Oral Oncology 92 (2019) 67–76

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Clinically node-negative head and neck mucosal melanoma: An analysis of current treatment guidelines & outcomes

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ARTICLE INFO

Keywords:
Head and neck cancer
Melanoma
Antineoplastic protocols
Treatment adherence
Treatment outcome
Radiotherapy
Neck dissection

ABSTRACT

Objectives: To analyze head and neck mucosal melanoma (MM) treatment patterns, and their association with survival, relative to National Comprehensive Cancer Network (NCCN) guidelines.

Material & methods: Adult head and neck MM patients with clinically-staged T3/4aN0 disease were identified in a retrospective analysis of the National Cancer Database (2010–2014) and stratified into sinonasal cavity (SN) and oral cavity, oropharynx, larynx, or hypopharynx (non-SN) cohorts.

Results: We identified 353 SN and 79 non-SN MM cases. The majority of patients were treated with surgery (SN: 92.4%; non-SN 84.8%), within NCCN guidelines. Treatment within the non-SN MM NCCN recommendation of elective neck dissection (END) was approximately 26.6%. END is not recommended for SN MM and was not performed in 91.5% of cases. Radiotherapy (RT) is recommended in both SN and non-SN MM and was utilized in 63.5% of SN patients and 46.8% of non-SN patients.

END was not independently associated with OS compared to surgery alone (SN HR: 1.350 [95% CI: 0.733–2.485]; non-SN HR: 3.460 [95% CI: 0.912–13.125]). RT was independently associated with improved OS in SN MM cases (HR: 0.679 [95% CI: 0.479–0.963]), but not in non-SN MM cases (HR: 0.824 [95% CI: 0.331–2.051]).

Conclusion: The majority of patients with head and neck MM are not treated within NCCN guidelines. The use of recommended END in non-SN patients is low. Similarly, adjuvant RT utilization is low. Our analysis shows that while greater use of RT may increase survival rates in this disease, the utility of END is unclear.

Introduction

Mucosal melanoma (MM) is a rare, aggressive disease that accounts for < 1.5% of melanoma cases in the United States [1], with head and neck MM comprising the majority of cases [1,2]. Of these MM cases, over 70% originate from within the sinonasal tract (SN). Most of the remaining cases originate within the oral cavity, although they can rarely arise in the nasopharynx, oropharynx, hypopharynx, and larynx as well [2–4]. Although tobacco and alcohol use have been implicated in the MM development [5], no specific etiologic factors have been identified [6]. MM carries a poor 5-year overall survival (OS), reportedly ranging between 25 and 45% [3,7], with SN cases carrying the worst prognosis among subsites [4]. To convey this poor prognosis, the American Joint Committee on Cancer (AJCC) staging system begins at stage III for this disease [8].

The National Comprehensive Cancer Network (NCCN) treatment guidelines for stage III-IVA (encompassing an AJCC classification of T3/4AN0M0) vary by site [9]. Surgical resection of the primary tumor is recommended for all sites, while adjuvant radiation therapy (RT) should be "strongly considered." While the efficacy of surgery has been well-described in a large cohort [3], the role of RT is more controversial. Early work indicated favorable outcomes [10], though many recent studies have reported no difference in OS between those who did and did not receive RT [11,12]. RT is used primarily to prevent local recurrence, which often precedes distant metastasis, and can be as high as 79% [13]. Elective neck dissection (END) is recommended only in

Abbreviations: MM, Mucosal Melanoma; SN, Sinonasal; non-SN, Non-sinonasal (oral cavity, oropharynx, larynx, or hypopharynx); NCCN, National Comprehensive Cancer Network; END, Elective Neck Dissection; RT, Radiotherapy; ST, Systemic Therapy; ICD-O-3, International Classification of Disease for Oncology, Third Edition; CDCC, Charlson-Deyo Comorbidity Condition; OS, Overall Survival; SLNB, Sentinel Lymph Node Biopsy; CLND, Complete Lymph Node Dissection; NSLN, Non-Sentinel Lymph Nodes

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https://doi.org/10.1016/j.oraloncology.2019.03.017
Received 3 January 2019; Received in revised form 11 March 2019; Accepted 23 March 2019
Available online 28 March 2019
1368-8375/

the treatment of MM from the oral cavity, oropharynx, larynx, and hypopharynx (non-SN) subsites, but not from the SN subsite, presumably due to the increased risk of regional lymph node relapse and metastases from the non-SN subsites [14,15]. However, the majority of the literature surrounding MM are small case series.

The effectiveness of the current NCCN MM guidelines is hindered by the rarity of the disease and lack of randomized trials studying its treatment. Recent review articles have detailed the divide in the literature on the effectiveness of END and RT on survival; of note, these articles made no reference to the NCCN guidelines, perhaps indicating low awareness [16,17]. Even current staging guidelines are questioned, as multiple proposed staging mechanisms exist [16,17]. As such, we sought to analyze head and neck MM treatment patterns relative to NCCN guidelines, and analyze the association of recommended treatments with survival using a large national cohort.

Materials and methods

Data

The data was obtained from the National Cancer Database (NCDB) from 2010 to 2014, as data from 2004 to 2009 did not include TNM staging for these cases. A collaboration between the American College of Surgeons and the Commission on Cancer, the NCDB collects data from > 1500 hospital in the United States, representing over 70% of all new diagnoses of cancer as previously described [18]. The NCDB has been used in a number of studies to evaluate outcomes in the head and neck [19,20]. This study was determined to be exempt from institutional review by the Yale Human Investigation Committee.

