Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ ___4/25/2013_____

Srijana Rajbhandary Date

Does adjuvant radiation therapy post-surgery result in better survival in Mucosal Melanoma of the Head and Neck (MMHN) at the subsite level?

By

Srijana Rajbhandary
Degree to be awarded: MPH

Epidemiology

_____

Kevin C. Ward PhD, MPH, CTR
Thesis Faculty Advisor

Does adjuvant radiation therapy post-surgery result in better survival in Mucosal Melanoma of the Head and Neck (MMHN) at the subsite level?

By

Srijana Rajbhandary
Bachelor of Dental Surgery (BDS), B.P. Koirala Institute of Health Sciences, 2009

Thesis Faculty Advisor: Kevin C. Ward, PhD, MPH, CTR

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2013

Abstract

Does adjuvant radiation therapy post-surgery result in better survival in Mucosal Melanoma of the Head and Neck (MMHN) at the subsite level?

By Srijana Rajbhandary

Background: Previously conducted studies did not use population based data to explore the difference in survival for mucosal melanoma of the head and neck (MMHN) region at the subsite level among patients receiving surgery alone versus adjuvant radiation post-surgery.

Objectives: To explore whether the 5-year cause-specific survival for MMHN is different for surgery alone compared to adjuvant radiation therapy post-surgery at the subsite level (nasal mucosa, paranasal sinuses, oral cavity, and other sites).

Methods: We conducted a retrospective cohort study on MMHN using population-based Surveillance, Epidemiology, and End Results (SEER) registry data from 2001 to 2009. We used multivariable Cox proportional hazards regression models to compare the 5-year cause-specific survival of MMHN cases at various subsites.

Results: Of the 477 MMHN cases meeting study inclusion criteria, the highest number of cases originated from the nasal cavity (n= 234). There was no statistical evidence to prove a survival advantage of adjuvant radiation therapy post-surgery over surgery alone at any subsite.

Conclusion: In this analysis using population-based cancer registry data, adjuvant radiation therapy post-surgery did not result in improved survival for MMHN at any subsite.

Does adjuvant radiation therapy post-surgery result in better survival in Mucosal Melanoma of the Head and Neck (MMHN) at the subsite level?

By

Srijana Rajbhandary

Bachelor of Dental Surgery (BDS), B.P. Koirala Institute of Health Sciences, 2009

Thesis Faculty Advisor: Kevin C. Ward, PhD, MPH, CTR

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2013

Contents

Does adjuvant radiation therapy post-surgery result in better survival in Mucosal Melanoma of the Head and Neck (MMHN) at the subsite level?

Literature Review

Mucosal Melanoma

Primary mucosal melanomas are malignant lesions derived from dendritic melanocytes, the pigment cells, in the mucosal membrane lining the respiratory, gastrointestinal and urogenital tracts. Results from several studies have failed to establish human papilloma virus, herpes virus, polyomaviruses, and snuffing or dipping as etiologic factors of mucosal melanoma [1-4]. However, some recent studies indicate occupational exposure to formaldehyde and genetic predisposition, such as KIT mutations and somatic mutations of GNAQ, to be strongly associated with mucosal melanoma [5-7].

The American Cancer Society estimates that 76,250 new cases of cutaneous melanoma and 4,990 new cases of non-epithelial melanoma occurred in the year 2012 [8]. In contrast to cutaneous melanoma, non-epithelial melanomas are rare. A study conducted using the National Cancer Data Base (NCDB) in the United States for 1985–1994 reported the distribution of melanoma in the ocular region to be 5.5 % and in mucosal sites to be 1.3% of all melanomas[9]. Most of the mucosal melanomas occur in the nasal cavity, accessory sinuses (paranasal sinuses), oral cavity, anal and rectal region, vulva and vagina [10]. Because of the general inaccessibility of these sites, the majority of these lesions are usually diagnosed at an advanced clinical stage.

Mucosal Melanoma of the Head and Neck (MMHN*) Region*

In the United States, mucosal melanomas of the head and neck region account for 55% of all mucosal melanomas [12]. A recent study conducted using population-based Surveillance, Epidemiology, and End Results (SEER) registry data from 1973 to 2007, reported the most common primary site of mucosal melanoma in the head and neck region to be the nasal cavity (49.1%) followed by the paranasal sinuses (23.1%) and oral cavity (18.8%). This study identified age >70 years, tumor size >2cm, nodal metastasis and the presence of distant metastasis as independent predictors of poorer survival [13]. Similarly, a study conducted by Patel et al., identified clinical stage at presentation, tumor thickness greater than 5 mm, vascular invasion on histologic studies, and the development of distant failure as independent prognostic factors for survival in patients with mucosal melanoma of the head and neck region [16].

The primary sites of mucosal melanoma in the head and neck region are inconspicuous on routine examination. Clinical symptoms are therefore important for diagnosis. The most common clinical symptoms of melanomas in the nasal cavity are epistaxis and nasal obstruction. The lesions of the oral cavity commonly appear as pigmented and friable masses occasionally followed by odynophagia. Nasopharyngeal melanomas commonly present as serous otitis media [14].

Treatment modalities and survival of Mucosal Melanoma of the Head and Neck (MMHN)

The 5-year overall survival is poor among cases diagnosed with mucosal melanoma of the head and neck (MMHN) region. The overall survival rate for MMHN has been reported in several different studies using various cohorts. In a study conducted by Temam et al., the 5-year survival was reported as 20% [15]. Disease specific survival as reported by Patel et al. was 44% among cases with oral lesions and 47% among cases with sino-nasal lesions [16]. The 5-year cause specific survival for all recorded cases in the SEER database for the period 1970 to 2007 is 39.3% for the oral cavity and 31.3% for the nasal cavity [29].

Surgical treatment, radiation therapy and systemic therapy are available treatment options for MMHN. The treatment guidelines provided by the National Comprehensive Cancer Network (NCCN) recommend surgical treatment followed by radiation therapy as the standard treatment regime for cases diagnosed prior to stage IV [19]. However, there is controversy regarding the survival advantage of adjuvant radiation therapy for MMHN cases [11, 19-25, 15, 26-27]. For advance staged lesions there is no definitive treatment guideline available. The NCCN recommends that patients with advanced disease be entered on clinical trials if available or receive radiotherapy or systemic therapy. Traditionally, the most frequently used chemotherapeutic agents are dacarbazine, the platinum analogs, the nitrosoureas and the microtubular toxins [11]. Most of the newer systemic drugs are still in the clinical trial phase. Recent systemic therapies are targeted

at c-KIT and NRAS mutations. Results with Imatimib have been found to be encouraging. [28].

Haematogenous dissemination is the primary route of spread for these lesions. A study conducted at the University of California, Los Angeles (UCLA) Medical Center reported that local control of lesions is attributed to better survival in cases with MMHN [18]. However, local control with either surgery or radiotherapy post-surgery has not been very successful. The rates of local, regional and distant recurrences are high (50–90%, 20–60% and 30–70%, respectively) [11].

A number of prior studies have failed to establish better overall survival with adjuvant radiation therapy post-surgery as compared to surgery alone [11, 19-25]. Yii et al. examined 89 patients treated at the Royal Marsden Hospital with mucosal melanoma of the head and neck and concluded that there was not a statistically significant advantage of adjuvant radiation therapy in reducing the local recurrence or improving survival [19]. Similarly Lund et al. failed to establish a difference in local control and survival for patients treated with surgery followed by radiation therapy over patients treated with surgery alone [25].

