 0.60–0.81)). Moreover, compared with LTD intervention, patients treated with resection were less likely to experience delay (OR, 0.70; 95% CI, 0.63–0.78).

Estimates of Survival Probability

In this cohort, the median survival was 37.7 months for delayed patients and 36.6 months in patients without surgical delay. Figure 3 presents the Kaplan-Meier estimates of wait time to surgery, and Fig. 4 details the unadjusted stage-specific survival probability. For all stages combined, compared with patients without delay, delayed patients had significantly better 5-year survival for LTD (29.1 vs. 27.6%; $P = .001$) and resection (44.1 vs. 41.0%; $P < .001$). Likewise, this trend was correspondingly observed for 3-year survival (delayed vs. non-delayed: LTD (45.1 vs. 42.8%); resection (61.8 vs. 56.7%)) and 1-year survival (delayed vs. non-delayed: LTD (82.7 vs. 74.8%); resection (85.4 vs. 80.1%)). For stage-specific 5-year survival, a more-favorable prognosis was observed in delayed patients who underwent LTD for stage II (28.7 vs. 23.6%; $P = .008$) and stage III disease (11.9 vs. 11.4%; $P = .003$) and surgical resection for stage III disease (27.2 vs. 22.0%; $P = .002$). In sum, no comparison revealed a significantly higher survival probability among patients without delay.

Independent Factors Associated with Risk-Adjusted Overall Survival

As indicated in Table 2, patients who received surgery > 60 days after diagnosis date had a 7% decreased risk of death than patients with wait time ≤ 60 days (HR, 0.93; 95% CI, 0.87–0.99; $P = .027$). Compared with cases treated in comprehensive community cancer programs, those who received care in academic research cancer programs had a 14% decreased risk of mortality (HR, 0.86; 95% CI, 0.79–0.94). Of the demographic factors, Asian race was a predictor of decreased mortality risk (HR, 0.76; 95% CI, 0.68–0.84). Significant prognostic factors for worse survival consisted of Medicaid (HR, 1.12; 95% CI, 1.00–1.24) and Medicare insurance coverage (HR, 1.12; 95% CI, 1.03–1.22), Charlson-Deyo score ≥ 2 (HR, 1.19; 95% CI, 1.09–1.29), stage II (HR, 1.11; 95% CI, 1.03–1.20) and stage

Table 1 Demographic and clinical characteristics based on wait time from diagnosis to surgery

Characteristics	Wait time to surgery		
	≤ 60 days ($n = 7115$; n (%))	> 60 days ($n = 4987$; n (%))	P value
Facility classification			
Comprehensive community cancer program	1487 (20.9)	916 (18.4)	< .001
Community cancer program	192 (2.7)	114 (2.3)	
Academic research cancer program	4730 (66.5)	3563 (71.5)	
Integrated network cancer program	468 (6.6)	318 (6.4)	
Unknown/other	238 (3.4)	76 (1.5)	
Age at diagnosis	62.8 ± 11.8	62.0 ± 10.3	< .001
Gender			
Male	5055 (71.1)	3716 (74.5)	< .001
Female	2060 (29.0)	1271 (25.5)	
Race/ethnicity			
Non-Hispanic Caucasian	4266 (60.0)	2793 (56.0)	<.001
Black	933 (13.1)	810 (16.2)	
Asian	873 (12.3)	564 (11.3)	
Hispanic	670 (9.4)	587 (11.8)	
Unknown	373 (5.2)	233 (4.7)	
Insurance status			
Private	2621 (36.8)	1726 (34.6)	<.001
Medicaid	873 (12.3)	829 (16.6)	
Medicare	3159 (44.4)	2098 (42.1)	
Not insured	266 (3.7)	197 (4.0)	
Unknown	196 (2.8)	137 (2.8)	
Travel distance to facility			
≤10 miles	2791 (39.2)	1971 (39.5)	.015
10.1–50 miles	2626 (36.9)	1731 (34.7)	
50.1–100 miles	819 (11.5)	593 (11.9)	
>100 miles	754 (10.6)	613 (12.3)	
Unknown	125 (1.8)	79 (1.6)	
Charlson-Deyo comorbidity score			
0	3486 (49.0)	2352 (47.2)	.016
1	2070 (29.1)	1434 (28.8)	
≥ 2	1559 (21.9)	1201 (24.1)	
AJCC TNM stage			
I	3980 (55.9)	2893 (58.0)	< .001
II	1811 (25.5)	1401 (28.1)	
III	1324 (18.6)	693 (13.9)	
Alpha-fetoprotein level			
Normal	1814 (25.5)	1313 (26.3)	< .001
Elevated	3446 (48.4)	2628 (52.7)	
Unknown	1855 (26.1)	1046 (21.0)	
Tumor size			
< 2 cm	780 (11.0)	724 (14.5)	< .001
2–5 cm	3485 (49.0)	2832 (56.8)	
> 5 cm	2584 (36.3)	1269 (25.5)	
Unknown	266 (3.7)	162 (3.3)	
Tumor grade			
Well differentiated	1241 (17.4)	902 (18.1)	< .001
Moderately differentiated	2198 (30.9)	1268 (25.4)	
Poorly differentiated/undifferentiated	1063 (14.9)	461 (9.2)	

