Association of surgical interval and survival among hospital and non-hospital based patients with melanoma in North Carolina

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Abstract

Surgical excision is important for melanoma treatment. Delays in surgical excision after diagnosis of melanoma have been linked to decreased survival in hospital-based cohorts. This study was aimed at quantifying the association between the timeliness of surgical excision and overall survival in patients diagnosed with melanoma in hospital- and non-hospital-based settings, using a retrospective cohort study of patients with stage 0–III melanoma and using data linked between the North Carolina Central Cancer Registry to Medicare, Medicaid, and private health insurance plan claims across the state. We identified 6,496 patients diagnosed between 2004 and 2012 with follow-up through 2017. We categorized the time from diagnostic biopsy to surgical excision as < 6 weeks after diagnosis, 6 weeks to 90 days after diagnosis, and > 90 days after melanoma diagnosis. Multivariable Cox regression was used to estimate differences in survival probabilities. Five-year overall survival was lower for those with time to surgery over 90 days (78.6%) compared with those with less than 6 weeks (86%). This difference appeared greater for patients with Stage 1 melanoma. This study was retrospective, included one state, and could not assess melanoma specific mortality. Surgical timeliness may have an effect on overall survival in patients with melanoma. Timely surgery should be encouraged.

Keywords Melanoma · Surgery · Delays · Quality of care · Insurance · Medicare · Medicaid · Private insurance · Disparities

Abbreviations

CIPHR	Cancer information and population health resource
NCCCR	North Carolina Central Cancer Registry
AJCC	American joint committee on cancer
NCI	National cancer institute

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Introduction

Nearly 100,000 people were diagnosed with melanoma in 2019. Based on Surveillance, Epidemiology, and End Results (SEER) data, the incidence of invasive melanoma increased more than threefold over the past 40 year [1]. Melanoma is responsible for over 7,000 deaths annually, and it is estimated that patients with melanoma potentially lose an average of over 20 years of life as a result of melanoma mortality [2]. Timely surgical excision is an important part of melanoma treatment and, depending on stage of disease, is often the definitive intervention. Recently, the COVID-19 pandemic has resulted in delays in cancer surgery, particularly for early stage cancers, which may have important implications for quality and equity of care.

In cancer, delays in treatment can result in increased morbidity and mortality. For example, in breast cancer, shortening of delays to surgery has been associated with benefits

comparable to some standard treatments [3]. Previous studies in melanoma have revealed that surgical delays greater than 6 weeks, the suggested upper limit of standard of care, between diagnosis and surgery are common and disproportionately affect non-white and low-income patients, who are also at increased risk of poor clinical outcomes [4–7]. These potentially preventable delays longer than 6 weeks without definitive treatment could result in tumor progression and worse survival outcomes [8]. While delays are a metric used to assess quality of care received, less is known about how these delays affect survival. Small studies assessing the association between timeliness of surgery and survival found no effect on survival [9, 10]. In contrast, a recent U.S. national study of patients with melanoma showed that a delay in surgery of 90 days or more had a negative impact on overall survival; however, this study included only patients with melanomas diagnosed in hospitals, whereas most melanomas are diagnosed in the outpatient setting [11]. Our study sought to address this gap in knowledge.

Using a unique data set linking data from a state-wide cancer registry with insurance claims, we sought to quantify the association between surgical delay and overall survival among a diverse, insured population with widely varying access to care. In addition, we examined whether the relationship between delays in care and survival differs by initial stage at diagnosis.

Methods

Data source and study population

This was a retrospective cohort study of patients with incident stage 0–III melanoma. The data were obtained from the University of North Carolina Cancer Information Population Health Resource (CIPHR), a data resource that links cancer data from the North Carolina Central Cancer Registry to administrative and claims data from Medicare, Medicaid, and private health insurance plans across the state [12]. These data cover 70% of the cancer patients in North Carolina. We included patients aged 20–100 years whose only cancer diagnosis was melanoma. Patients were diagnosed between 2004 and 2012 and were followed for up to 5 years after diagnosis through 2017. Eligible patients were included if they had continuous enrollment in their insurance plan from 6 months prior through 12 months after diagnosis. Patients were included if they had a skin biopsy, defined as either an excision, skin biopsy, or shave removal procedure code, occurring within 30 days before or 7 days after melanoma diagnosis. Patients were excluded if their diagnosis was only identified from death certificate or autopsy. In addition, patients were excluded if they did not undergo an excision within the first year after being diagnosed with melanoma. Moreover, patients with Stage IV tumors were excluded from this analysis because delays could have been due to inoperability. Observations with missing or incomplete data for biopsy, excision, or stage at diagnoses were excluded from the analytic sample. The University of North Carolina Institutional Review Board approved the study. Informed consent was waived due to the retrospective nature of the study.