In contrast to these results, a few small retrospective case series studies have identified fewer distant metastasis and better local control with adjuvant radiation therapy [17, 28-29]. Temam et al., reported better local control with adjuvant radiation therapy post surgery (26% without local recurrence among surgery alone vs. 62% recurrence among

postoperative radiotherapy) [15]. In a study by Nakashima et al., early (within 60 days) postoperative radiation therapy for MMHN was found to have better local control with a longer disease-free survival [27].

The limitations of past studies are extremely small sample sizes and inadequate exploration of survival rates following different treatment modalities at the subsite level in the head and neck region. To address this gap in knowledge, this retrospective cohort study analyzed the survival of head and neck mucosal melanoma at the subsite level using data from the population-based Surveillance, Epidemiology, and End Results (SEER) registry from 2001 to 2009. The study aims to explore whether treatment with adjuvant radiation therapy post-surgery results in better 5-year cause-specific survival for MMHN at the following subsites: nasal cavity, paranasal sinuses, oral cavity, and other sites.

Introduction:

Mucosal melanomas of the head and neck (MMHN) are rare malignant lesions with poor overall survival [8-9, 15-16]. In the United States, mucosal melanomas account for 1.3% of all melanoma cases [9]. Of all mucosal melanoma cases, 55.4% occur in different subsites of the head and neck region [12]. Subsites are established predictors for survival of mucosal melanoma in the head and neck region. Tumors in the nasal cavity and oral cavity have improved survival relative to tumors in the nasopharynx and paranasal sinuses [13].

Analyzing and comparing survival among different treatment modalities helps in making recommendations for treatment guidelines and policies to improve survival. The two most common treatment modalities for MMHN are surgery and surgery followed by radiation. The treatment guidelines provided by the National Comprehensive Cancer Network recommend surgical treatment followed by radiation therapy as the standard treatment regime for cases diagnosed prior to stage IV [17]. Although a few small retrospective case series studies have reported fewer distant metastasis and better local control with adjuvant radiation therapy [15, 26-27], there is no established overall survival benefit of adjuvant post-operative radiation therapy over surgery alone [11, 19-25]. Previously conducted studies had small sample sizes and survival rates were not explored at the subsite level within the head and neck. To address these gaps in knowledge, this retrospective cohort study used population-based registry data to analyze the cause specific survival of MMHN at the subsite level. The study aims to explore whether treatment with adjuvant radiation therapy post-surgery results in improved 5-

year cause specific survival for patients diagnosed with MMHN at following subsites: nasal cavity, paranasal sinuses, oral cavity, and other sites.

Materials and Methods:

We identified 558 cases diagnosed with mucosal melanoma originating from the head and neck region during 2001 to 2009 through the population-based Surveillance, Epidemiology, and End Results (SEER) registry [29]. Cases were defined using the following primary site and histology codes from the International Classification of Diseases for Oncology 3rd Edition (Primary sites codes: C01.9-C02.4, C02.8-C03.1, C03.9-C04.1, C04.8-C05.2, C05.8-C06.2, C06.8-C06.9, C07.9- C08.1, C08.8- C09.1 , C09.8- C10.4 , C10.8- C11.3, C11.8-C11.9 , C12.9 - C13.2, C13.8- C14.2 , C14.8, C30.0 - C31.3, C31.8-C32.3, C32.8 -C32.9; Histology codes 8720-8799: nevi and melanomas). Data on treatment modalities, cancer subsite, survival and other control factors (age, sex, race, stage, year of diagnosis, SEER registry and marital status) were extracted using publicly available SEER*Stat software 8.0.4 [29].

For analyses, we classified primary sites into 4 major groups: oral cavity, paranasal sinuses, nasal cavity and other sites. Cancers from the salivary glands, tonsils and pharynx were included among the other site group. We excluded cases originating from the lips. We used SEER summary stage [30] to categorize stage at diagnosis into local, regional or distant. The SEER registries were classified into four regions; Northeast, South, North Central and West. Age was categorized as <50, 50-69 and ≥70 years and race was grouped as white, black and other. Marital status was dichotomized into

married versus not married. Treatment was categorized into surgery and surgery followed by radiation. Survival was calculated in months from the time of diagnosis until either 5 years post-diagnosis, death from a head or neck cancer (event), death from any other cause, the date of last contact for patients lost to follow-up or the study endpoint (December 31, 2009). Two cases identified through death certificate only were excluded because they contributed no survival time. Cases not treated with either surgery alone or surgeries followed by radiation were also excluded. The final cohort included 477 cases.

Statistical analysis:

We compared categorical variables within treatment categories using chi-square tests of proportions with $P<0.05$ (2-sided) determined as the cut-off for statistical significance. Kaplan-Meier curves with corresponding log-rank tests and Wilcoxon tests for statistical significance were constructed to examine patient survival according to each individual study variable. These analyses were done for all MMHN subsites combined. Variables associated with either survival on univariate Kaplan Meier analysis or treatment modality on chi-square test of proportions were included in all subsite specific multivariable Cox proportional hazard regression models used to assess the association between survival and treatment at the head and neck subsite level. Proportional hazard assumptions were evaluated using graphical methods (log-log survival curves), goodness of fit tests and time dependent covariates. Final models were stratified on variables that did not satisfy at least two of the three proportional hazard assumptions. Collinearity was assessed

using condition indexes and variance decomposition proportions. None of the predictive factors considered were found to be collinear.

The final Cox model (model i) used to compare cause-specific survival among surgery alone compared to adjuvant radiation post-surgery for all head and neck subsites combined was stratified on stage and adjusted for age, marital status and subsite.

$h_g(t, \mathbf{X}) = h_{0g}(t) \exp[\beta_1 \text{treatment} + \beta_2 \text{age} + \beta_3 \text{marital status} + \beta_5 \text{subsite}]$ ------ (i)

$g = 1, 2, 3, 4$

Strata of stages defined as localized, regional, distant metastasis and unknown.

The final Cox model (model ii) used to compare cause-specific survival among surgery alone compared to adjuvant radiation post-surgery within the oral cavity was adjusted for stage, age and marital status.

$h(t, \mathbf{X}) = h_0(t) \exp[\beta_1 \text{treatment} + \beta_2 \text{age} + \beta_3 \text{marital status} + \beta_4 \text{stage}]$ ------ (ii)

The final Cox model (model iii) used to compare cause-specific survival among surgery alone compared to adjuvant radiation post-surgery within the nasal cavity was stratified on stage and adjusted for age and marital status.

$h_g(t, \mathbf{X}) = h_{0g}(t) \exp[\beta_1 \text{treatment} + \beta_2 \text{age} + \beta_3 \text{marital status}]$ ------ (iii)

$g = 1, 2, 3, 4$

Strata of stages defined as localized, regional, distant metastasis and unknown

The final Cox model (model iv) used to compare cause-specific survival among surgery alone compared to adjuvant radiation post-surgery within the paranasal sinuses was adjusted for age, stage, gender, marital status and race.

$h(t, \mathbf{X}) = h_0(t) \exp[\beta_1 \text{treatment} + \beta_2 \text{ age} + \beta_3 \text{stage} + \beta_4 \text{gender} + \beta_5 \text{ marital status} + \beta_6 \text{ race}]$ -------- (iv)

The final Cox model (model v) used to compare the cause specific survival among surgery alone compared to adjuvant radiation post-surgery within other sites was adjusted for age, stage, gender, marital status, year of diagnosis and race.