Table 1 (continued)

Characteristics	Wait time to surgery		
	≤ 60 days ($n = 7115$; n (%))	> 60 days ($n = 4987$; n (%))	P value
Unknown	2613 (36.7)	2356 (47.2)	
MELD score	13.0 ± 8.6	13.1 ± 8.5	.75
Surgical intervention of primary site			
Local tumor destruction	3291 (46.3)	3057 (61.3)	< .001
Surgical resection	3824 (53.8)	1930 (38.7)	

III disease (HR, 1.51; 95% CI, 1.37–1.67), elevated AFP level (> 500 ng/ml) (HR, 1.23; 95% CI, 1.15–1.33), and primary tumor > 5 cm (HR, 1.24; 95% CI, 1.09–1.40). Compared with LTD, surgical resection was associated with a 27% decreased risk of death (HR, 0.73; 95% CI, 0.67–0.80).

Overall Survival Using Other Wait Time Cutoffs

As shown in Table 3, wait time to surgery was dichotomized in a range of cutoff points from 50 to 100 days. In risk-adjusted overall survival, delayed patients consistently presented improved outcomes. Patients with a wait time longer than 50 days (HR, 0.93; 95% CI, 0.87–0.99), 70 days (HR, 0.91; 95% CI, 0.85–0.97), 80 days (HR, 0.93; 95% CI, 0.86–0.99), 90 days (HR, 0.91; 95% CI, 0.84–0.98), and 100 days (HR, 0.92; 95% CI, 0.84–0.99) all demonstrated decreased risk of death compared with those without delayed surgery.

Discussion

To our knowledge, this is the first study utilizing large-scale data to investigate the association of surgical delay and HCC outcomes, as well as the factors associated with wait time to surgery. As the NCDB is a national database that consists of hospital registry data collected from commission-accredited cancer programs across the USA, findings generated from this study should be more generalizable than results obtained from studies of single centers. Although it is often assumed that delay in surgery has a harmful impact on cancer prognosis, we observed that delay was associated with more optimal outcomes. This finding was consistently observed in unadjusted 5-year survival, as well as in covariate-adjusted overall survival based on wait time intervals ranging from 50 to 100 days. With the exception of a study conducted by Akce et al.,[16] which found delay to be associated with decreased risk of death among patients from the Department of Veterans Affairs treated with curative surgery, liver-directed therapy, or chemotherapy for BCLC stage C HCC (HR, 0.50; 95% CI, 0.37–0.67), other studies of hepatocellular carcinoma patients have reported that either prolonged wait time to surgery was linked with shortened survival[9, 11–14] or that no significant association was observed.[15] In contrast with the majority of existing studies utilizing medical records, this retrospective analysis that is based on large comprehensive clinical data provides a different perspective.

While findings of this study are counterintuitive, previous research that investigated the impact of delays in diagnosis-to-treatment, first hospital visit-to-treatment, and general practitioner referral-to-treatment in lung,[19–21] colon,[22] endometrial,[23] and bladder[24] cancers also found similar trends in which prolonged wait time to surgery was associated with more optimal outcomes. A plausible explanation of this phenomenon is that tumor aggressiveness may influence delay, with more severe and advanced cases being referred to have more urgent treatments. This is also known as the waiting-time paradox, which is caused by the inclusion of patients with more severe conditions who invariably present early and have poor outcomes due to disease advancement.[10] In other words, the disease itself, such as its aggressiveness may have an influence on treatment delay; thus, delay could be a confounding factor.[23] A study that comprised 769 patients surgically treated for colon cancer found that for every quartile increase in delay, odds of mortality decreased by a ratio of 0.78.[22] The authors speculated that the advanced and high-risk cases were referred for workup and scheduled to be operated on sooner; therefore, with prioritization, delay did not pose a substantial risk of worsening prognosis.[22] Furthermore, studies conducted in lung cancer patients suggested that cases with severe signs and higher symptom burden are likely to receive prompt treatment, while candidate patients of curative treatments might have to wait longer.[19–21] As a plausible explanation for our finding, the triage effect of operating on less urgent patients at a later time may have led to reasonable delays as a result of completing more comprehensive preoperative evaluation and staging for patients with less aggressive tumors. In our analysis, we observed that patients with primary tumor ≥ 2 cm and of poorly differentiated or undifferentiated grade (i.e., tumor biology) were significantly less likely to experience delay. Thus comparatively, patients with less aggressive tumor biology were treated at later times. These observations support our speculation about the practice of case prioritization.