Variables

The primary outcome was overall survival, defined as the time from surgical excision to death from any cause. Survival data were obtained from data in the North Carolina Central Cancer Registry through 2017, which allowed assessment of survival at 1, 3 , and 5 years after diagnosis; patients were censored if no event was observed within 5 years of follow-up. Our primary explanatory variable was surgical delay, defined as the time between biopsy and definitive surgical excision and categorized into the following categories: <6 weeks after diagnosis, 6 weeks to 90 days after diagnosis, and >90 days after melanoma diagnosis. We excluded surgical delays beyond 365 days due to small number of cases. Potential confounders of the treatment–outcome relation included the following: Age at diagnosis, sex, race/ethnicity, American Joint Committee on Cancer (AJCC) 6th edition clinical stage of disease, tumor site, insurance coverage at diagnosis, urban vs. rural residence, year of diagnosis, specialty of the physician making the diagnosis (dermatologist vs. other), excision facility (North Carolina National Cancer Institute center vs. other), and comorbid conditions. Stage of disease was categorized as stages 0, IA, IB, II, and III; tumor site as head/neck, upper extremities, lower extremities, trunk, and other skin not otherwise specified; and insurance coverage at diagnosis as having any private, Medicare only, and any Medicaid. Residence was dichotomized as rural and urban based on the Rural Urban Commuting Area codes [13]. Comorbidities were assessed using the Charlson Comorbidity Index and were categorized as 0 vs. 1 or more comorbid condition present during the 6 months prior to diagnosis.

Data analysis

We estimated frequencies and proportions for categorical variables, and medians and interquartile ranges for continuous variables. Between-group differences in proportions and medians were assessed with chi-square tests and Kruskal–Wallis one-way analysis of variance, respectively. To estimate the effect of surgical delay on overall survival, we estimated adjusted survival probabilities from multivariable Cox regression models. We calculated survival differences and corresponding 95% confidence limits as

the difference between surgical delay grouping's survival probabilities at 1, 3, and 5 years of follow-up. The reference group comprised patients who received surgical excision < 6 weeks after diagnosis. The proportional hazards assumption was violated; consequently, we were not able to present estimates of the hazard ratio. Age at diagnosis was treated as a restricted quadratic spline with knots at the 5th, 35th, 65th, and 95th percentiles in our statistical model [14]. Moreover, to allow for flexible modeling, we allowed age to interact with other covariates in the model. The final statistical model including this flexibility had a much lower Akaike Information Criterion compared with the model with no interactions, suggesting a better model fit. ($AIC_{Final\ Model} = 13,687$, $AIC_{Main\ effects\ model} = 13,785$). Multicollinearity of variables in the final model was assessed using the variance inflation factor of 5. Variables in the Cox regression model included the following: age at diagnosis, gender, race, insurance coverage, year of diagnosis, stage at diagnosis, rurality, cancer group, whether the same provider performed the biopsy and the excision, whether a diagnostic test was performed by a dermatologist, whether the excision was conducted at a North Carolina National Cancer Institute Center, and the presence of 1 or more comorbid conditions. In order to assess effect heterogeneity, we looked across categories of stage at diagnosis. For this analysis, we collapsed stage at diagnosis into Stage 0, Stages IA/IB, and Stages II/III and ran separate multivariable models to estimate survival probabilities and differences within each stratum of stage at diagnosis. We attempted to investigate cause-specific mortality; however, the frequency of events was too low to allow us to model the multivariable relationship.

Results

Analytic sample

Our analytic sample comprised 6,496 patients (Figure S1). The sample was predominantly male (58%), non-Hispanic White (98%), insured by Medicare (62%), had Stage 0 disease (50%), and had melanomas located primarily in the head/neck (31%), upper extremities (27%), and trunk (27%) (Table 1). Figure 1 presents the distribution of surgical delay among the entire analytic sample; most patients had excision performed within 6 weeks of biopsy (84%), followed by 6 weeks to 90 days (12%), and 90–365 days after biopsy (4%). The distribution of patient comorbidities was similar across biopsy–excision intervals (Table S1).