Patient population

The study population included patients ≥18 years of age who had a melanoma primary in the head and neck, excluding those with external lip or middle ear cases. This was obtained by utilizing the International Classification of Disease for Oncology, Third Edition (ICD-O-3) histological code 8720. The patients were categorized into SN and non-SN cohorts based upon ICD-O-3 topological codes. The SN cohort included patients with codes C30.0 (nasal cavity) and C31.0-C31.9 (accessory sinuses). The non-SN cohort included patients with codes C00.3-C00.9 (lip), C01.9 (base of tongue), C01.0-C01.9 (other and unspecific parts of tongue), C03.0-C03.9 (gums), C04.0-C04.9 (floor of mouth), C05.0-C05.9 (palate), C06.0-C06.9 (other and unspecified parts of the mouth), C09.0-C09.9 (tonsil), C10.0-C10.9 (oropharynx), C11.0-C11.9 (nasopharynx), C12.9 (pyriform sinus), C13.0-13.9 (hypopharynx), C14.0-C14.8 (other and ill-defined sits in lip, oral cavity, and pharynx), and C32.0-C32.9 (larynx). Cases were excluded if they had an AJCC clinical T classification greater than T4a, clinical N classification greater than N0, or a clinical M classification greater than M0, as these may represent unresectable tumors. Cases were also excluded if they were missing data on TNM staging, RT administration, or END administration. Finally, prior to survival analysis, cases were excluded for missing vital status, which included all 2014 cases (Fig. 1).

Variable definitions

In 2013, the definition of immunotherapy changed to include drugs that were previously classified as chemotherapy. Therefore, to prevent a flawed analysis, patients were classified as having systemic therapy (ST) if they received chemotherapy and/or immunotherapy regardless of type or number of agents (the NCDB does not provide drug-specific data). Patients who received external-beam radiation were considered to have received RT. Patients were considered to have undergone surgery if they underwent surgery at the primary site. Patients who had at least one lymph node removed (or were labeled as "regional lymph nodes surgically removed, but number not documented, not documented as sampling or dissection," [n = 2]) and pathologically examined up until after the completion of the primary surgical procedure were considered to have underwent END; though a "regional lymph node surgery" variable exists in the dataset, it was coded incorrectly before 2012, requiring us to utilize the aforementioned definition.

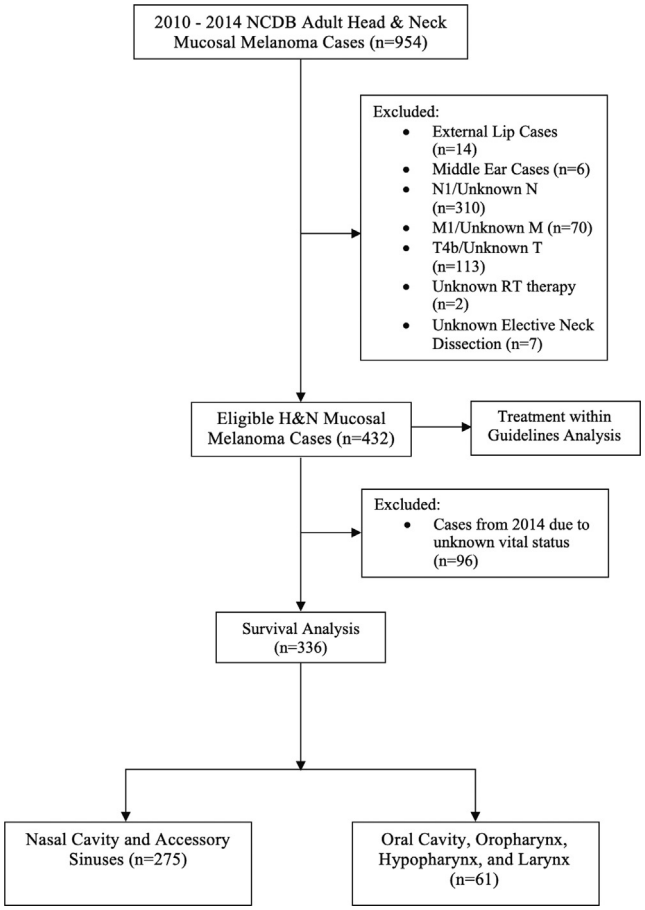


Fig. 1. CONSORT diagram of inclusion and exclusion criteria.

Statistical analysis

Rates of treatments within NCCN version 1.2018 guidelines were obtained by finding the ratio of those who obtained NCCN guideline-adherent care to the total number of patients [9]. Chi-square tests or Fisher's Exact tests, as appropriate, were performed to analyze differences in age, sex, race, Charlson-Deyo comorbidity condition (CDCC) score, AJCC clinical T stage, surgical intervention, END intervention, and RT intervention between the SN and non-SN cohorts. In comparing average number of nodes removed between those with no identified positive nodes and those with ≥1 positive node(s) identified, independent-samples *t*-test was employed, utilizing Levene's test to determine whether to assume an equal variance.

Univariate survival analyses on OS were performed via Kaplan-Meier two-tailed log rank tests pooled over strata. Multivariate analyses controlling for the above variables were performed via a Cox proportional hazards model. Further subgroup survival analyses were performed using a stricter definition of END (≥5 removed nodes), as was done previously [21], after excluding cases with missing number of examined nodes. Data analyses was performed using SPSS 25.0 (IBM Corp., Armonk, NY) and significance was defined at the $p < 0.05$ level.

Table 1
Treatment within National Comprehensive Cancer Network (NCCN) Guidelines in Clinically N0/M0 Mucosal Melanoma Patients.

