Impact of Treatment Delay in Head and Neck Mucosal Melanoma on Overall Patient Survival

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Abstract

Objectives Head and neck mucosal melanoma (HNMM) is a rare malignancy with high mortality. This study evaluates the impact of treatment delays on overall survival in HNMM.

Design/Setting/Participants A retrospective review of patients with surgically managed HNMM treated with adjuvant radiation was performed from the 2004–2016 National Cancer Database.

Main Outcome Measures Durations of diagnosis-to-treatment initiation (DTI), surgery-to-radiotherapy initiation (SRT), duration of radiotherapy (RTD), surgery-to-immunotherapy initiation (SIT), diagnosis-to-treatment end (DTE), and total treatment package (TTP) were calculated.

Results A total of 1,011 patients (50.7% female, 90.5% Caucasian) met inclusion criteria. Median DTI, SRT, RTD, SIT, DTE, and TTP were 30, 49, 41, 102, 119, and 87 days, respectively. Only longer DTE was associated with decreased mortality (hazard ratio, 0.720; 95% confidence interval, 0.536–0.965; $p = 0.028$).

Conclusion DTI, SRT, RTD, SIT, and TTP do not significantly affect overall survival in patients with HNMM who undergo surgery and adjuvant radiation. Longer DTE is associated with improved survival in this population.

Level of Evidence 4.

Keywords
- mucosal melanoma
- treatment delay
- survival
- head and neck cancer
- sinonasal cancer

Introduction

Head and neck mucosal melanoma (HNMM) is a rare and aggressive tumor arising from melanocytes in the mucosa of the head and neck. It comprises ~1% of all melanomas and is increasing in incidence.[1–4] Most patients with HNMM in the United States are >50 years of age and are primarily Caucasian.[3–5] The presenting symptoms of HNMM most commonly include nasal obstruction and epistaxis for sinonasal lesions, and a mass or oral bleeding for oral lesions.[6,7] Due to the nonspecific nature of these symptoms, HNMM is often diagnosed late and many patients already have advanced disease. Nodal metastasis and distant metastasis are found in approximately 20 to 40% and 30 to 50% of patients, respectively.[6,8] Five-year survival is estimated to be between 24 and 33%.[5,8–11]

Older age, higher T stage, nodal metastasis, and distant metastasis are associated with poorer overall survival, and tumor site (specifically nasal cavity and oral cavity) is associated with improved overall survival as compared with paranasal sinus tumors.[5,6,9] Treatment options include surgery in the majority of cases, followed by radiation in approximately one-half of patients.[7–9] However, surgery has not been demonstrated to improve overall survival unless negative margins are achieved.[11–13] Chemotherapy and immunotherapy are also used, especially in nonsurgical cases. As HNMM exhibits a different molecular profile than cutaneous melanoma, further

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studies are needed to establish a role for immunotherapy in mucosal melanoma.[14–16] While treatment delay has been demonstrated to negatively affect survival in cutaneous melanoma,[17] there has not been study of the impact of treatment delay on survival in HNMM. Accordingly, various metrics for treatment delay have been found to negatively impact head and neck cancer outcomes.[18–22] We aim to study if treatment delay, described as diagnosis-to-treatment initiation (DTI), surgery-to-radiotherapy initiation (SRT), duration of radiotherapy (RTD), surgery-to-immunotherapy initiation (SIT), diagnosis-to-treatment end (DTE), and total treatment package (TTP), affect survival in HNMM.

Materials and Methods

Data Source

Due to the deidentified nature of the database used, this study was exempt from institutional review board approval. The National Cancer Database (NCDB) is a national, hospital-based registry including data from over 1,500 institutions each year.[23] The 2004–2016 NCDB database was queried for all surgically managed HNMM treated that received adjuvant radiation, with or without adjuvant chemotherapy and immunotherapy. Analyses involving immunotherapy were performed using a subset of patients who underwent surgery, adjuvant radiation therapy, and adjuvant immunotherapy. Anatomic site codes C4.0-C14.8 and C30.0–33.9 and histology codes 8720–8723, 8730, 8743, 8745, 8746, and 8770–8773 were included. All cases with missing information on survival or information on duration between diagnosis and treatment were excluded.