$h(t, \mathbf{X}) = h_0(t) \exp[\beta_1 \text{treatment} + \beta_2 \text{ age} + \beta_3 \text{stage} + \beta_4 \text{marital status} + \beta_5 \text{ race} + \beta_6 \text{gender} + \beta_7 \text{year of Diagnosis}]$ --------- (v)

Statistical analyses were carried out using SAS 9.3 (Copyright (c) 2002-2010 by SAS Institute Inc., Cary, NC, USA). This study received IRB approval from the Emory University IRB.

Results:

Analyses included 477 cases of mucosal melanoma in the head and neck region, summarized in Table 1. Of these cases, 240 (50.31%) were treated with surgery alone and 237 (49.69 %) were treated with surgery followed by radiation. There was a significant difference in treatment modality by age group with 60% (n=144) among cases treated with surgery alone and 50% (n=119) among cases treated with post-operative radiation being age $\geq$ 70 years while 29% (n=69) among cases treated with surgery alone

and 40% (n=94) among cases treated with post-operative radiation being age 50-69 years (p=0.041). Approximately 64% (n=152) among cases treated with post-operative radiation were married while 52% (n=124) among cases treated with surgery alone were unmarried (p=0.001). 53% (n=125) among cases treated with post-operative radiation and 45% (n=109) among cases treated with surgery alone originated from the nasal cavity while 13% (n=32) among cases treated with post-operative radiation and 27% (n=64) among cases treated with surgery alone originated from the oral cavity (p=0.003). The majority of cases were reported from the western SEER region.

Site specific Kaplan-Meier survival curves comparing surgery alone and radiation post-surgery are shown in figures 1-4 and indicate no statistically significant differences in survival by cancer subsite. For the oral cavity, survival was generally higher for the group treated with radiation post-surgery compared to surgery alone. For the paranasal sinuses, there was a crossover effect with survival initially being higher in the first 15 months for the radiation post-surgery group and then higher in subsequent months for the group treated with surgery alone. No discernible differences were noted for nasal cavity or other sites. Kaplan-Meier analysis for all cancer subsites combined also found no significant differences in survival by treatment group (figure 5).

The Kaplan-Meier survival plots to determine the significant of other variables on survival are shown in figures 6-13. Statistically significant differences were observed among age groups (p=0.03 by Wilcoxon test), stage groups (p<0.0001 by log rank test) and subsites (p<0.0001 by log rank test).

On multivariate analysis, there was lack of statistical evidence to justify a survival advantage of adjuvant radiation therapy post-surgery for all subsites combined as well as for each of the individual subsite considered alone (Table 2). Cause specific 5-year survival among all cases treated with surgery alone compared to radiation post-surgery was not significantly different [Hazard ratio (HR) 0.90, 95% CI: 0.68-1.19] (Table2). Similarly, there was no survival advantage among cases treated with adjuvant radiation post-surgery in the oral cavity [HR=1.33, 95% CI: 0.61-2.89], nasal cavity [HR=0.94, 95% CI: 0.63-1.41], paranasal sinuses [HR=0.69, 95% CI: 0.40-1.19], or at other sites [HR=1.31, 95% CI: 0.52-3.34].

Discussion:

The results of this retrospective cohort study show that at the population level in SEER data there is no statistical evidence to support a survival benefit of post-surgical adjuvant radiation therapy over surgery alone for MMHN cases at the subsite level. Although our data suggest differential survival among different treatment modalities at the cancer subsite level, our findings are in support with previously conducted smaller case series studies that reported no additional survival benefit of adjuvant radiation therapy in MMHN cases [11, 19-25]. Studies conducted by Yii et al. and Lund et al. failed to establish a difference in local control and survival for patients treated with surgery followed by radiation therapy over patients treated with surgery alone [19,25].

In some literature, local control of MMHN has been associated with longer survival [20]. Some smaller case series studies have demonstrated local control with adjuvant radiation therapy [15, 26-27]. Temam et al., reported better local control with adjuvant radiation therapy post surgery (26% without local recurrence among surgery alone vs. 62% recurrence among postoperative radiotherapy) [15] and Nakashima et al., reported better local control with a longer disease-free survival in early (within 60 days) postoperative radiation therapy [27]. We were unfortunately unable to assess local control as it is not captured in SEER data.

There are some limitations of the study that need to be addressed. Although data on surgery and radiation post-surgery are recorded within the SEER database, their ascertainment is not 100 percent complete due to the manner in which SEER data is collected. In addition, systemic therapy is not available in the public use SEER data. However, systemic therapies are not extensively used in the treatment of these malignancies because they are not well established and many drugs are still under clinical trial phase. Therefore, it can be anticipated that the inclusion of systemic therapy in the analysis would not have likely altered our conclusion. Patients with advanced stage lesions could have been possibly treated with adjuvant therapy and their poor survival could be attributed to their stage and age. However, it is unlikely that such cases would alter our conclusions because we adjusted for stage and age in all of our multivariate analysis. Finally, we were unable to assess local control of disease using SEER data. If radiation therapy provided a benefit in this regard, we were unable to tell using our data.

Our study is the first one to our knowledge to use population based surveillance data to analyze the difference in survival by treatment modality for MMHN at the subsite level. Furthermore, we used data from 2001 to 2009 assuming that cases reported in past decade would capture the latest trends and treatment guidelines for MMHN.

Recommendations:

Radiation therapy is associated with many adverse health effects including hair loss, nausea, vomiting and sexual changes. It confers to additional financial burden for the patient and potentially a poorer quality of life. It is important to weigh the survival advantage of radiation therapy over its spectrum of ill effects. Therefore, adjuvant radiation therapy in patients presenting with mucosal melanoma at different subsites of head and neck region should be given prudently.

Our study adds to the evidence of no survival advantage for adjuvant radiation post-surgery over surgery alone. Randomized controlled clinical trials in the future could provide stronger evidence based on evaluation of both local control and disease specific survival versus the harmful effects of adding radiation to the treatment regimen.

Tabel 1. Characteristics of the study population by type of treatment received.

	Surgery only (N=240)	Surgery +Radiation (N=237)	p-value*
Variables	n (%)	n (%)	
Age(years)			
<50	27 (11.25)	24 (10.13)	0.041
50-69	69 (28.75)	94 (39.66)	
≥70	144 (60.00)	119 (50.21)	
Gender			
Male	121 (50.42)	122 (51.48)	0.817
Female	119 (49.58)	115 (48.52)	
Married			
Yes	116 (48.33)	152 (64.14)	0.001
No	124 (51.67)	85 (35.86)	
Race			
White	213 (88.75)	205 (86.50)	0.375
Black	7 (2.92)	13 (5.49)	
Other[±]	20 (8.33)	19 (8.02)	
Regions in the United States			
Northeast	35 (14.58)	39 (16.46)	0.248
South	27 (11.25)	40 (16.88)	
North Central	26 (10.83)	26 (10.97)	
West	152 (63.33)	132 (55.70)	
Stage			
Localized only	103 (42.92)	89 (37.55)	0.220
Regional metastasis	80 (33.33)	101 (42.62)	
Distant site/s/node(s) involved	43 (17.92)	35 (14.77)	
Unknown[¶]	14 (5.83)	12 (5.06)	
Subsite			
Oral cavity	64 (26.67)	32 (13.50)	0.003
Nasal Cavity	109 (45.42)	125 (52.74)	
Para nasal sinuses	49 (20.42)	65 (27.43)	
Other sites	18 (7.50)	15 (6.33)	
Year of diagnosis			
2001	20 (8.33)	19 (8.02)	0.635
2002	30 (12.50)	21 (8.86)	
2003	23 (9.58)	20 (8.44)	
2004	30 (12.50)	26 (10.97)	
2005	31 (12.92)	27 (11.39)	
2006	29 (12.08)	24 (10.13)	
2007	26 (10.83)	32 (13.50)	