	Clinical Profile				NCCN Guidelines, Treatments Received, & Rate of Treatment within Guidelines											
					Surgical Resection			Elective Neck Dissection			Radiotherapy			Systemic Therapy		
	Stage	T	N	M	NCCN	Received[n (%)]	Rate of Treatment within Guidelines	NCCN	Received[n (%)]	Rate of Treatment within Guidelines	NCCN	Received[n (%)]	Rate of Treatment within Guidelines	NCCN	Received[a] [n (%)]	Rate of Treatment within Guidelines
Sinonasal Cavity (n = 353)	III-IVa	3-4a	0	0	R	326 (92.4%)	92.4%	NR	30 (8.5%)	91.5%	SC	224 (63.5%)	63.5%	NR	43/341 (12.6%)	87.4%
Oral Cavity, Oropharynx, Larynx, or Hypopharynx (n = 79)	III-IVa	3-4a	0	0	R	67 (84.8%)	84.8%	R	21 (26.6%)	26.6%	SC	37 (46.8%)	46.8%	NR	12/77 (15.6%)	84.4%
Chi-Square p-value					0.034			< 0.001			0.006			0.486		

R = Recommended.
NR = Not Recommended.
SC = Strongly Consider.
[a] Missing Data.

Results

Treatment patterns relative to NCCN guidelines

We identified a total of 432 T3-4a, N0, M0 melanoma cases. Of these 353 (81.7%) were SN, while 79 (18.3%) were non-SN in origin. The majority were treated surgically, in concordance with NCCN recommendations (SN: 92.4% vs non-SN: 84.8%). END is not recommended in SN MM cases and was not employed in 91.5% of cases. Conversely, END is recommended in non-SN cases, but was performed in only 26.6% of cases. Depending on T classification, RT is either recommended or stated that it should be "strongly considered" in both SN and non-SN MM cases; its utilization was 63.5% for SN cases and 46.8% for non-SN cases. ST is not recommended in MM cases and was not utilized in the majority of cases (SN: 87.4%; non-SN: 84.4%) (Table 1).

Characteristics of T3-4a, N0, M0 head and neck MM patients stratified by primary site

After excluding patients with missing survival status (n = 96), we identified 336 MM cases: 275 (81.8%) SN and 61 (18.2%) non-SN cases. Patients were predominantly white (92.9%) and > 65 years of age (69.6%), with similar numbers of the sexes (50.3% male and 49.7% female). There was a low comorbidity burden (78.9% had a CDCC score of 0) and most patients presented with an T classification of T3 (68.2%), as opposed to T4a (31.8%). While most patients received surgery (90.8%), most did not receive END (88.7%), and slightly over half received RT (59.8%).

In comparing the demographics of SN MM cases to non-SN MM cases, SN patients were more likely to be > 75 (48.4% vs. 36.1%; p = 0.026) and female (52.4% vs. 37.7%, p = 0.038). There were no differences in race (p = 0.783), CDCC scores (p = 0.807), or clinical T classification (p = 0.461). While we found no difference in surgical (p = 0.231) or RT management (p = 0.061) between the groups, non-SN patients were more likely to received END (24.6% vs. 8.4%; p < 0.001) (Table 2).

Number of nodes removed and occurrence of positive nodes

Of the 23 ENDs performed within the SN cohort with known survival, the mean number of removed nodes was 16.96 ± 22.9 (treating one case with ≥90 nodes removed as 90 nodes removed). Four (17.4%) yielded ≥1 positive node. There was no association between number of nodes removed and the presence of ≥1 positive node upon *t*-test with equal variance not assumed (no positive nodes found: 13.84 ± 17.66 nodes removed; ≥1 positive node found: 31.75 ± 40.27 nodes removed; p = 0.443).

Excluding cases with an unknown number of nodes removed (n = 2) within the non-SN cohort with known survival, the mean number of removed nodes in 13 cases was 28.3 ± 18.91. Six of 15 (40.0%) yielded ≥1 positive node. There was no association between number of nodes removed and the presence of ≥1 positive node upon *t*-test with equal variance assumed (no positive nodes found: 23.27 ± 21.27 nodes remove; ≥1 positive node found: 35.40 ± 13.35 nodes removed; p = 0.305).

Survival outcomes associated with NCCN guidelines and AJCC T classification for SN MM

In the SN cohort, Kaplan-Meier analysis revealed no significant OS difference between patients who did and who did not receive END (p = 0.752; Fig. 2A) and 3-year OS was comparable (END performed: 42.2% [SE: 11.1%]; END not performed: 43.3% [SE: 3.7%]). However, univariate analysis revealed a significant OS advantage in SN MM cancer patients who received RT (p = 0.021; Fig. 2B). Those who received RT had a 3-year OS of 48.0% (SE: 4.4%), while those who did

Table 2
Univariate Chi-Square Analysis of Demographics of Mucosal Melanoma Patients Stratified by Site.