Package Time Variables

Six treatment intervals were calculated. DTI was defined as days from initial diagnosis to surgical treatment. SRT was defined as days from surgery to initiation of adjuvant radiation. RTD was defined as days between initiation to completion of RT. SIT was defined as days from surgery to initiation of immunotherapy. DTE was defined as days from diagnosis to completion of treatment (both surgery and RT). TTP was defined as days from primary surgery to completion of treatment (including surgery, radiation, chemotherapy, and immunotherapy, if applicable). Delays in treatment in all six intervals were split into two groups based on the median time.

Charlson–Deyo comorbidity index was used to represent comorbidities.[24] Insurance status was represented as a binary variable of private insurance/managed care versus noninsured, Medicaid, Medicare, and others. Facility type was similarly binarized as academic centers versus nonacademic (i.e., community or integrated network cancer centers). Age was split into groups of <51, ≥ 51–61, ≥ 61–71, and ≥ 71 years. Regional radiation dose was split into two groups based on 50 Gy as a median value.

Statistical Analysis

Patient socioeconomic, clinicopathologic, and treatment-related variables were identified and compared between modality groups via the chi-squared test. Association of individual variables with package time intervals was evaluated via multivariable logistic regression. Following this, impact of treatment delays on all-cause mortality was evaluated via multivariate Cox proportional hazard regression while controlling for confounding variables. All variables initially contained at least one missing value, except for the treatment intervals variables, as we removed all cases with missing dependent variables. All statistical analyses were performed in the Python programming language. A significance level of 0.05 was used for all tests.

Results

Baseline Population Characteristics

Using the above-mentioned criteria, 1,011 patients were identified. Mean age was 67.0 ± 12.7 years. The majority of patients were female (50.7%) and Caucasian (90.5%). Most patients had government insurance (59.6%) and were treated at an academic facility (63.8%). Primary tumor was most common on the sinonasal tract (84.6%), followed by the oral cavity (15.4%). Tumor staging at time of diagnosis was T3 in 53.1% and T4 in 46.9%. Most patients did not have nodal or distant metastatic disease at time of presentation (87.4 and 94.6%, respectively). Surgical margins were positive in 26.3%. Radiation dose was $\geq$50 Gy in 63.9%. The majority of patients did not undergo adjuvant chemotherapy (89.7%) or immunotherapy (90.8%). Demographic information is available in ►**Table 1**. Median and mean treatment times are available in ►**Table 2**. Two-year overall survival was 61.6% (95% confidence interval [CI], 58.7–64.7%) and 5-year overall survival was 33.4% (95% CI, 30.3–36.8%).

Predictors of Treatment Delay

Multivariate analysis was used to analyze the associations between treatment variables on treatment delay, results of which are available in ►**Table 3**. On multivariate analysis, longer DTI was associated with treatment at an academic facility (odds ratio [OR], 1.550; 95% CI, 1.067–2.257; $p = 0.022$), oral cavity primary site (OR, 1.957; 95% CI, 1.126–3.463; $p = 0.019$), and nodal metastasis at the time of presentation (OR, 2.647; 95% CI, 1.411–5.166; $p = 0.003$). Patients with longer DTI were less likely to have distant metastasis (OR, 0.320; 95% CI, 0.110–0.839; $p = 0.026$) and receive adjuvant immunotherapy (OR, 0.422; 95% CI, 0.223–0.776; $p = 0.006$). Patients with longer SRT were also less likely to have distant metastasis (OR, 0.373; 95% CI, 0.139–0.908; $p = 0.037$). Longer DTE was associated with oral cavity primary site (OR, 2.139; 95% CI, 1.140–4.151; $p = 0.020$). Lastly, patients age $\geq$ 70 years were less likely to have an extended TTP (OR, 0.584; 95% CI, 0.364–0.928; $p = 0.024$). RTD and SIT were not associated with any variables on multivariate analysis.