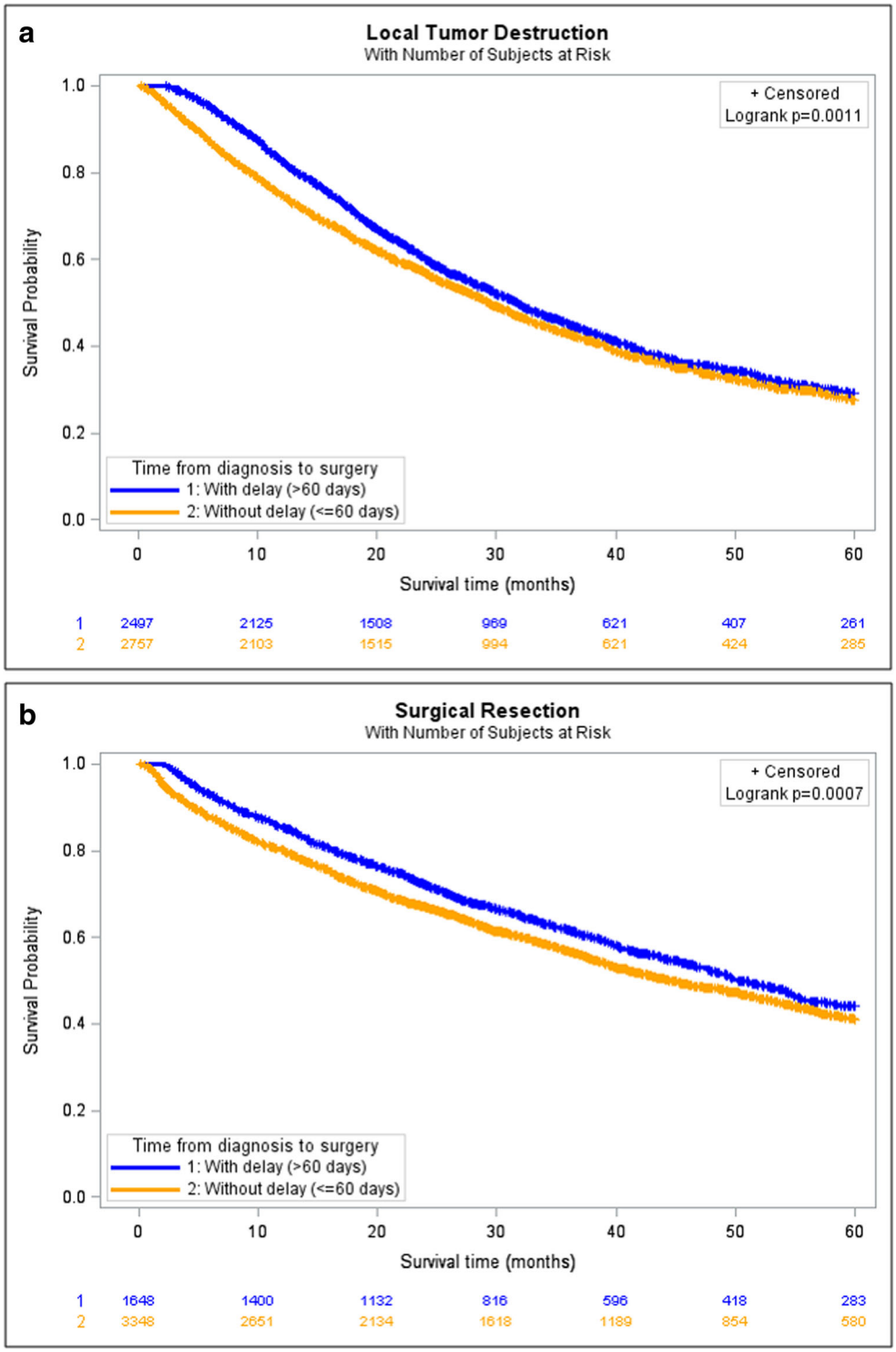