Differences in survival probabilities

The proportion of patients who survived after 5 years of follow-up decreased with increased time to surgery from 86.4% (less than 6 weeks) to 78.6% (greater than 90 days) (Table 1). Survival probabilities were lower with increasing surgical delay time throughout the course of follow-up (Fig. 2a). These probabilities ranged from 99.9% survival after 1 year of follow-up to 74.9% survival after 5 years of follow-up (Table 2). The absolute differences in survival probabilities (S_{Diff}) for those undergoing excision 90–365 days compared with those < 6 weeks were moderate but increased over time: at 1 year, (S_{Diff}: −5.1%; 95% CL −8.0, −2.1), at 3 years (S_{Diff}: −11.6%; 95% CL −18.7, −4. 6), and at 5 years of follow-up (S_{Diff}: −15.0%; 95% CL −24.6%, −5.5%).

The effects of excision delay varied by cancer stage (Table 3; Fig. 2a–d). Survival in stage 0 was not statistically different across biopsy to surgical intervals. Specifically, among patients with stage I disease, those whose surgical excision took place 90–365 days after biopsy had a −51.3% (95% CL −72.0%, −30.6%) decrease in 5 year-survival compared with those whose excision occurred < 6 weeks. Among patients with stage II/III disease, at 1 year of follow-up, there was a moderate, but not statistically significant difference (−12.8% [95% CL −26.0%, 0.4%]) in survival probabilities between those with excisions 90–365 days after diagnosis vs. < 6 weeks.

Sensitivity analysis

Our sensitivity analysis utilizing a different categorization for surgical delays greater than the 6-week guideline found similar results as our primary analysis: we observed a similar pattern where greater surgical delay interval was associated with worse survival. The most pronounced difference was among those who were treated more than 16 weeks after biopsy (data not shown).

Discussion

We assessed the association of surgical delay on overall survival. We found that patients whose surgery was performed 90–365 days after biopsy had significantly lower probabilities of survival compared with those whose surgery was performed within the guideline-recommended 6 weeks of diagnosis.

Our findings are qualitatively similar to the effect of a 90-day or longer delay on overall survival reported by Conic and colleagues [11]. In their study, the hazard ratios for all-cause mortality were 1.1 (95% CL 1.0, 1.2) for 90–119 day delays and 1.1 (95% CL 1.0, 1.2) for ≥ 120-day surgical delays following biopsy. Similarly, among their Stage I subgroup, they reported hazard ratios of 1.3 (95% CL 1.1, 1.5) and 1.4 (95% CL 1.2, 1.7) for the 90–119 and ≥ 120-day delay surgery groups. As in our current study, Conic et al. found no difference in survival for surgical delays in patients

Table 1 Characteristics of the study sample stratified by biopsy–excision interval (n = 6,477)