Survival Analysis

On univariate Cox hazard analysis, older age (hazard ratio [HR], 1.279; 95% CI, 1.100–1.486; $p = 0.001$), government insurance (HR, 1.303; 95% CI, 1.112–1.526; $p = 0.001$), T4 stage (HR, 1.390; 95% CI, 1.163–1.663; $p < 0.001$), N1 stage

Table 1 Demographic information for patients with HNMM treated with surgery and adjuvant radiation in the NCDB

Variables	Number (%)
Age, y	
<70	547 (54.1)
≥ 70	464 (45.9)
Sex	
Male	513 (50.7)
Female	498 (49.3)
Race	
White	905 (90.5)
Black	48 (4.8)
Asian	28 (2.8)
Insurance	
Private	391 (40.4)
Government	576 (59.6)
Facility type	
Nonacademic	357 (36.2)
Academic	630 (63.8)
Charlson–Deyo score	
0	815 (80.6)
≥ 1	196 (19.4)
Primary site	
Sinonasal tract	855 (84.6)
Oral cavity	156 (15.4)
T stage	
T3	406 (53.1)
T4	359 (46.9)
N stage	
N0	539 (87.4)
N1	78 (12.6)
M stage	
M0	924 (94.6)
M1	53 (5.4)
Surgical margins	
Negative	588 (73.7)
Positive	210 (26.3)
Radiation dose, Gy	
<50	338 (36.1)
≥ 50	597 (63.9)
Adjuvant chemotherapy	
No	907 (89.7)
Yes	104 (10.3)
Adjuvant immunotherapy	
No	907 (90.8)
Yes	92 (9.2)

Table 2 Median and mean treatment times for patients with HNMM treated with surgery and adjuvant radiation in the NCDB

	Median (range)	Mean (SD)
DTI (d)	30 (0–187)	33.8 (27.8)
SRT (d)	49 (1–955)	57.7 (49.4)
DTE (d)	119 (5–975)	128.2 (58.4)
RTD (d)	41 (1–124)	36.4 (16.3)
TTP (d)	87 (5–975)	93.9 (53.5)
SIT (d)	102 (8–425)	105.9 (61.8)

Abbreviations: DTE, diagnosis-to-treatment end; DTI, diagnosis-to-treatment initiation; RTD, duration of radiotherapy; SD, standard deviation; SIT, surgery-to-immunotherapy initiation; SRT, surgery-to-radiotherapy initiation; TTP, total treatment package.

(HR, 2.158; 95% CI, 1.636–2.846; $p<0.001$), M1 stage (HR, 2.957; 95% CI, 2.187–3.998; $p<0.001$), and (microscopic) positive margins (HR, 1.349; 95% CI, 1.117–1.630; $p=0.002$) were associated with increased mortality. Female sex (HR, 0.778; 95% CI, 0.668–0.905; $p=0.001$), treatment at an academic facility (HR, 0.778; 95% CI, 0.668–0.905; $p=0.027$), radiation dose >50 Gy (HR, 0.813; 95% CI, 0.691–0.956; $p=0.012$), and adjuvant immunotherapy (HR, 0.754; 95% CI, 0.570–0.998; $p=0.049$) were associated with decreased mortality. Primary tumor site did not influence survival in this analysis (HR, 1.029; 95% CI, 0.836–1.267; $p=0.785$), nor did chemotherapy administration (HR, 1.139; 95% CI, 0.895–1.450; $p=0.291$). On multivariate Cox hazard analysis, only DTE was associated with decreased mortality (HR, 0.720; 95% CI, 0.536–0.965; $p=0.028$). These results are available in ►**Table 4** and ►**Table 5**. Delay in treatment as characterized by longer DTI, SRT, RTD, SIT, and TTP was not associated with overall survival (►**Fig. 1**).