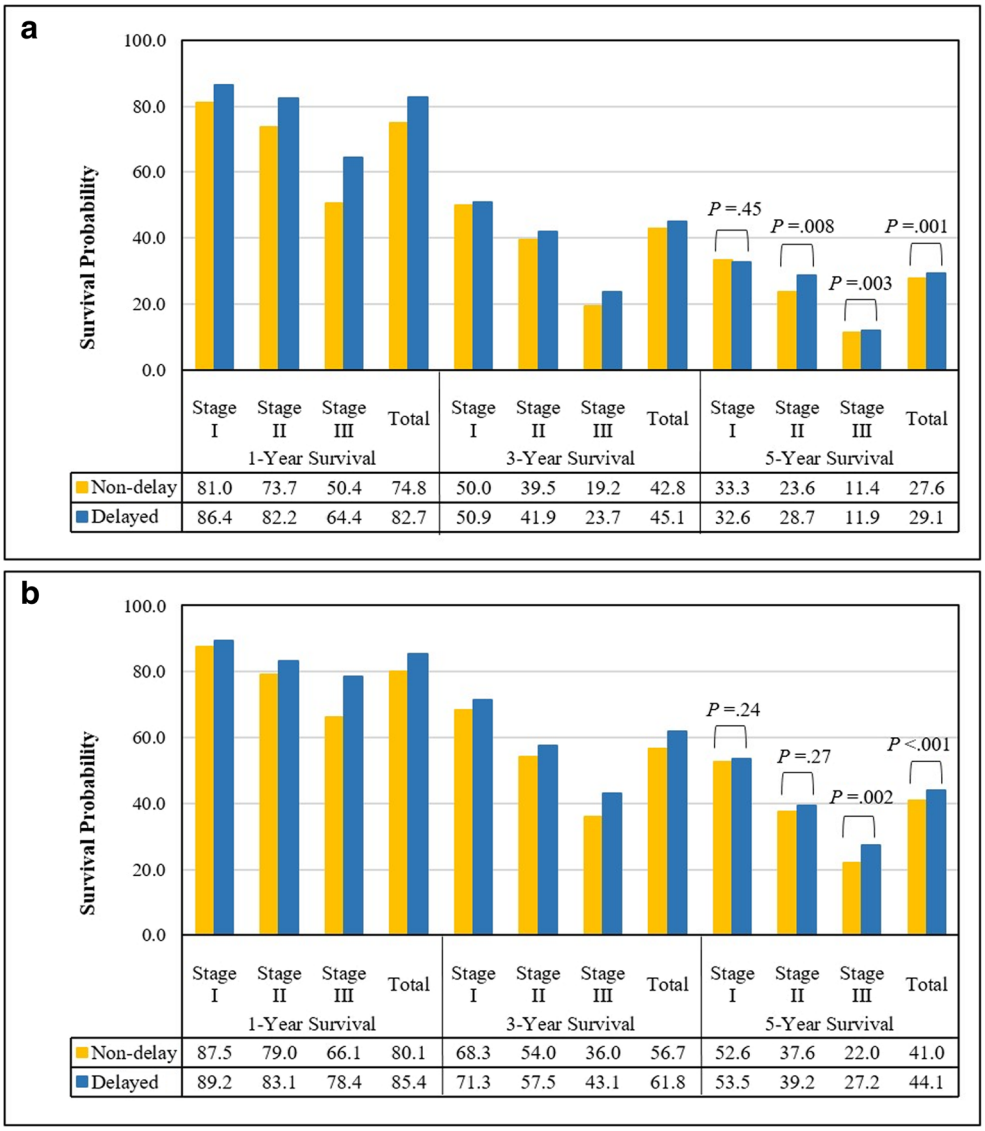