	All Non-SCC Cases (n = 336)	Sinonasal Cavity (n = 275)	Oral Cavity, Oropharynx, Larynx, and Hypopharynx (n = 61)	p-value
Age				0.026[b]
18–54	40 (11.9%)	20–30[a] (7.2–10.9%)	10–20[a] (16.4–32.8%)	
55–64	62 (18.5%)	50–60[a] (18.2–21.8%)	< 10[a] (< 16.4%)	
65–74	79 (23.5%)	63 (22.9%)	16 (26.2%)	
> 75	155 (46.1%)	133 (48.4%)	22 (36.1%)	
Sex				0.038
Male	169 (50.3%)	131 (47.6%)	38 (62.3%)	
Female	167 (49.7%)	144 (52.4%)	23 (37.7%)	
Race				0.783[b]
White	312 (92.9%)	250–260[a] (90.9–94.5%)	50–60[a] (82.0–98.4%)	
Non-White/Unknown	24 (7.1%)	10–20[a] (3.6–7.3%)	< 10[a] (< 16.4%)	
Charlson-Deyo Score				0.807[b]
0	265 (78.9%)	218 (79.3%)	47 (77.0%)	
1	58 (17.3%)	40–50[a] (14.5–18.2%)	10–20[a] (16.4–32.8%)	
≥2	13 (3.9%)	10–20[a] (3.6–7.2%)	< 10[a] (< 16.4%)	
Clinical T Stage				0.461
T3	229 (68.2%)	185 (67.3%)	44 (72.1%)	
T4a	107 (31.8%)	90 (32.7%)	17 (27.9%)	
Surgical Therapy				0.231[b]
No Surgery	31 (9.2%)	20–30[a] (7.3–10.9%)	< 10[a] (< 16.4%)	
Surgery	305 (90.8%)	250–260[a] (90.9–94.5%)	50–60[a] (82.0–98.4%)	
Elective Neck Dissection				< 0.001
Not Performed	298 (88.7)	252 (91.6%)	46 (75.4%)	
Performed	38 (11.3%)	23 (8.4%)	15 (24.6%)	
Radiotherapy				0.061
No Radiotherapy	135 (40.2%)	104 (37.8%)	31 (50.8%)	
Radiotherapy	201 (59.8%)	171 (62.2%)	30 (49.2%)	

[a] Cells Suppressed to Prevent Identification of Patients within Cells with < 10 Cases as Per NCDB Data Use Agreement.
[b] Fisher's Exact Test.

not had a 3-year OS of 35.0% (SE: 5.5%). There was a difference in OS noted between AJCC T3 and T4a classifications (p = 0.004). The 3-year OS of T3 and T4a patients was 47.2% (SE: 4.3%) and 35.0% (SE: 5.8%), respectively.

Adjusting for demographic and oncologic factors, non-surgical therapy was found to be associated with decreased OS when compared to surgical therapy (HR: 2.063; 95% CI: 1.208–3.525; p = 0.008; Table 3), while no OS advantage was noted for END (compared to surgery alone, HR: 1.350; 95% CI: 0.733–2.485; p = 0.336). RT remained an independent predictive factor for improved OS (HR: 0.679; 95% CI: 0.479–0.963; p = 0.030). T4a patients had poorer OS than T3 patients (HR: 1.626; 95% CI: 1.146–2.305; p = 0.006).

Survival outcomes associated with NCCN guidelines and AJCC T classification for non-SN MM

With regards to non-SN patients, Kaplan-Meier analysis revealed no significant OS differences between patients who did and who did not receive END (p = 0.330; Fig. 3A). Three-year OS was comparable (END performed: 35.0% [SE: 14.7%]; END not performed: 56.2% [SE:8.4%]). Similarly, there was no difference in OS based upon RT administration (p = 0.822; Fig. 3B), revealing a comparable 3-year OS (RT cohort: 47.6% [SE: 10.0%]; non-RT cohort: 43.3% [SE:11.2%]). There was no OS difference between T3 and T4a patients (p = 0.313; Fig. 3C) and 3-year OS was comparable (T3 cohort: 53.6% [SE: 8.2%]; T4a cohort: 42.7% [SE: 15.9%]).

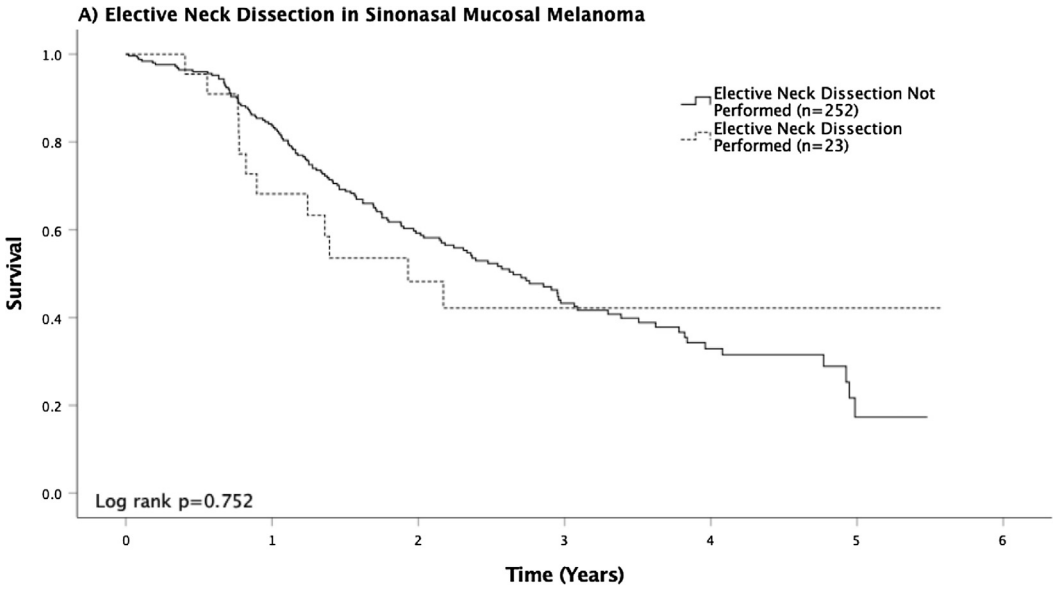
Non-surgical therapy, compared to surgical therapy, was independently associated with decreased OS on multivariate analysis (HR: 7.542; 95% CI: 2.019–28.169; p = 0.003; Table 3). Neither END (compared to surgery alone, HR: 3.460; 95% CI: 0.912–13.125; p = 0.068) nor RT (HR: 0.824; 95% CI: 0.331–2.051; p = 0.678) were associated with OS, though END's p-value may be approaching significance (notably in the direction of decreased survival), and this may be a product of our small sample size. Notably, an AJCC clinical T classification of T4a did not carry a significant OS reduction (compared to T3, HR: 0.797; 95% CI: 0.187–3.395; p = 0.758).