Characteristic		Overall sample		Within 6 weeks of biopsy		6 weeks – 90 days after biopsy		90 – 365 days after biopsy		*P*-value
		N = 6477	%	*n* = 5430	%	*n* = 809	%	*n* = 238	%	
Age at diagnosis	Median, (IQR)	69	57, 77	69	57, 76	70	60, 77	69.5	60, 77	0.0794
Gender	Female	2700	41.7	2277	41.9	333	41.2	90	37.8	0.4284
	Male	3777	58.3	3153	58.1	476	58.8	148	62.2	
Race	NH White	6362	98.2	5337	98.3	789	97.5	236	99.2	0.1680
	Other	115	1.8	93	1.7	20	2.5	2	0.8	
Insurance Type	Any Private	2108	32. 6	1818	33.5	227	28.1	63	26.5	< 0.0001
	Medicare only	4021	62.1	3347	61.6	521	64.4	153	64.3	
	Any Medicaid	348	5.4	265	4.9	61	7.5	22	9.2	
ZIP code at diagnosis	Rural	2551	34.8	1858	34.2	312	38.6	81	34.0	0.0516
Year of diagnosis	2004	373	5.8	305	5.7	44	5.4	24	10.1	0.0063
	2005	559	8.6	475	8.8	64	7.9	20	8.4	
	2006	590	9.1	483	8.9	82	10.1	25	10.5	
	2007	693	10. 7	586	10.8	81	10.0	26	10.9	
	2008	796	12.3	660	12.2	94	11.6	42	17.7	
	2009	846	13.1	713	13.2	104	12.9	29	12.2	
	2010	829	12.8	725	13.3	84	10.4	20	8.4	
	2011	826	12.8	680	12.5	121	15.0	25	10.5	
	2012	965	14. 9	803	14.8	135	17.0	27	11.3	
Stage at diagnosis	Stage 0	3228	49.8	2747	50.6	372	46.0	109	45.8	< 0.0001
	Stage IA	1545	23.9	1341	24.7	155	19.2	49	20.6	
	Stage IB	952	14.7	773	14.2	140	17.3	39	16.4	
	Stage II	507	7.8	386	7.1	91	11.3	30	12.6	
	Stage III	245	3.8	183	3.4	51	6.3	11	4.6	
Cancer location	Head/neck	2008	31.0	1608	29.6	310	38.8	90	37.8	< 0.0001
	Upper extremities	1727	26.7	1482	27.3	195	24.1	50	21.0	
	Lower extremities	955	14.7	793	14.6	129	16.0	33	13.9	
	Trunk	1762	27.2	1525	28.1	173	21.4	64	26.9	
	Other skin, NOS	25	0.4	22	0.4	2	0.3	1	0.4	
Biopsy and Excision performed by same provider	Yes	3795	58.6	3238	59.6	394	48.7	163	68.5	< 0.0001
Dermatologist diagnosed	Yes	5210	80.4	4425	81.5	616	76.1	169	71.0	< 0.0001
Excision at NCI Center	Yes	1046	16.2	846	15.6	181	22.4	19	8.0	< 0.0001
Comorbidity Index	0	4946	76.4	4175	76.9	599	74.0	172	72.3	0.0655
	≥ 1	1531	23.6	1255	23.1	210	26.0	66	27.7	
Survival > 5 years after excision	Yes	55,466	85.6	4690	86.4	669	82.7	187	78.6	0.0001

Table 1 (continued)

Characteristic		Overall sample		Within 6 weeks of biopsy		6 weeks – 90 days after biopsy		90 – 365 days after biopsy		*P*-value
		N = 6477	%	*n* = 5430	%	*n* = 809	%	*n* = 238	%	
Melanoma specific mortality ≤ 5 years of excision	Yes	219	3.4	158	2.9	44	5.4	17	7.1	< 0.0001

IQR interquartile range, *NH* non Hispanic, *NOS* not otherwise specified, *NCI* national cancer institute

Reported *p*-values are based on Kruskal–Wallis one-way ANOVA for age at diagnosis, and Chi-square tests for categorical variables

with stages II and III melanoma. Despite similar findings, their population differed in that the data used was from the National Cancer Database (NCDB) which only contains information on hospital-based patients, whereas most melanomas, particularly stage I melanomas, are diagnosed and treated in the outpatient setting [15]. Nevertheless, both our estimates of differences in survival probabilities in the overall sample as well as those diagnosed with stage I disease support evidence for the association of surgical delay on overall survival among patients with stage I melanoma, supporting evidence that timely surgery may be an important intervention to improve overall survival.

It was notable that the surgical delays were not associated with lower survival in higher stage disease. It is possible that stage I melanomas were incompletely biopsied or incompletely staged; therefore, delays in surgery resulted in further growth of residual tumor and potential for future metastasis. Estimates of monthly growth rates of invasive melanomas have been modeled between 0.11 mm/month and 0.49 mm/month [8, 16]. However, it is perhaps more plausible that our findings in early stage melanoma (Stage I) were dissimilar to findings in later stages (Stage II/III) because of small numbers in the latter group, which could have affected our results. It is also possible that patients with significant delays in surgery had disease burden not captured by the Charlson Comorbidity Index (Table 1). However, when stratifying delays by individual co-morbid conditions, disease burden is distributed similarly across biopsy–excision intervals (Table S1). While this does not prove that overall survival differences are attributed to melanoma, these findings do suggest that co-morbidity may not explain the differences entirely. Future studies analyzing the contributions of the adjusted covariates may provide further risk factor identification.