Discussion

In this analysis of 1,011 patients with HNMM treated with surgery and radiation in the NCDB, we found median durations of treatment for DTI, SRT, RTD, SIT, DTE, and TTP to be 30, 49, 41, 102, 119, and 87 days, respectively. Of these measures of treatment delay, only DTE was associated with overall survival, and longer DTE was associated with a lower overall survival. In addition, several different variables were associated with treatment delay and overall survival in sinonasal mucosal melanoma.

Surgical resection with or without radiation therapy remains the standard of care and has been demonstrated to yield improved survival compared with radiation alone.[9] However, prior studies have failed to demonstrate a difference in overall survival between patients who have undergone surgery for HNMM and those who have undergone surgery with adjuvant radiation.[9,11,25] While adjuvant radiation may result in improved locoregional control after surgery, an improvement in overall survival in patients treated with adjuvant radiation has not been consistently

Table 3 Cox hazard multivariate analysis of factors affecting overall survival in HNMM treated with surgery and adjuvant radiation

Variables	DTI delayed		SRT delayed		DTE delayed	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age, y						
<70	1 [Reference]		1 [Reference]		1 [Reference]	
≥70	1.157 (0.747–1.793)	0.514	0.777 (0.506–1.186)	0.244	0.844 (0.530–1.340)	0.472
Sex						
Male	1 [Reference]		1 [Reference]		1 [Reference]	
Female	0.871 (0.609–1.245)	0.450	1.050 (0.741–1.488)	0.785	0.833 (0.560–1.237)	0.365
Race						
White	1 [Reference]		1 [Reference]		1 [Reference]	
Black	1.087 (0.513–2.343)	0.828	0.858 (0.410–1.791)	0.683	0.935 (0.404–2.173)	0.875
Asian	1.368 (0.469–4.099)	0.564	0.839 (0.286–2.403)	0.742	0.539 (0.140–1.772)	0.326
Insurance						
Private	1 [Reference]		1 [Reference]		1 [Reference]	
Government	0.977 (0.624–1.529)	0.920	1.319 (0.858–2.037)	0.208	1.134 (0.697–1.849)	0.613
Facility type						
Nonacademic	1 [Reference]		1 [Reference]		1 [Reference]	
Academic	1.550 (1.067–2.257)	**0.022**	0.967 (0.672–1.391)	0.857	1.354 (0.897–2.048)	0.150
Charlson–Deyo score						
0	1 [Reference]		1 [Reference]		1 [Reference]	
≥1	1.066 (0.690–1.650)	0.775	1.149 (0.754–1.757)	0.520	1.071 (0.671–1.712)	0.775
Primary site						
Sinonasal tract	1 [Reference]		1 [Reference]		1 [Reference]	
Oral cavity	1.957 (1.126–3.463)	**0.018**	1.648 (0.973–2.830)	0.066	2.139 (1.140–4.151)	**0.020**
T stage						
T3	1 [Reference]		1 [Reference]		1 [Reference]	
T4	0.926 (0.646–1.326)	0.674	0.925 (0.653–1.310)	0.661	1.025 (0.689–1.525)	0.904
N stage						
N0	1 [Reference]		1 [Reference]		1 [Reference]	
N1	2.647 (1.411–5.166)	**0.003**	0.993 (0.554–1.782)	0.982	1.035 (0.520–2.074)	0.922
M stage						
M0	1 [Reference]		1 [Reference]		1 [Reference]	
M1	0.320 (0.110–0.839)	**0.026**	0.373 (0.139–0.908)	**0.037**	0.935 (0.211–4.114)	0.927
Adjuvant chemotherapy						
No	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	0.748 (0.387–1.440)	0.385	~	~	~	~
Adjuvant immunotherapy						
No	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	0.422 (0.223–0.776)	**0.006**	~	~	~	~
	RTD delayed		**TTP delayed**		**SIT delayed**	
Variables	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
Age, y						
<70	1 [Reference]		1 [Reference]		1 [Reference]	
≥70	0.662 (0.417–1.049)	0.079	0.584 (0.364–0.928)	**0.024**	0.883 (0.092–8.633)	0.913