2008	27 (11.25)	39 (16.46)
2009	24 (10.00)	29 (12.24)

* Chi- square proportional test
± American Indian/AK Native, Asian/Pacific Islander
¶ Unknown/not-staged/unspecified

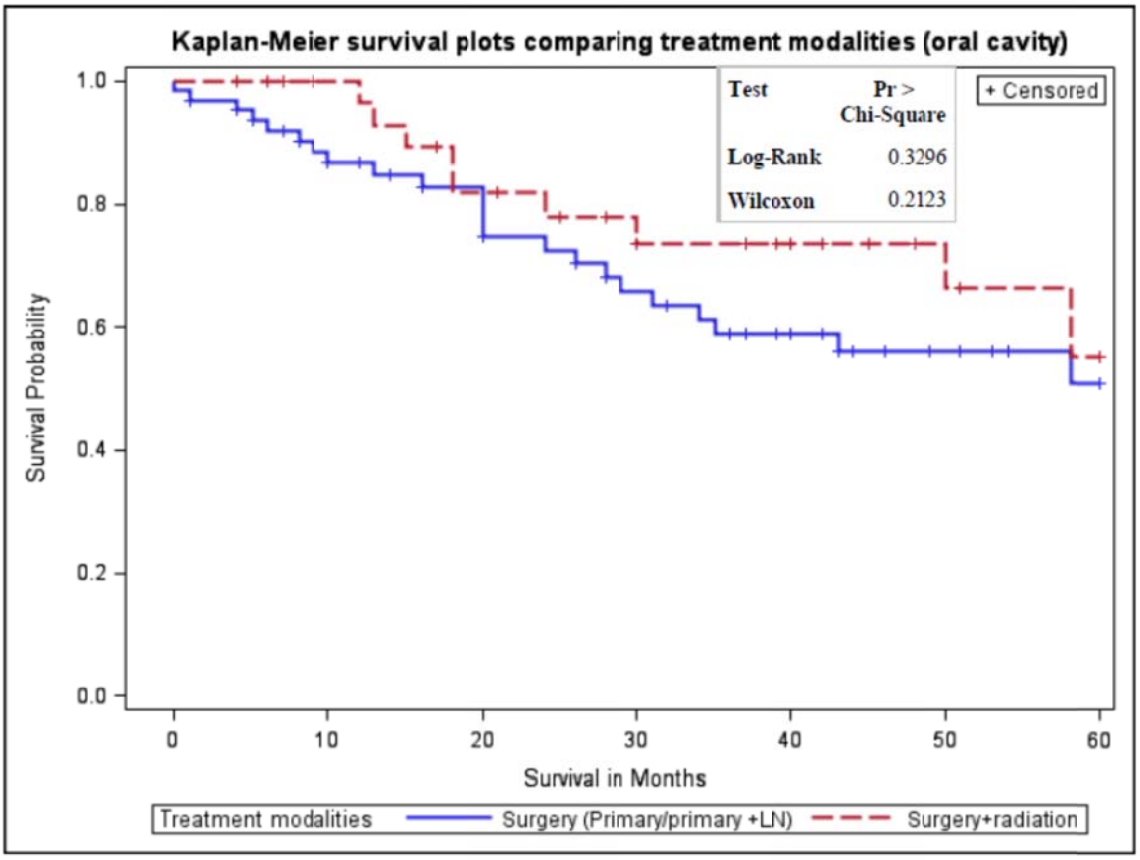

Figure 1 Kaplan-Meier survival plots comparing treatment modalities (oral cavity).

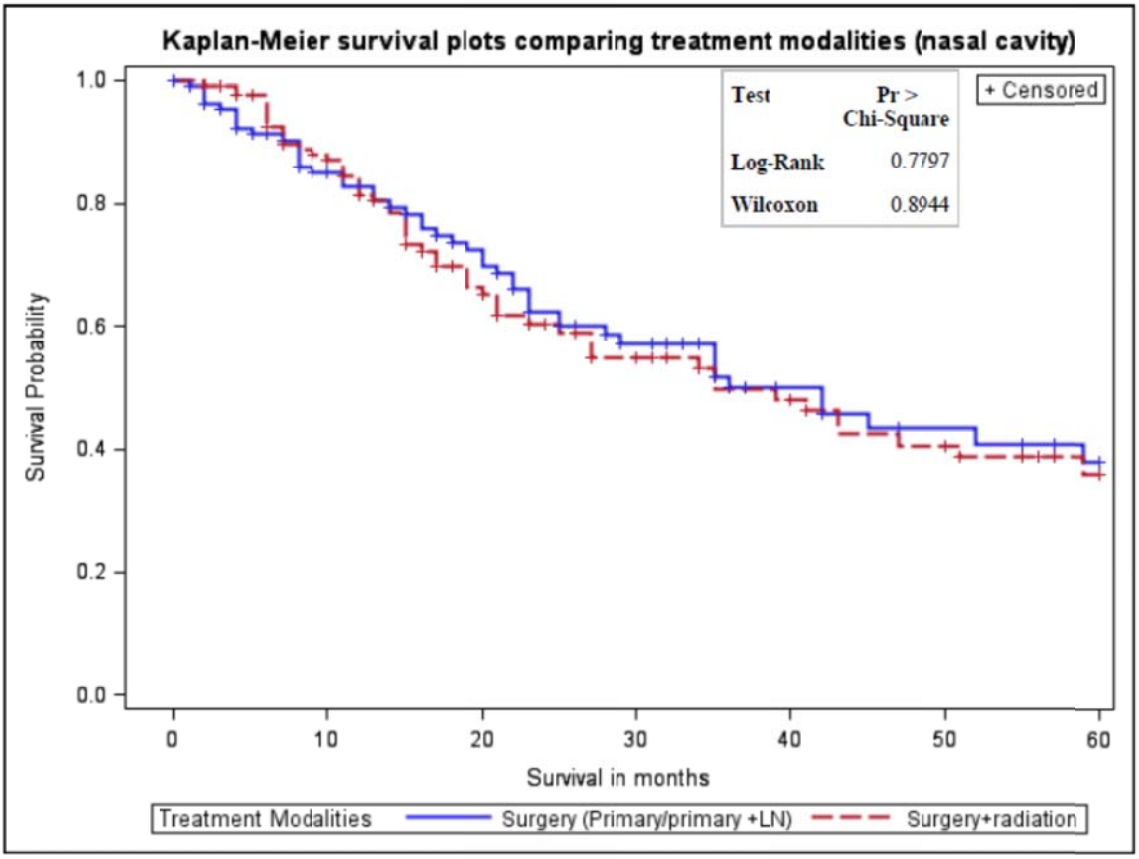

Figure 2 Kaplan-Meier survival plots comparing treatment modalities (nasal cavity).