The National Academy of Medicine identified timely delivery of health care services as one of six priorities for quality health improvement in the U.S [17]. Delays affecting morbidity and mortality have also been shown in lung, bladder, and rectal cancers [18–20]. In this study, we demonstrated an association between overall survival and treatment timeliness; however, it is less clear what the factors, including patient, provider, or tumor level that could explain this association. A recent US national study of melanoma patients treated in a hospital setting showed factors associated with longer time to surgery include nonwhite race, less education, higher comorbidity burden, advanced stage, and head or neck melanoma [21]. In particular, black patients have been shown to have longer time to surgery for hospital-based melanoma [22]. Some of these delays may be explained by a higher proportion of acral lentiginous melanoma which may require coordination between unconnected specialties, worsening delays. Compared with white patients and patients with higher socioeconomic status (SES), black

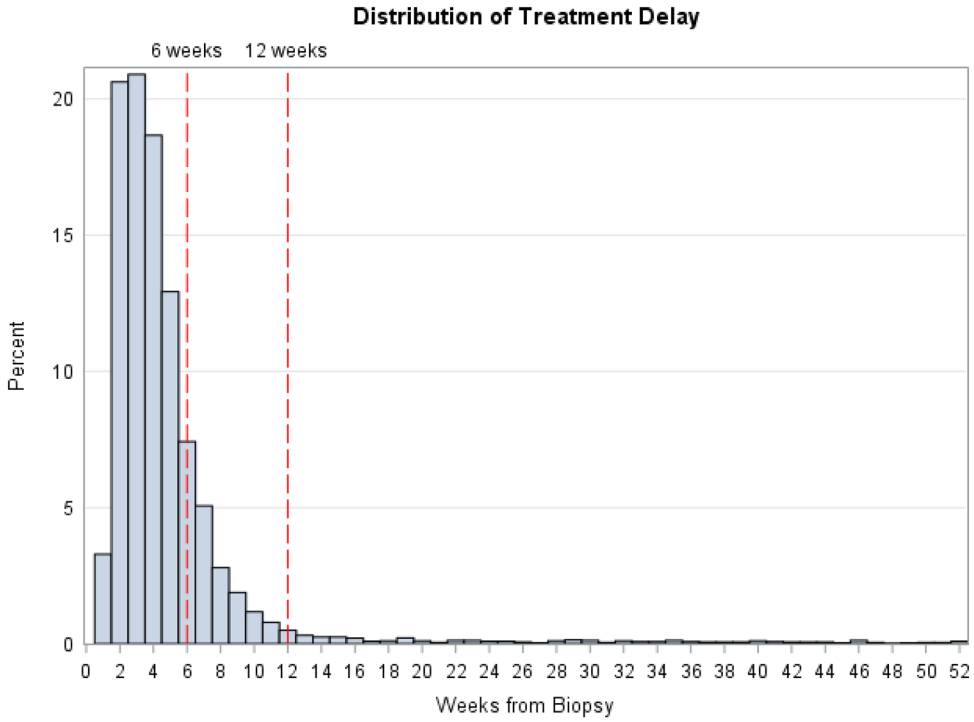

Fig. 1 Distribution of Surgical Delay

patients and poor patients have lower melanoma survival regardless of stage of disease [23, 24]. While sources of these disparities could be due to differences in tumor biology or delays in diagnosis, the lack of receipt of timely surgical care could also be a contributing factor. Therefore, further research should investigate whether potentially closing that gap in surgical delay could reduce melanoma associated disparities in outcomes, a subject of our future work.

Limitations

Our analytic sample was focused exclusively on insured patients from North Carolina diagnosed between 2004 and 2012, so our estimates of the effect may not be generalizable to other populations outside of the state. In addition, given our inclusion criteria of continuous insurance through 12 months after diagnosis, we may have missed patients who frequently cycle on and off insurance coverage. Another limitation is the relatively sparse data observed in later surgical delay categories. However, the proportion of patients with late excisions in our sample is similar to those previously reported [11]. In addition, our estimates of the effect of surgical delay on survival outcomes are based on the untestable assumptions that our models are correctly specified and there is no uncontrolled confounding. We had insufficient power to evaluate melanoma-specific survival due to the low number of observed events in our cohort; consequently, we were unable to assess whether there is an effect of surgical delay on mortality attributed to melanoma, a limitation of previous national studies [11]. Despite the inability to assess melanoma-specific survival, our findings add to the growing literature on variation in melanoma care which may adversely affect outcome [4, 11, 21, 22]. As more early stage melanomas are diagnosed over time (a significant proportion outside of the hospital setting), understanding these patterns of care will be important for potentially designing interventions to reduce disparities in melanoma outcome. Finally, because of the nature of the data and in context of our exclusion criteria, we cannot comment on surgical excisions beyond 365 days.