(*Continued*)

Table 3 (*Continued*)

Sex						
Male	1 [Reference]		1 [Reference]		1 [Reference]	
Female	1.048 (0.705–1.558)	0.818	0.767 (0.516–1.139)	0.189	0.777 (0.185–3.052)	0.720
Race						
White	1 [Reference]		1 [Reference]		1 [Reference]	
Black	1.399 (0.608–3.297)	0.431	1.329 (0.573–3.153)	0.508	6.033 (0.278–330.446)	0.299
Asian	0.409 (0.106–1.350)	0.157	0.759 (0.217–2.464)	0.648	0.255 (0.009–3.615)	0.329
Insurance						
Private	1 [Reference]		1 [Reference]		1 [Reference]	
Government	0.718 (0.442–1.166)	0.181	1.341 (0.825–2.196)	0.239	1.653 (0.303–9.943)	0.562
Facility type						
Nonacademic	1 [Reference]		1 [Reference]		1 [Reference]	
Academic	0.764 (0.504–1.154)	0.202	0.808 (0.534–1.221)	0.312	0.657 (0.152–2.662)	0.557
Charlson–Deyo score						
0	1 [Reference]		1 [Reference]		1 [Reference]	
$\geq$1	0.862 (0.540–1.373)	0.532	0.764 (0.477–1.216)	0.257	1.046 (0.130–10.067)	0.966
Primary site						
Sinonasal tract	1 [Reference]		1 [Reference]		1 [Reference]	
Oral cavity	0.880 (0.475–1.632)	0.684	1.565 (0.843–2.965)	0.161	0.695 (0.052–6.668)	0.760
T stage						
T3	1 [Reference]		1 [Reference]		1 [Reference]	
T4	0.907 (0.609–1.350)	0.630	0.941 (0.631–1.400)	0.763	2.458 (0.653–10.166)	0.193
N stage						
N0	1 [Reference]		1 [Reference]		1 [Reference]	
N1	0.630 (0.314–1.240)	0.184	0.604 (0.299–1.195)	0.152	3.305 (0.371–50.421)	0.318
M stage						
M0	1 [Reference]		1 [Reference]		1 [Reference]	
M1	1.007 (0.226–4.494)	0.992	1.093 (0.246–4.864)	0.903	0.085 (0.002–0.933)	0.086

Abbreviations: CI, confidence interval; DTE, diagnosis-to-treatment end; DTI, diagnosis-to-treatment initiation; OR, odds ratio; RTD, duration of radiotherapy; SIT, surgery-to-immunotherapy initiation; SRT, surgery-to-radiotherapy initiation; TTP, total treatment package.

demonstrated in prior literature.[7,26–30] While this study finds that there is no significant effect of delay in time from surgery to radiation, we find that radiation dose $\geq$ 50 Gy (in patients who have also undergone surgery) does improve overall survival in this patient population compared with radiation dose $<$ 50 Gy. Lastly, we find that median time of SRT was 49 days, which is longer than the 6-week interval recommended in the National Comprehensive Cancer Network guidelines. This may be due to extended healing time after surgery or surgical complications, especially if skull base resection or complex tissue reconstruction was performed. External referrals into specialized treatment centers, care coordination among numerous subspecialties, insurance authorization, and simulation and planning of radiation are also likely contributors to this delay.