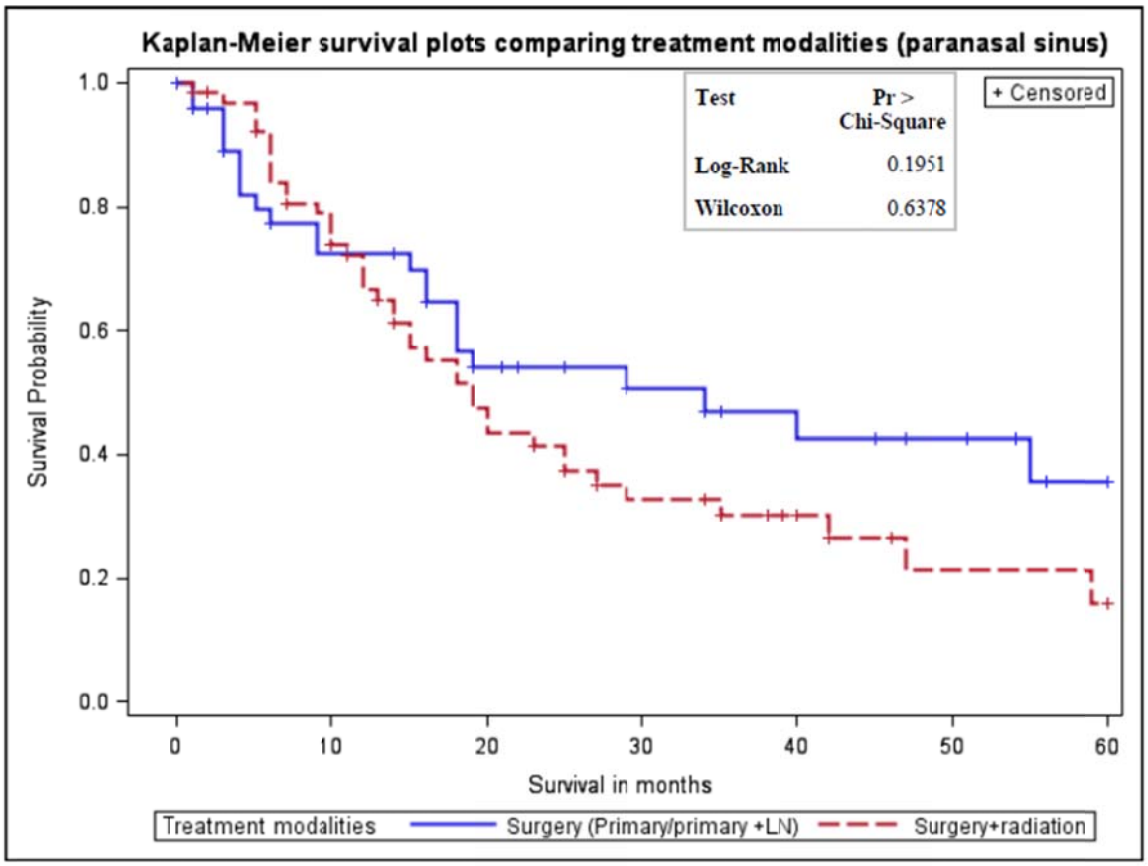

Figure 3 Kaplan-Meier survival plots comparing treatment modalities (paranasal sinus).

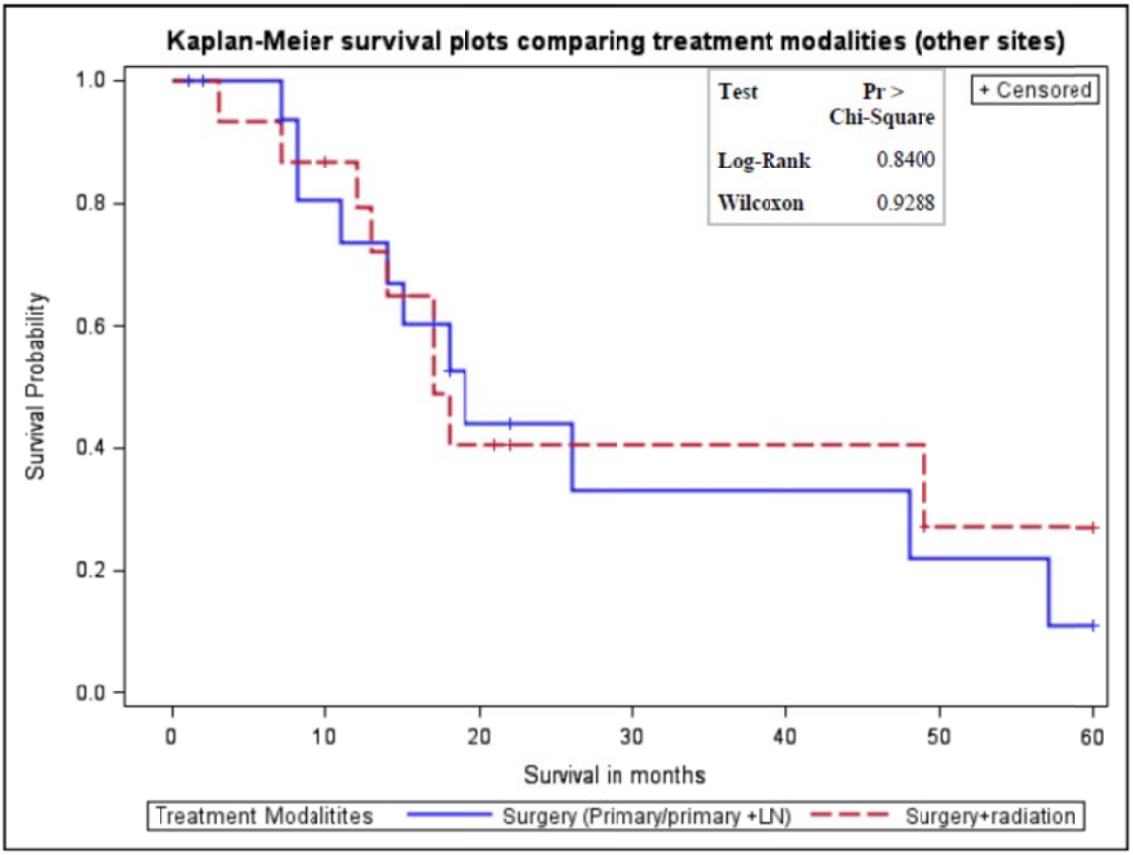

Figure 4 Kaplan-Meier survival plots comparing treatment modalities (other sites).