Conclusions

Timely surgical excision is associated with improved overall survival. Efforts should be made to ensure timeliness of surgery for patients with melanoma in order to reduce potential disparities in receipt of quality cancer care [4,11,21,22].

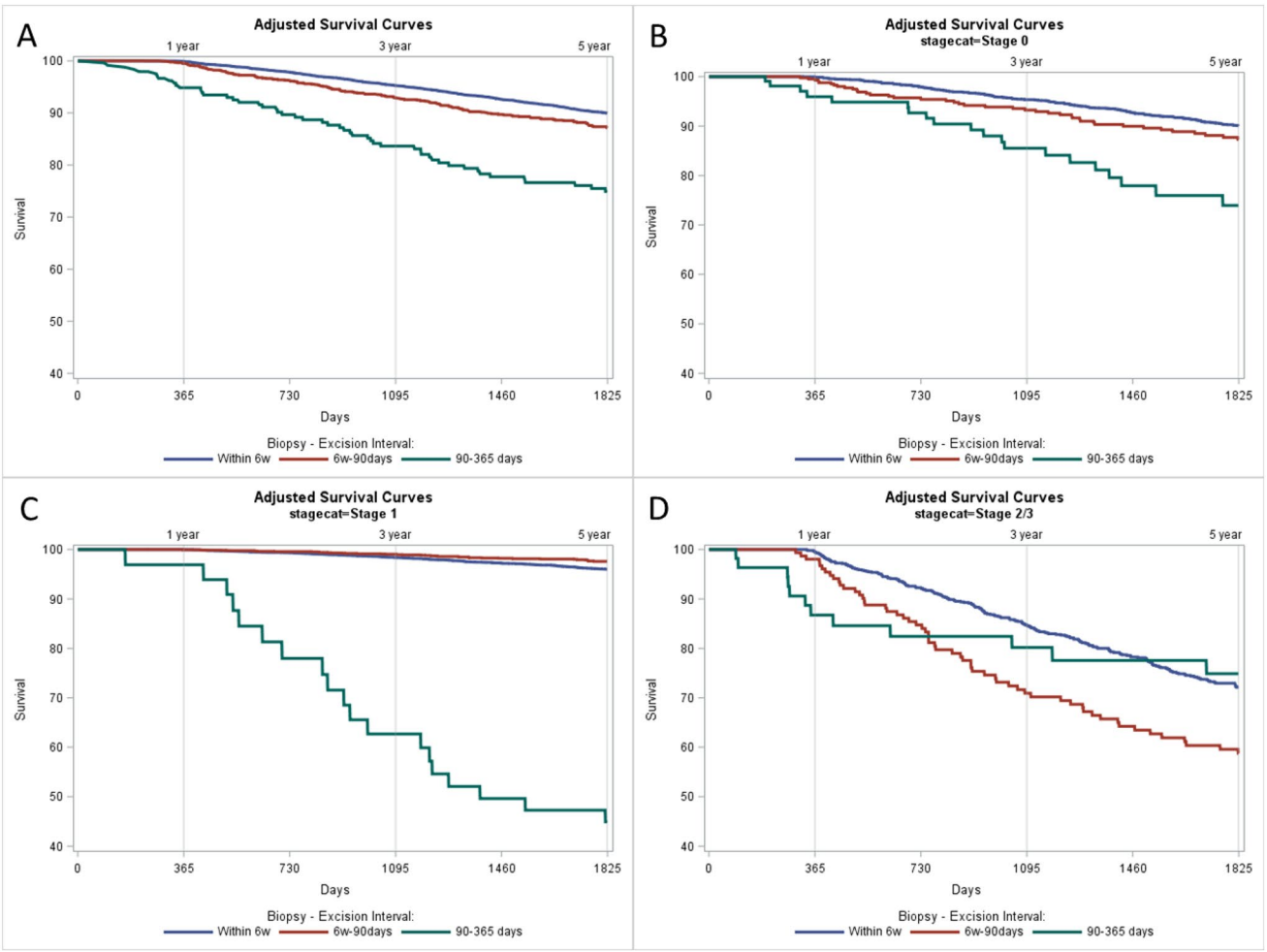

Fig. 2 Overall and stage-stratified adjusted survival probabilities according to biopsy – excision interval