Risk factors for worse overall survival on multivariate analysis were age $\geq$ 71, male sex, positive surgical margins, government insurance, and a nonacademic treatment facility. Older age (particularly above 70 years old) has been demonstrated to be a negative prognostic factor in several previous studies,[5–7,9] presumably because of poorer overall health, comorbidities, and ability to withstand the treatment course. Male sex was also associated with poorer overall survival, despite our cohort being evenly distributed between genders, a risk factor that has not been previously identified in the literature. As no gender-specific tumor factors have been previously demonstrated, this finding could be interpreted as a result of the overall shorter lifespan of men compared with women. Negative surgical margins have been demonstrated to be one of the only positive prognostic factors in HNMM.[11–13] We also find that positive surgical margins are associated with increased mortality, highlighting the importance of complete surgical resection when possible.

Table 4 Univariate Cox hazard analysis demonstrating the impact of treatment variables on overall survival in HNMM treated with surgery and adjuvant radiation

Treatment variables	HR (95% CI)	*p*-Value
Age, y		
<70	1 [Reference]	
≥70	1.279 (1.100–1.486)	**0.001**
Sex		
Male	1 [Reference]	
Female	0.778 (0.668–0.905)	**0.001**
Race		
White	1 [Reference]	
Black	1.152 (0.807–1.645)	0.436
Asian	0.848 (0.531–1.356)	0.492
Insurance		
Private	1 [Reference]	
Government	1.303 (1.112–1.526)	**0.001**
Facility type		
Nonacademic	1 [Reference]	
Academic	0.839 (0.718–0.980)	**0.027**
Charlson–Deyo score		
0	1 [Reference]	
≥1	1.040 (0.861–1.258)	0.683
Primary site		
Sinonasal tract	1 [Reference]	
Oral cavity	1.029 (0.836–1.267)	0.785
T stage		
T3	1 [Reference]	
T4	1.390 (1.163–1.663)	<**0.001**
N stage		
N0	1 [Reference]	
N1	2.158 (1.636–2.846)	<**0.001**
M stage		
M0	1 [Reference]	
M1	2.957 (2.187–3.998)	<**0.001**
Surgical margins		
Negative	1 [Reference]	
Positive	1.349 (1.117–1.630)	**0.002**
Radiation dose, Gy		
< 50	1 [Reference]	
≥50	0.813 (0.691–0.956)	**0.012**
Adjuvant chemotherapy		
No	1 [Reference]	
Yes	1.139 (0.895–1.450)	0.291
Adjuvant immunotherapy		
No	1 [Reference]	
Yes	0.754 (0.570–0.998)	**0.049**

Table 5 Multivariate Cox hazard analysis demonstrating the impact of treatment delay on overall survival in HNMM treated with surgery and adjuvant radiation

Treatment delay (d)	HR (95% CI)	*p*-Value
DTI		
<30	1 [Reference]	
≥30	0.875 (0.671–1.141)	0.323
SRT		
<49	1 [Reference]	
≥49	1.053 (0.812–1.363)	0.698
DTE		
<119	1 [Reference]	
≥119	0.720 (0.536–0.965)	**0.028**
RTD		
<41	1 [Reference]	
≥41	1.005 (0.715–1.413)	0.976
TTP		
<87	1 [Reference]	
≥87	0.874 (0.653–1.170)	0.365
SIT		
<102	1 [Reference]	
≥102	0.675 (0.290–1.574)	0.363

Abbreviations: CI, confidence interval; DTE, diagnosis-to-treatment end; DTI, diagnosis-to-treatment initiation; HR, hazard ratio; RTD, duration of radiotherapy; SIT, surgery-to-immunotherapy initiation; SRT, surgery-to-radiotherapy initiation; TTP, total treatment package.

Treatment at academic facilities appeared to be associated with decreased mortality on univariate analysis, though this finding requires further investigation. Academic facilities commonly have the most highly specialized surgeons, oncologists, and radiation oncology teams working together in close proximity, a factor that is likely beneficial for patients with this relatively rare and challenging disease. Radiation dose > 50 Gy and adjuvant immunotherapy were also associated with decreased mortality. These findings emphasize the importance of considering referring patients with recently diagnosed HNMM to academic facilities where coordination of adjuvant treatment in a multidisciplinary setting can occur. Lastly, negative prognostic factors for overall survival in HNMM also include T4 stage, N1 stage, and M1 stage, which correlates with the American Joint Committee on Cancer (AJCC) 7th edition TNM staging system for mucosal melanoma.