Subgroup survival analyses utilizing a stricter definition of END

After removing cases with an unknown number of nodes removed (n = 2), we performed survival subgroup analyses utilizing a stricter definition of END (≥5 nodes surgically removed). Twelve of 275 SN MM patients (4.4%) and 12 of 59 non-SN MM patients (20.3%) had ≥5 nodes removed. Similar to previous findings, we found no difference in survival between those who did and did not have ≥5 nodes removed in either cohort upon univariate analyses (SN MM: p = 0.217; non-SN MM: p = 0.459; Supplementary Figs. 1 and 2). Upon multivariate analysis, having had ≥5 nodes removed was not associated with increased survival in both the SN MM (HR: 2.043; 95% CI: 0.920–4.537; p = 0.079) and non-SN MM (HR: 3.069; 95% CI: 0.833–11.315; p = 0.092) cohorts, compared to surgery alone (Supplementary Table 1). Correspondingly, all other previously observed survival associations held.

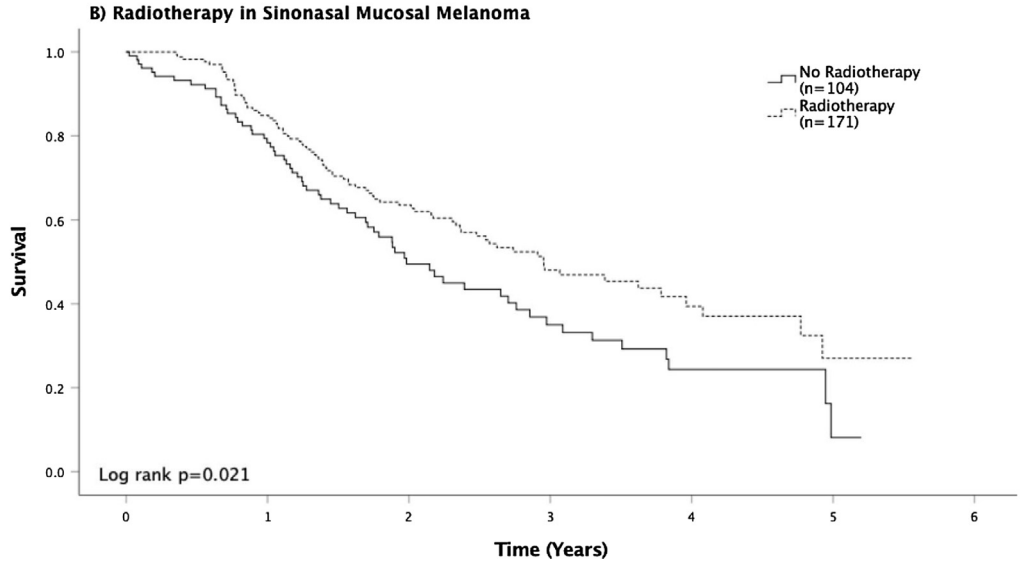
Discussion

Though the MM incidence has been rising steadily by about 2.4% since 1987 [22], it remains a poorly understood cancer with a poor prognosis. Due to the scarcity of larger studies on best treatment practices, generally accepted guidelines remain elusive. Of the 30 treatment-related studies referenced in the NCCN guidelines [9], 10 are articles regarding cutaneous melanoma (CM) [23–32]. Such extrapolation of results from CM is problematic as MM has a much lower 5-year OS (49% vs. 88%; p < 0.001) and 5-year disease-free survival



Number at Risk

END Not Performed:					
252	201	113	56	24	4
END Performed:					
23	15	8	7	7	7



Number at Risk

No Radiotherapy:					
104	78	35	19	9	1
Radiotherapy:					
171	138	86	42	17	4

Fig. 2. Kaplan-Meier Curve for SN MM stratified by (A) Elective Neck Dissection, (B) Radiotherapy, and (C) T-Stage.

(18% vs. 94%) than CM [33], tends to present with advanced disease due to the relative lack of clear symptoms [16,34], likely does not have the same epidemiologic associations [35], and appears to have different oncogenetic drivers [36]. Of the remaining 20 treatment-related sources, 16 are retrospective cases series [11,12,34,36–48], primarily conducted at single-institutions with homogenous samples [15], and 4 are review articles [5,15,49,50]. Due to the rarity of MM, no prospective randomized trials exist to guide therapy. In the present study, we analyze treatment within these guidelines, and its associations with OS utilizing a large, national cohort of over 300 clinically node-negative patients.