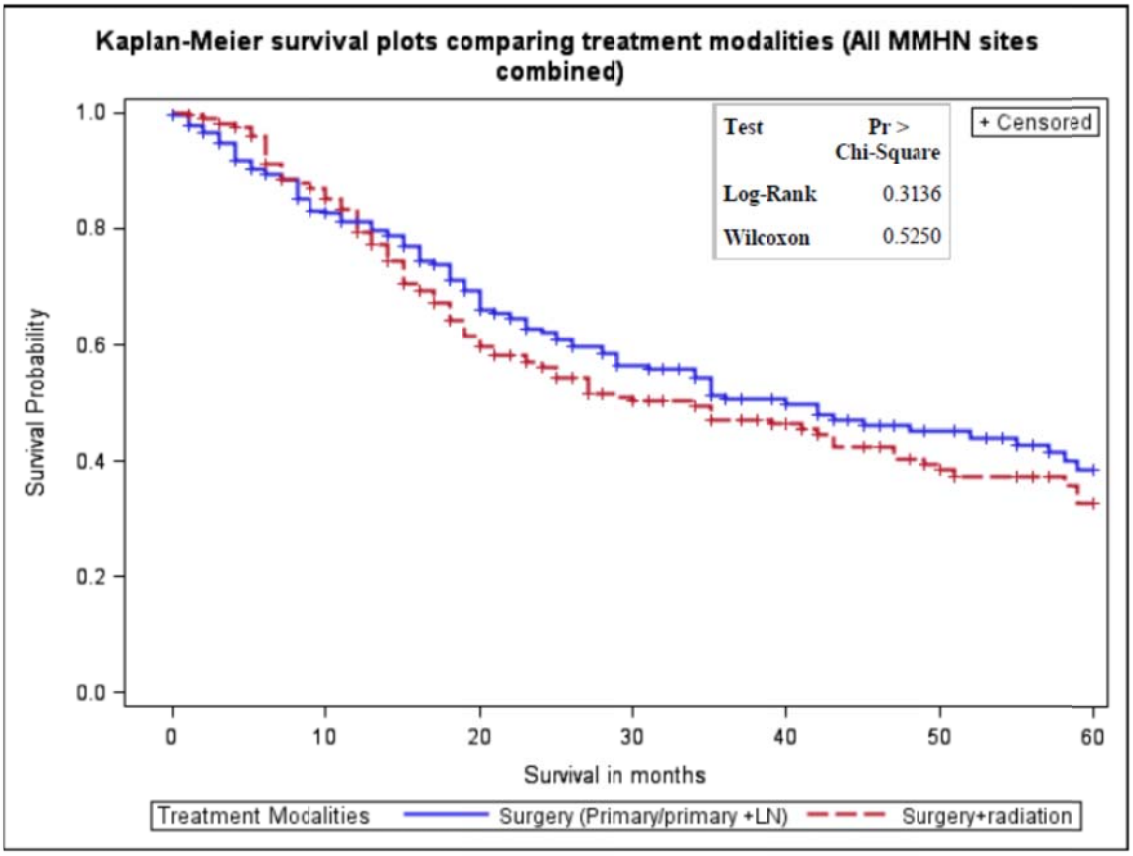

Figure 5 Kaplan-Meier survival plots comparing treatment modalities (All MMHN sites combined).

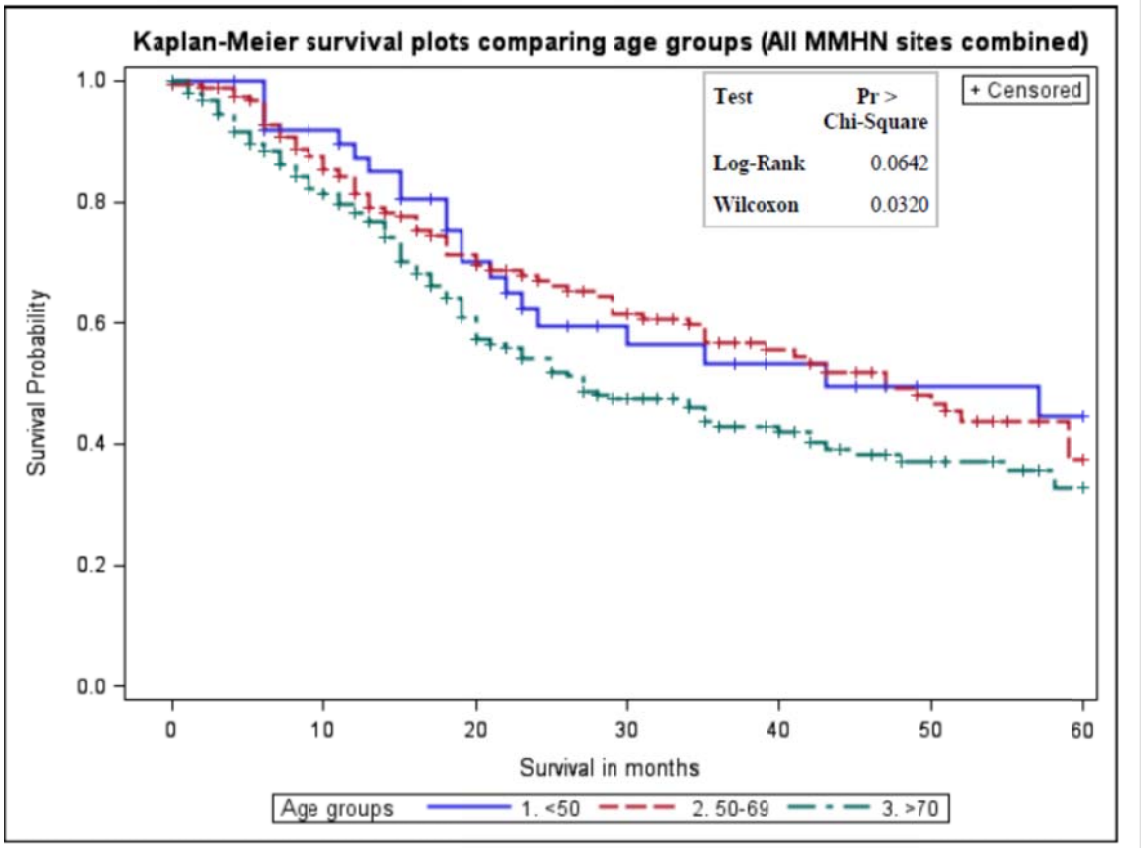

Figure 6 Kaplan-Meier survival plots comparing age groups (All MMHN sites combined).