While academic institutions were associated with a significantly longer DTI, DTI did not have a significant effect on overall survival and therefore can be considered a less critical factor in the treatment of patients with HNMM. In fact, this study demonstrates that only increased DTE affects overall survival in HNMM and is associated with decreased mortality. DTE includes not only treatment delay, but also the time period in which the patient is undergoing any type of treatment. For this reason, a shorter DTE may mean that

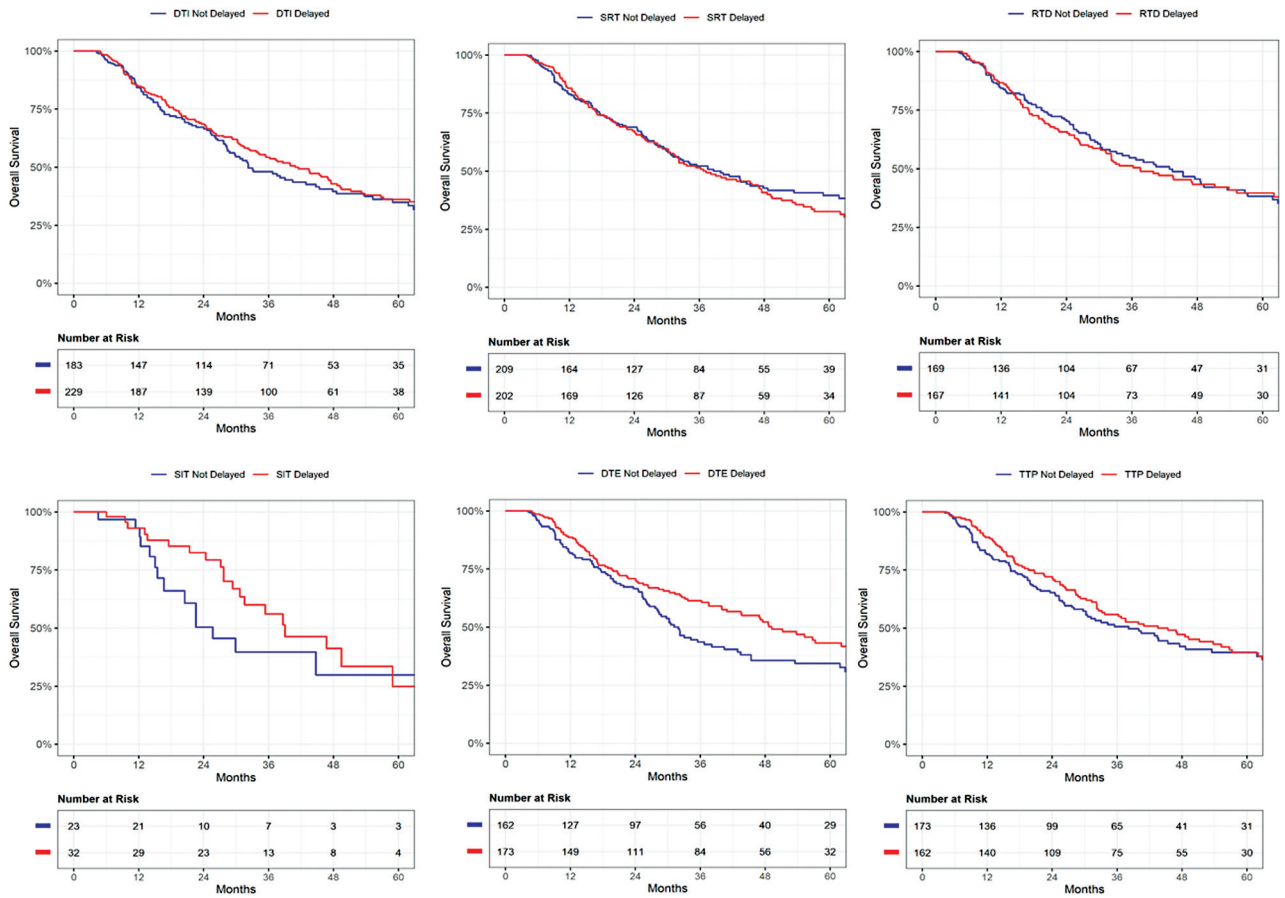

Fig. 1 Kaplan–Meier curve demonstrating no significant difference in survival between those with treatment delay in (**A**) DTI, (**B**) SRT, (**C**) RTD, (**D**) SIT, and (**F**) TTP. (**E**) A significant difference in survival in patients with longer DTE.

the patient succumbed to the disease more quickly, while a longer DTE corresponds to longer duration of treatment and control of disease. In clinical practice, this also means that referral to an academic institution, prioritizing surgical margins performed by a skilled surgical team, and providing courses of adjuvant radiation therapy and immunotherapy as needed are more important for overall survival than completing a treatment course quickly. This must of course be weighed against delaying surgery so long that the disease is unresectable and negative margins cannot be achieved. Furthermore, though not possible to separate out all specific details of treatment, it is possible that longer immunotherapy treatment duration, which can be for several months, plays a role in long-term disease control and thus has a positive impact on survival. Also interestingly, chemotherapy did not affect survival in this analysis, suggesting that radiation therapy and immunotherapy are currently more important adjuvant therapies in HNMM.

Lastly, our 2- and 5-year survival rates of 61.6 and 33.4%, respectively, are on the high end of recently reported data.[5,6,9–11] Though survival remains poor in patients with HNMM, ongoing research in immunotherapy and the optimal treatment algorithms for HNMM patients are promising avenues for future improvement.