Surgery has consistently been recommended in the treatment of N0 MM throughout the literature [5], and its effectiveness has been shown in a national cohort [3]. We accordingly have found high utilization of surgery. Conversely, the role of ST in MM is unclear [15]. As such, ST is not currently NCCN-recommended, and we found that most patients do not receive ST in practice. However, as immunotherapy is increasingly utilized in CM, and given that MM recurrence is high, immunotherapy may prove to be a promising therapy adjuvant to surgery. Indeed, there has been one report of a complete response of a stage IV anal MM

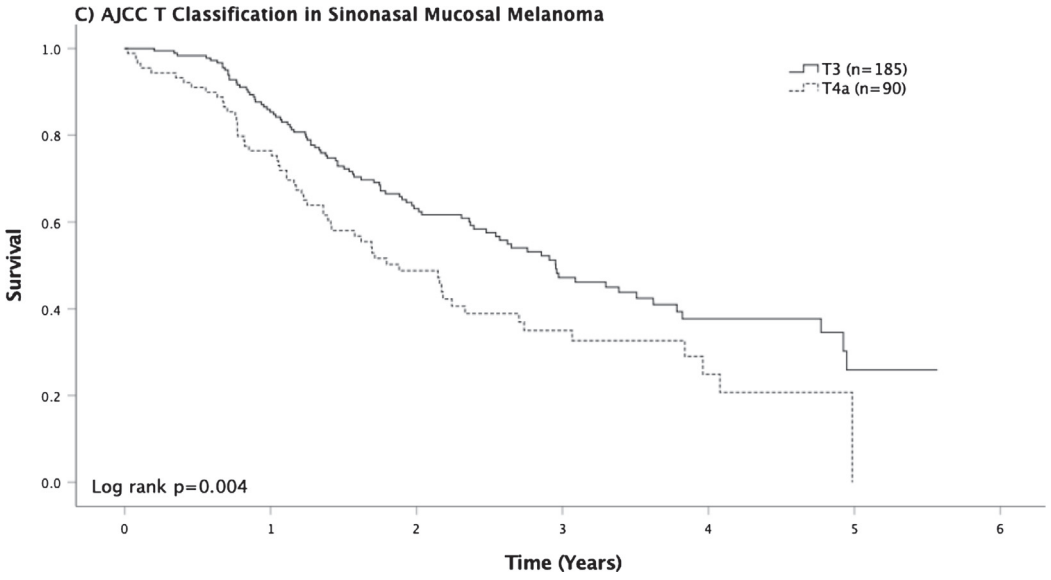
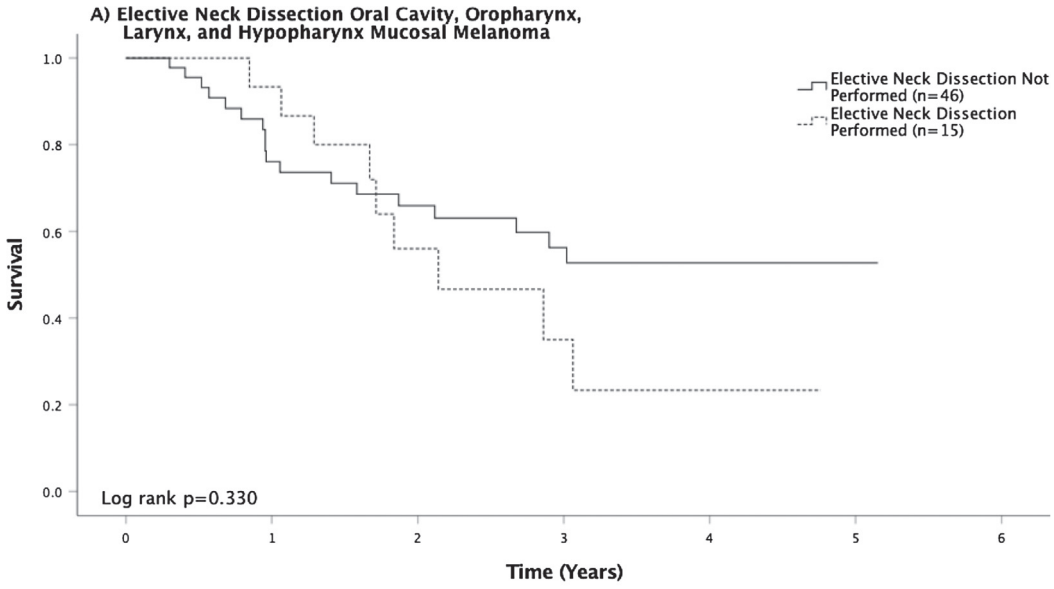


Fig. 2. (*continued*)

Table 3
Multivariate Cox Regression in Both Subsites.