Fig. 3 Kaplan-Meier survival estimates of wait time to surgery: **a** Local tumor destruction (n = 5254). **b** Surgical resection (n = 4996)

For comparison of 5-year survival between delayed versus non-delayed patients (Fig. 4), the strength of association or difference in survival probability increased in advanced disease stage. For instance, among stage I patients who underwent resection, the difference in 5-year survival probability between the two wait time groups was only 0.9% (53.5 subtract 52.6); however, stage III patients presented a survival difference of 5.2% (27.2 subtract 22.0). A similar trend was also observed in patients treated with LTD, in which significant association was observed in stage III patients but not those with stage I disease. Likewise, Akce and colleagues demonstrated that delay was associated with decreased risk of mortality in HCC patients with BCLC stage C, but no association was detected for BCLC stage 0-A or BCLC stage



	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total
	1-Year Survival				3-Year Survival				5-Year Survival			
Non-delay	81.0	73.7	50.4	74.8	50.0	39.5	19.2	42.8	33.3	23.6	11.4	27.6
Delayed	86.4	82.2	64.4	82.7	50.9	41.9	23.7	45.1	32.6	28.7	11.9	29.1

	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total
	1-Year Survival				3-Year Survival				5-Year Survival			
Non-delay	87.5	79.0	66.1	80.1	68.3	54.0	36.0	56.7	52.6	37.6	22.0	41.0
Delayed	89.2	83.1	78.4	85.4	71.3	57.5	43.1	61.8	53.5	39.2	27.2	44.1

Fig. 4 Survival probability of 1, 3, and 5 years, stratified by wait time to surgery, surgical intervention, and disease stage: **a** local tumor destruction and **b** surgical resection

B.[16] These results further strengthen our speculation about the practice of prioritizing more serious cases in advanced stage. Furthermore, our descriptive result indicated that 71.5% of delayed patients were treated in academic research cancer programs, while this number was lower for non-delayed patients (66.5%). In this cohort, patients who were treated in academic cancer centers had the most favorable outcome. Since academic hospitals are more suited to manage the complicated and multi-disciplinary care that HCC surgeries often require,[25] patients with less urgent conditions who were treated at a later time likely received more comprehensive preoperative assessment and postoperative follow-up offered in academic research cancer centers.

Another explanation for our finding is that this study examined survival starting from diagnosis rather than from the onset of symptoms. It is known that an assessment that begins from an earlier time point would likely avoid lead-time bias, and the increase in survival could be due to earlier diagnosis. In covariate-adjusted analysis, we were not able to account for certain potential confounding factors, including liver disease etiology, clinical indications of liver dysfunction (such as presence of hepatic encephalopathy and ascites), and laboratory values/scores (such as liver enzymes and Child-Turcotte-Pugh score) due to unavailability or largely missing values. Although risk-adjusted analyses included disease stage and tumor grade, stage is based on structural involvement and grade is determined by pathological appearance; these factors were not able to fully characterize direct liver function.

Currently, there is scarce research using covariates-adjusted analysis to investigate the predictors of delay in HCC surgery (Supplemental Table 1). Consistent with our finding, a study using records abstracted from the Pennsylvania Cancer Registry found that HCC patients who underwent resection, lobectomy or partial hepatectomy were 52% less likely than patients treated with locoregional intervention to experience surgical delay.[18] In addition, the same

Table 2 Cox proportional hazards frailty model to estimate adjusted risk of overall mortality

Characteristics	Adjusted HR	95% CI	*P* value
Wait time to surgery			
Wait time ≤ 60 days	Reference		
Wait time > 60 days	0.93	0.87–0.99	.027
Facility classification			
Comprehensive community cancer program	Reference		
Community cancer program	1.04	0.83–1.30	.76
Academic research cancer program	0.86	0.79–0.94	< .001
Integrated network cancer program	1.05	0.91–1.21	.51
Age at diagnosis	1.01	1.00–1.01	< .001
Gender			
Male	Reference		
Female	0.95	0.88–1.02	.14
Race/ethnicity			
Non-Hispanic Caucasian	Reference		
Black	1.05	0.95–1.15	.38
Asian	0.76	0.68–0.84	< .001
Hispanic	1.01	0.90–1.12	.93
Insurance status			
Private	Reference		
Medicaid	1.12	1.00–1.24	.042
Medicare	1.12	1.03–1.22	.009
Not insured	1.04	0.85–1.26	.71
Travel distance to facility			
≤10 miles	Reference		
10.1–50 miles	0.92	0.85–0.99	.029
50.1–100 miles	1.03	0.92–1.15	.60
>100 miles	1.03	0.92–1.16	.61
Charlson-Deyo comorbidity score			
0	Reference		
1	0.99	0.92–1.07	.85
≥2	1.19	1.09–1.29	< .001
AJCC TNM stage			
I	Reference		
II	1.11	1.03–1.20	.008
III	1.51	1.37–1.67	< .001
Alpha-fetoprotein level			
Normal	Reference		
Elevated	1.23	1.15–1.33	< .001
Tumor size			
< 2 cm	Reference		
2–5 cm	1.03	0.93–1.14	.61
> 5 cm	1.24	1.09–1.40	< .001
Tumor grade[a]			
Well differentiated	Reference		
Moderately differentiated	0.97	0.88–1.07	.53
Poorly differentiated/undifferentiated	1.08	0.95–1.23	.22
Unknown	1.07	0.97–1.18	.19
Surgical intervention of primary site			
Local tumor destruction	Reference		
Surgical resection	0.73	0.67–0.80	< .001