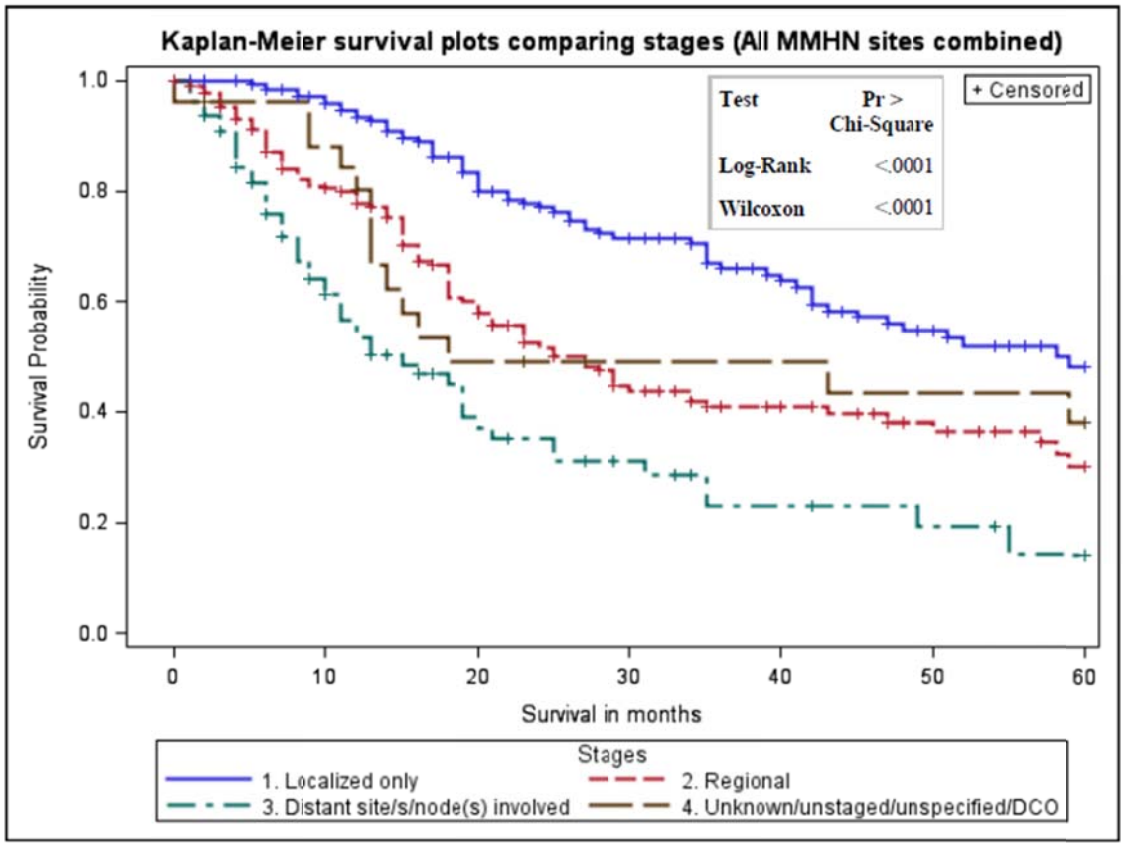

Figure 7 Kaplan-Meier survival plots comparing stages (All MMHN sites combined).

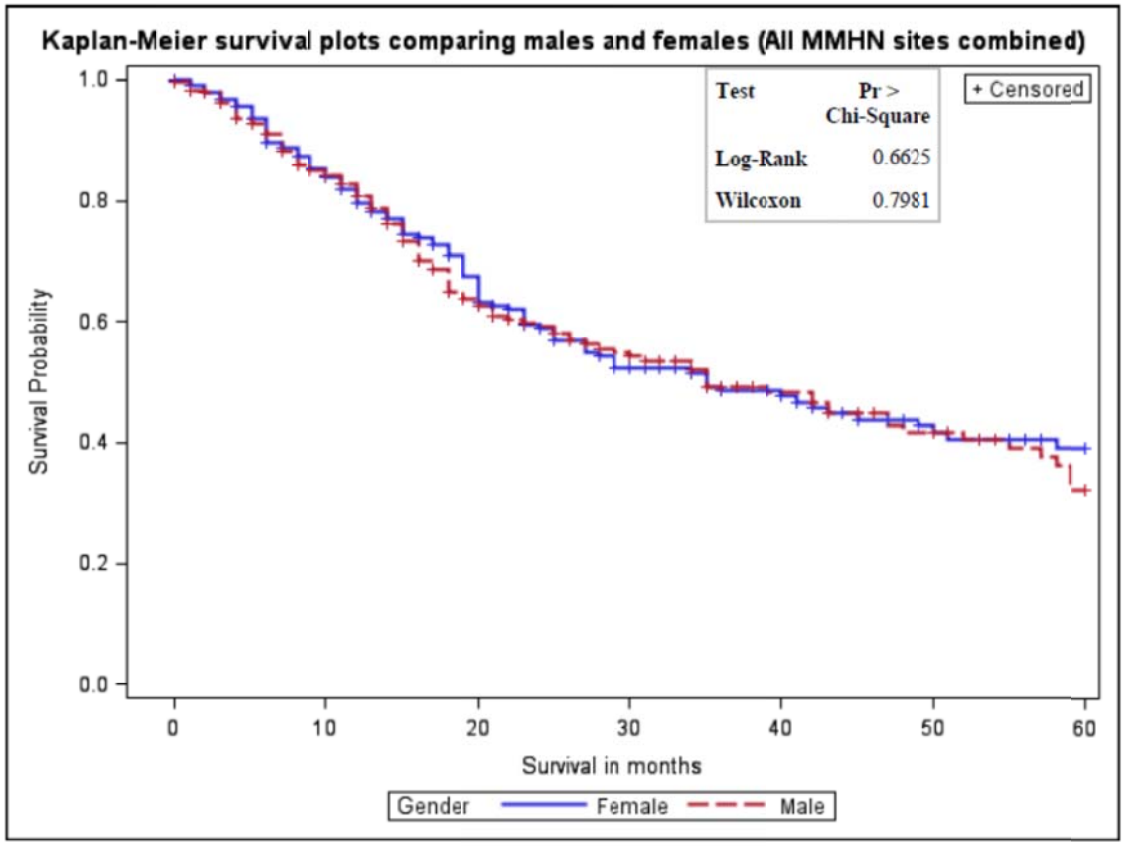

Figure 8 Kaplan-Meier survival plots comparing males and females (All MMHN sites combined).

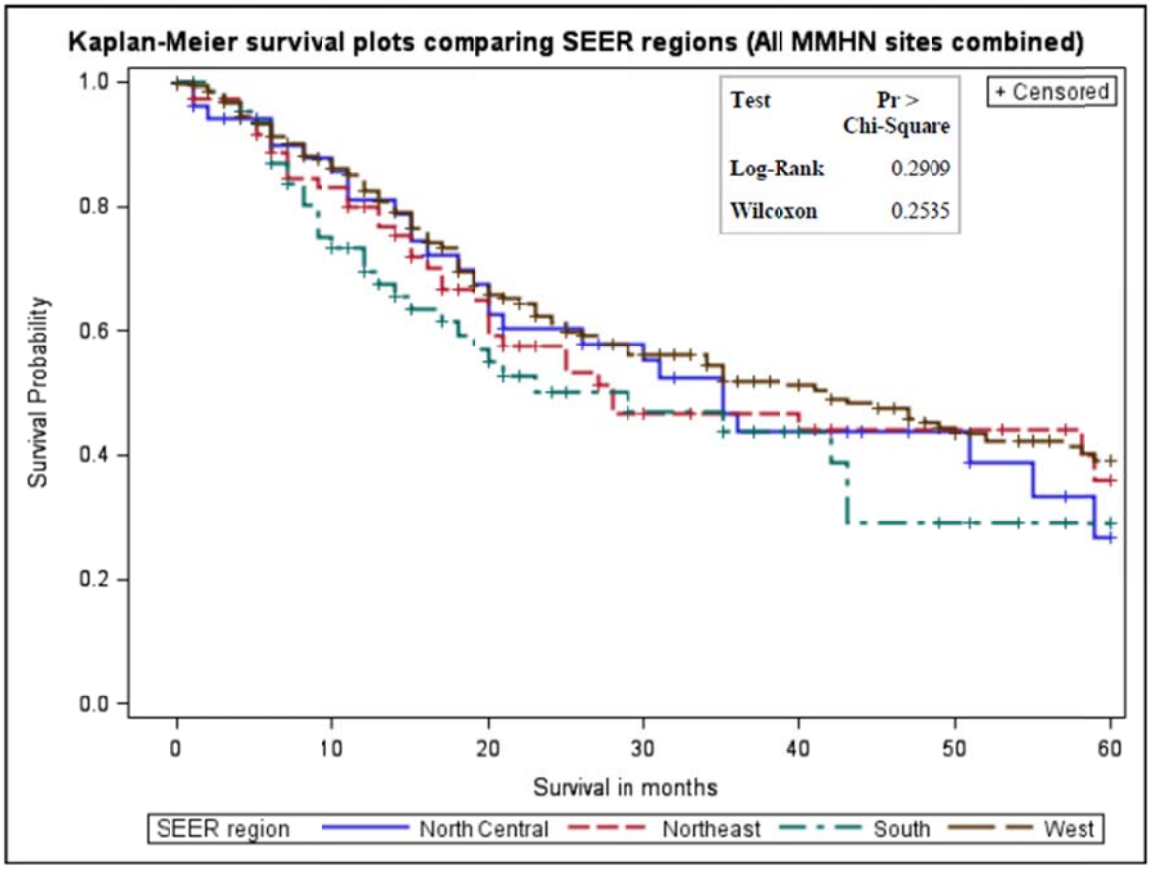

Figure 9 Kaplan-Meier survival plots comparing SEER regions (All MMHN sites combined).