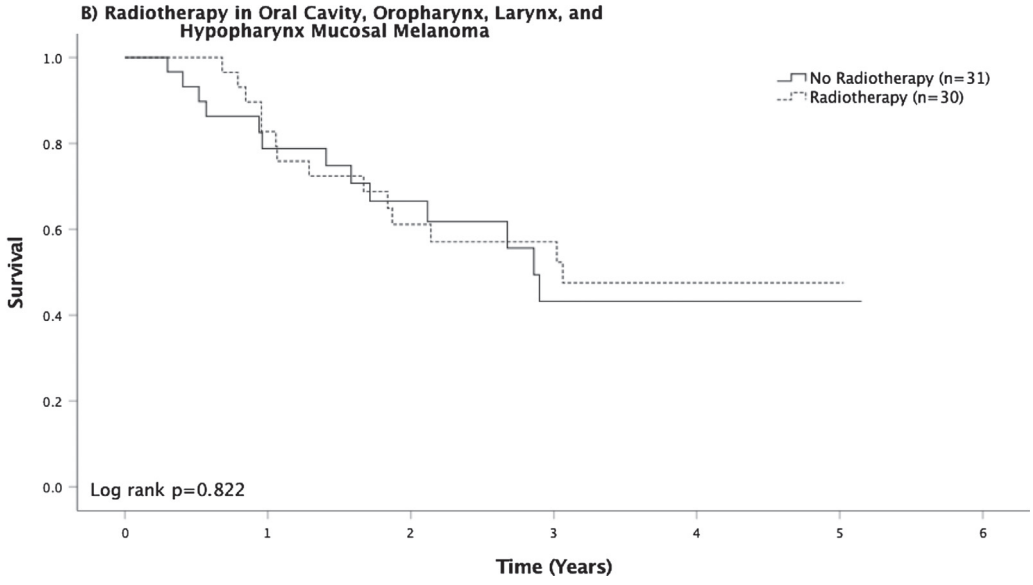
	Sinonasal Cavity (n = 275)		Oral Cavity, Oropharynx, Larynx, and Hypopharynx (n = 60[a])	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age				
18–54	1.000	Reference	1.000	Reference
55–64	0.445 (0.221–0.893)	0.023	0.059 (0.005–0.711)	0.026
65–74	0.662 (0.362–1.212)	0.182	0.748 (0.207–2.707)	0.658
> 75	0.871 (0.497–1.529)	0.631	3.248 (0.997–10.582)	0.051
Sex				
Male	1.000	Reference	1.000	Reference
Female	1.021 (0.725–1.437)	0.907	1.841 (0.761–4.452)	0.176
Race				
White	1.000	Reference	1.000	Reference
Non-White/Unknown	1.457 (0.809–2.623)	0.210	0.784 (0.075–8.210)	0.839
Charlson-Deyo Score				
0	1.000	Reference	1.000	Reference
1	0.877 (0.565–1.359)	0.556	1.063 (0.324–3.493)	0.919
≥2	1.330 (0.575–3.080)	0.505	[b]	[b]
Clinical T Stage				
T3	1.000	Reference	1.000	Reference
T4a	1.626 (1.146–2.305)	0.006	0.797 (0.187–3.395)	0.758
Surgical Therapy				
No Surgery	2.063 (1.208–3.525)	0.008	7.542 (2.019–28.169)	0.003
Surgery without END	1.000	Reference	1.000	Reference
Surgery with END	1.350 (0.733–2.485)	0.336	3.460 (0.912–13.125)	0.068
Radiotherapy				
No Radiotherapy	1.000	Reference	1.000	Reference
Radiotherapy	0.679 (0.479–0.963)	0.030	0.824 (0.331–2.051)	0.678

END = Elective Neck Dissection.
[a] 1 case was dropped from original sample of 61 for purposes of analysis due to being censored before earliest event in a stratum.
[b] Insufficient sample size for analysis.



Number at Risk

END Not Performed:					
46	31	24	16	12	3
END Performed:					
15	14	7	3	1	0



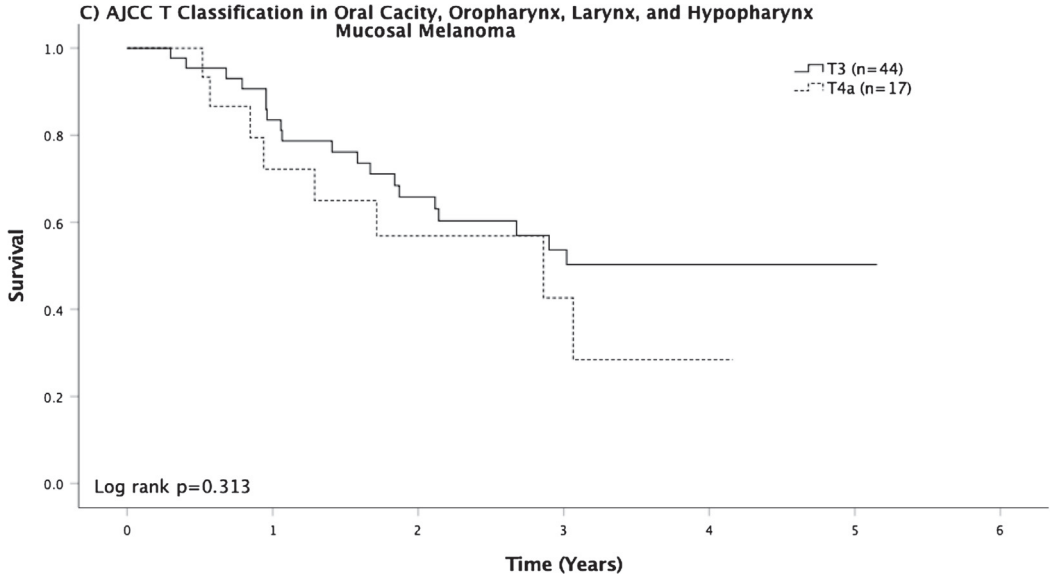
Number at Risk

No Radiotherapy:					
31	21	15	7	7	1
Radiotherapy:					
30	24	16	12	6	2

Fig. 3. Kaplan-Meier Curve for non-SN MM stratified by (A) Elective Neck Dissection, (B) Radiotherapy, and (C) T-Stage.

treated with surgery and sorafenib [51]. As the definition of immunotherapy in the NCDB database changed in 2013 to include drugs previously classified as chemotherapy, as well as missing data, we were unable to effectively analyze the effect of immunotherapy in a clinically-meaningful way. However, the KEYNOTE study (NCT01295827, NCT01704287, and NCT01866319) evaluating immunotherapy efficacy in all melanoma types, found preliminary beneficial results for Pembrolizumab in the treatment of advanced MM, and has an estimated April 2019 completion date [52].