Table 2 Adjusted survival probabilities and survival differences according to biopsy–excision interval ($n = 6{,}477$)

Timing of follow-up	(A) <6wks	(B) 6wks – 90 days	(C) 90–365 days	(B vs A) Survival difference	LCL	UCL	*P*-value	(C vs A) Survival difference	LCL	UCL	*P*-value
1-year	99.9	99.6	94.8	−0.4	−0.8	0.1	0.140	−5.1	−8.0	−2.1	<0.001
3-year	95.2	92.9	83.6	−2.3	−7.2	2.6	0.349	−11.6	−18.7	−4.6	0.001
5-year	89.9	87.1	74.9	−2.8	−11.5	5.9	0.533	−15.0	−24.6	−5.5	0.002

–Biopsy-excision interval within 6 weeks is the reference group

–Survival difference (S_{Diff}) adjusting for age at diagnosis, gender, race, insurance, year of diagnosis, stage at diagnosis, rurality, cancer group, whether the same provider performed the biopsy and the excision, whether a diagnostic test was performed by a dermatologist, whether excision was conducted at a North Carolina National Cancer Institute Center, and the presence of 1 or more Charlson comorbid conditions

–LCL: 95% Lower confidence limit; UCL: 95% upper confidence limit

–The null-value for comparison is $S_{Diff} = 0$ (i.e. Survival in both groups is the same)

Table 3 Stage-Stratified adjusted survival probabilities and survival differences according to biopsy–excision interval ($n = 6,477$)

Timing of follow-up	(A) <6wks	(B) 6wks – 90 days	(C) 90–365 days	(B vs A) Survival difference	LCL	UCL	*P*-value	(C vs A) Survival difference	LCL	UCL	*P*-value
Stage 0											
1-year	99.9	99.5	95.9	−0.4	−1.4	0.6	0.393	−4.0	−8.6	0.6	0.090
3-year	95.3	93.2	85.5	−2.1	−13.4	9.2	0.715	−9.8	−23.5	3.9	0.160
5-year	90.0	87.3	74.0	−2.7	−23.4	18.1	0.802	−16.0	−34.3	2.2	0.085
Stage I											
1-year	99.9	99.9	96.9	−0.0	−0.2	0.1	0.651	−3.1	−8.8	2.7	0.292
3-year	98.4	99.0	62.5	0.7	−1.9	3.3	0.616	−35.7	−54.2	−17.3	<0.001
5-year	96.0	97.6	44.7	1.6	−4.7	8.0	0.616	−51.3	−72.0	−0.6	<0.001
Stage II/III											
1-year	99.5	98.0	86.7	−1.5	−4.3	1.4	0.314	−12.8	−26.0	0.4	0.057
3-year	84.7	70.9	80.2	−13.8	−35.2	7.5	0.210	−4.6	−22.3	13.4	0.616
5-year	72.3	58.8	74.9	−13.5	−41.2	14.5	0.348	2.6	−19.9	25.2	0.819

–Biopsy-excision interval within 6 weeks is the reference group

–Survival difference (S_{Diff}) adjusting for age at diagnosis, gender, race, insurance, year of diagnosis, rurality, cancer group, whether the same provider performed the biopsy and the excision, whether a diagnostic test by dermatologist, whether excision was conducted at a North Carolina National Cancer Institute Center, and the presence of 1 or more Charlson comorbid conditions

–LCL: 95% Lower confidence limit; UCL: 95% upper confidence limit

–The null-value for comparison is $S_{Diff} = 0$ (i.e. Survival in both groups is the same)

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Compliance with ethical standards

Conflict of interest None reported.

IRB statement The University of North Carolina at Chapel Hill IRB approved this study.

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