[a] Missing values (41.1%) for tumor grade were grouped into "Unknown" category

Table 3 Adjusted risk of overall mortality based on wait time cutoffs range from 50 to 100 days, using a 10-day increment

Wait time to surgery	% patients with delay	Adjusted HR	95% CI	*P* value
> 50 days	49.8	0.93	0.87–0.99	0.35
> 60 days	41.2	0.93	0.87–0.99	0.27
> 70 days	33.7	0.91	0.85–0.97	0.07
> 80 days	27.8	0.93	0.86–0.99	0.48
> 90 days	23.3	0.91	0.84–0.98	0.18
> 100 days	19.5	0.92	0.84–0.99	0.40

Each comparison was referenced to the non-delayed group

study reported that male gender was a predictor of delay.[18] Corresponding to our results, a study that utilized the 1995–2005 NCDB file consisting of 1,228,071 patients who underwent resection for gastrointestinal and breast cancers observed that African American race and Medicaid insurance were demographic factors significantly associated with prolonged wait time to treatment.[26] Similar to our finding, previous studies have shown that longer travel distance to facility was a predictor of surgical delay in patients treated for cancers of the pancreas[27] and bladder.[28] We also found that cases with a primary tumor 2 cm or larger were less likely to experience delay. An explanation for this is that in comparison, resection resulted in a 30% decreased odds of delay, and 93.7% of resection procedures were performed on primary tumor ≥ 2 versus 80.9% for LTD. Additionally, we observed that patients without delay were more likely to be treated in centers that did not perform liver transplantation; as 30.1% of non-delayed patients were treated in non-transplant programs compared with 25.8% of delayed patients. This likely suggests that a number of patients underwent prompt surgery due to that transplant program was not available in where they received care.

There are several limitations in this study that should be noted. First, due to the retrospective nature of this database, information concerning to patient and physician treatment decision-making cannot be captured in detail. As a result, we could not assess the case prioritization approach in HCC surgical care, and its level of impact on our findings. As discussed previously, we were unable to examine certain clinical preoperative indications of liver dysfunction (presence of hepatic encephalopathy and hepatic ascites), and preoperative laboratory values/scores (liver enzymes and Child-Turcotte-Pugh score). Although data from which MELD score can be calculated are available (international normalized ratio of prothrombin time, bilirubin, and creatinine), this information is largely missing (67.3%) due to unavailability until 2010. Furthermore, since chemoembolization was coded as chemotherapy in the database, we were unable to distinguish between transarterial therapy and systemic chemotherapy; thus, we did not include chemotherapy in risk-adjusted analyses. In this cohort, survival analysis was based on all-cause death rather than HCC-specific death as cancer-specific survival data were not captured. These limitations should serve to call for an improvement in the quality of NCDB data and to include additional clinically relevant variables. Nevertheless, taking all factors into consideration, we believe that the strengths of this study outweigh its limitations.

To summarize, this analysis using NCDB data found that delay in HCC surgical treatment was associated with decreased risk of death, and this phenomenon was observed in patients who underwent LTD and resection. These findings should not be perceived as an encouragement to delay time to surgery or prolong wait time. Rather, the results suggest that a reasonable delay in surgery that is potentially based on tumor aggressiveness and severity does not appear to put patients at increased risk of death. Further studies are strongly warranted to understand and re-evaluate the advantages associated with undergoing early surgery for HCC. Additionally, it would be of significance to explore the impact of symptom-to-treatment delay or diagnostic delay on HCC outcomes.

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Author Contributions KX contributed to the study design, conceptualization, statistical analysis, and drafted the original paper. KMMI was responsible for data acquisition. SWG and FR also contributed to the study design and conceptualization, and JL assisted with statistical analysis. FR, PF, HW, and KMMI critically reviewed and edited the paper for important intellectual content. SWG supervised research activities.

Compliance with Ethical Standards

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Ethics Committee Approval The study was exempted from review by the University of Nebraska Medical Center Institutional Review Board.

Conflict of Interest The authors declare that they have no conflict of interest.

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