There are several limitations to this study, specifically those intrinsic to using a large patient registry such as the NCDB. The use of trained reviewers to input data from medical records into the NCDB may be associated with coding errors. The NCDB dataset contains a set number of variables and may not include all variables that are clinically relevant in HNMM. For instance, information regarding planned radiation dose and radiotherapy breaks is not included in the NCDB. The current analysis is also limited to patients who underwent surgery followed by adjuvant radiation therapy, which remains the most common treatment strategy for HNMM. We used specific Current Procedural Terminology (CPT) and International Classification of Diseases (ICD) codes to collect a homogenous group of HNMM patients; however, variations in care likely still exist, which could lead to heterogeneity. Lastly, the NCDB does not include the indications for treatment, and therefore we can only make assumptions by comparing the baseline characteristics of the groups that received treatment and those that did not. Because the NCDB does not include disease-specific survival, we are unable to ascertain if patients undergoing treatment are living with metastatic disease or not. However, all cases marked as palliative were excluded from our sample, so patients receiving treatment are theoretically treated with intent to cure. Despite these limitations, our study is the first to examine the impact of treatment delay on OS in HNMM patients and establishes benchmarks for institutions to compare against their own patient care.

Conclusion

DTI, SRT, RTD, SIT, and TTP do not significantly affect overall survival in patients with HNMM who undergo surgery and adjuvant radiation. A longer DTE is associated with improved survival in this population. Negative prognostic factors include age $\geq$ 71 years, government insurance, T4 stage, N1 stage, M1 stage, and positive surgical margins. Positive prognostic factors include female sex, academic treatment facility, radiation dose $>$ 50 Gy, and adjuvant immunotherapy. Median treatment times can be used as a reference for other institutions and future research studies.

Previous Presentation
Portions of this work were presented at the 2022 Triological Society Meeting in Coronado, CA, United States.

Conflict of Interest
None declared.

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