There is more controversy surrounding the benefit of END in patients with clinically-negative neck disease. The NCCN currently recommends END for non-SN, but not SN, MM. This may be partially explained by findings that regional lymph node relapse and nodal metastases are over three times more common in primary MM of the oral cavity as compared to the SN cavity [7,12,14,53]. However, our analysis shows that providers are not performing END in the majority of cases for MM of either site. In fact, we found no OS benefit to performing this invasive procedure, though we were unable to analyze the



Number at Risk

T3:	44	35	24	16	12	3
T4a:	17	10	7	3	1	0

Fig. 3. (*continued*)

difference in recurrence rates, and, in the case of non-SN MM, may be a product of our limited sample size. The incidence of finding a pathologically-positive node was higher in the non-SN cohort than the SN cohort (40% vs. 17.4%). While our analysis was limited by our liberal definition of END (≥1 node removed), we found parallel results in subgroup analyses utilizing using a stricter definition of END (≥5 node removed). A previous 2004–2012 NCDB study similarly found no survival benefit to a neck dissection, though they did not stratify by site and were not specifically looking at clinically node-negative patients [4]. A large, single-institution retrospective study of 90 clinically node-negative oral MM patients found that END conferred survival benefits in nodular MM (multivariate Cox regression $p = 0.002$), but not in macular MM (multivariate Cox regression $p = 0.17$) [54]. Furthermore, we found no association between the number of nodes removed and the presence of at least one pathologically positive node in either cohort, indicating that even more extensive neck dissections may not be worthwhile, though this analysis was limited by our small sample size. Interestingly, the role of neck dissections is currently being called into question in the management of CM.

END is rarely done in cases of CM, as management of the neck is guided by a sentinel lymph node biopsy (SLNB) [55]. Traditionally patients with a positive SLNB were always recommended to undergo a complete lymph node dissection (CLND) given the risk of occult nodal spread in the form of positive non-sentinel lymph nodes (NSLN). However, the clinical value of performing a CLND is being called into question [56] due to the elevated morbidity of CLND, development of certain scoring systems attempting to predict NSLN positivity and thus spare patients from CLND, and the lack of proven benefit in survival or recurrence when CLND was performed compared to observation [57]. As many of the treatments for MM are extrapolated from CM treatment, this controversy, along with our findings (no impact on survival, moderate incidence of finding a positive node, and no correlation between number of nodes removed and identification of positive nodes), seem to indicate that END may only be necessary in certain instances of non-SN, such as nodular types. Interestingly, only three studies comprising of a total of five patients evaluated the efficacy of SLNB in MM and found it correctly predicted histopathologic lymph node status [58–60]. The role of SLNB in MM warrants further investigation.

Similarly, the role of RT in MM is not established. NCCN guidelines state that RT should be “strongly considered,” due to the risk of micrometastases and residual disease [5]. We found RT administration to be moderate, with more frequent usage for SN cases than non-SN cases (63.5% vs. 46.8%, respectively). Interestingly, our data demonstrates that although RT did not impact OS in non-SN patients, it lead to an improved OS in SN patients. This is contrary to recent studies that have not found a survival benefit associated with RT [11,12,42]. In combination with work that has shown RT to increase local control [11,12], our results indicate that RT may be a useful surgical adjuvant, especially in SN MM. However, due to the high morbidity associated with RT, clinicians should be careful to weigh the potential costs and benefits in non-SN MM.

The current AJCC staging scheme was proposed in 2009 [8], though three other staging schemes had been proposed by various entities in the preceding decades [16,17]. Uniquely, this new staging scheme does not have T classifications of T1 or T2, and begins at stage III, due to its highly aggressive nature. T3 indicates mucosa-limited disease, while T4a indicates tumors that involve deep soft tissue, cartilage, bone, or skin. The degree of usage of this staging schema in clinical settings is not known [16,17], but our analysis only found a clear prognostic difference between T3 and T4a MM cancers at SN, but not non-SN, subsites. Schmidt et al, in their NCDB analysis also found no difference in survival between T3 and T4a MM patients, though they did not stratify by anatomic subsite [4]. Further investigation into tumor staging may be warranted to create clearer prognostic stages.

There are a number of limitations inherent to a retrospective database analysis that must be noted. A number of cases were excluded due to missing data, which may bias the data. We were also limited by the variables in the dataset. Certain prognostic factors, such as smoking status, as well as certain outcomes, such as local control and disease-free survival, are not captured by the NCDB. There may also have been selection bias with regards to which patients were assigned which treatments; it is likely that treatments like END and RT were reserved for patients with adverse features not captured in the dataset. Finally, as this is a rare disease, our sample sizes were limited, even in a large database study such as this, informing our decision to apply a loose definition of ≥1 node removal as an END. We attempted to mitigate

this limitation by performing a subgroup analysis utilizing a stricter definition and performing exploratory analyses on the association between node removal and the incidence of positive nodes. However, as such, specific treatment recommendations cannot be made.

Conclusion

We present an analysis of the NCCN MM guidelines on survival. As the guidelines are built on scant literature, their effectiveness has yet to be proven. Our results support a reexamination of the guidelines. The current guidelines seem well-suited to SN MM cases, but a reassessment on the value of recommending END and RT in non-SN MM may be warranted. Our results also indicate that the current AJCC staging scheme may be improved in order to reflect a clearer prognostic difference between stages. We found treatment patterns relative to NCCN guidelines to vary based on treatment modality, which may be due to the low incidence of MM and reflect clinicians' uncertainties regarding the efficacy of the current guidelines.

NCDB acknowledgement

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.

Conflict of interest

None declared.

Acknowledgement

NIH Heart, Lung, and Blood Institute [award number T35HL007649].

Role of funding source

This funding had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.03.017.

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