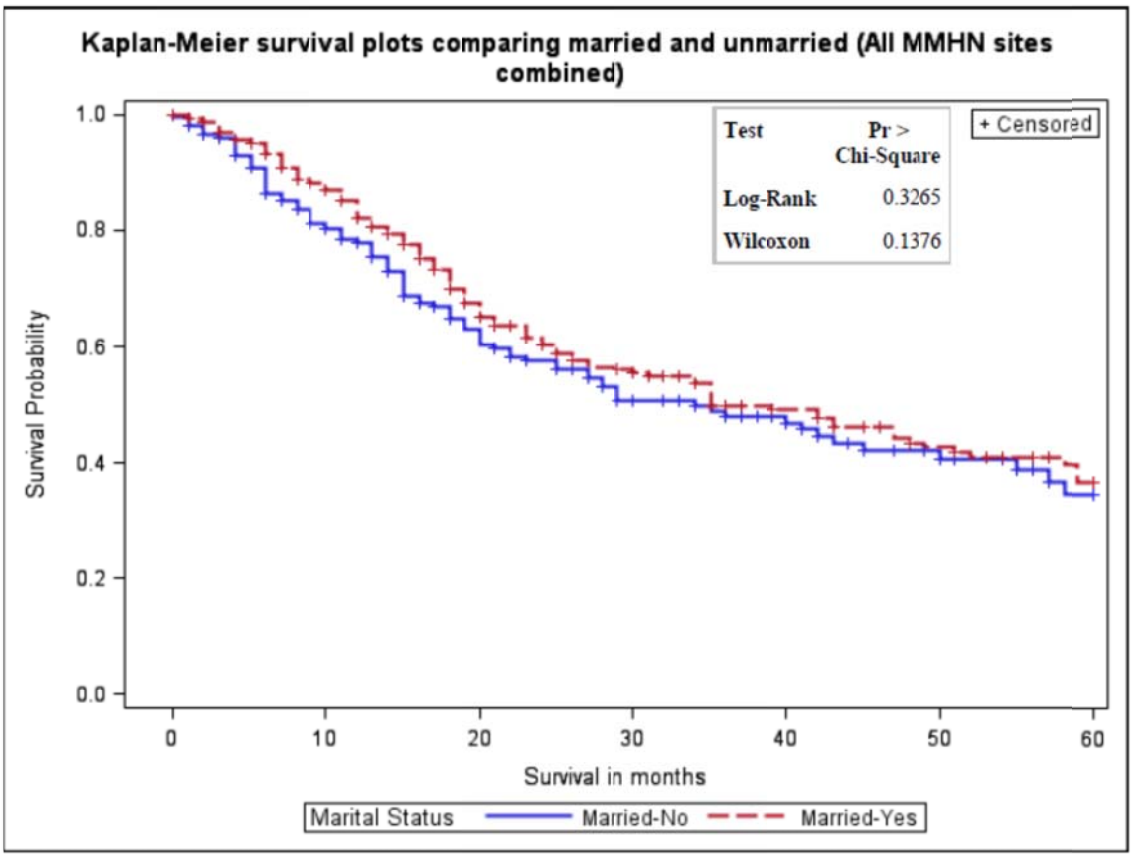

Figure 10 Kaplan-Meier survival plots comparing married and unmarried (All MMHN sites combined).

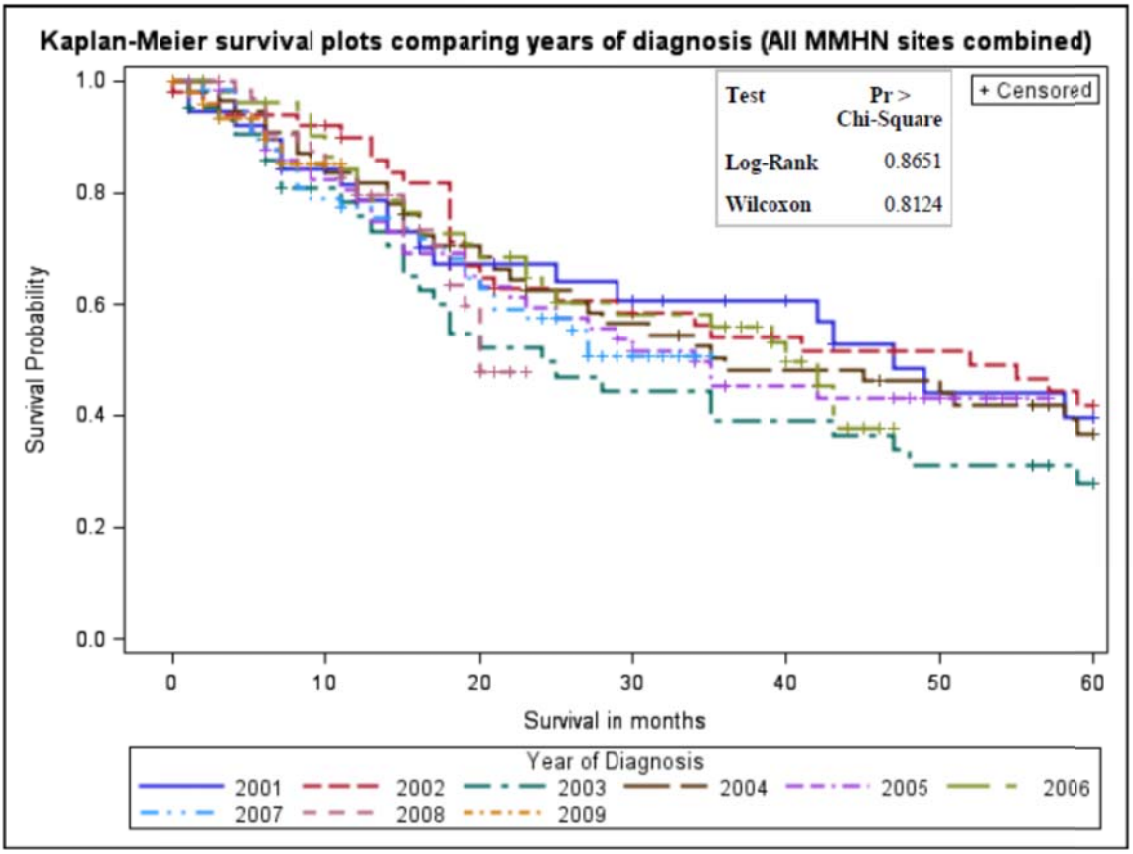

Figure 11 Kaplan-Meier survival plots comparing years of diagnosis (All MMHN sites combined).

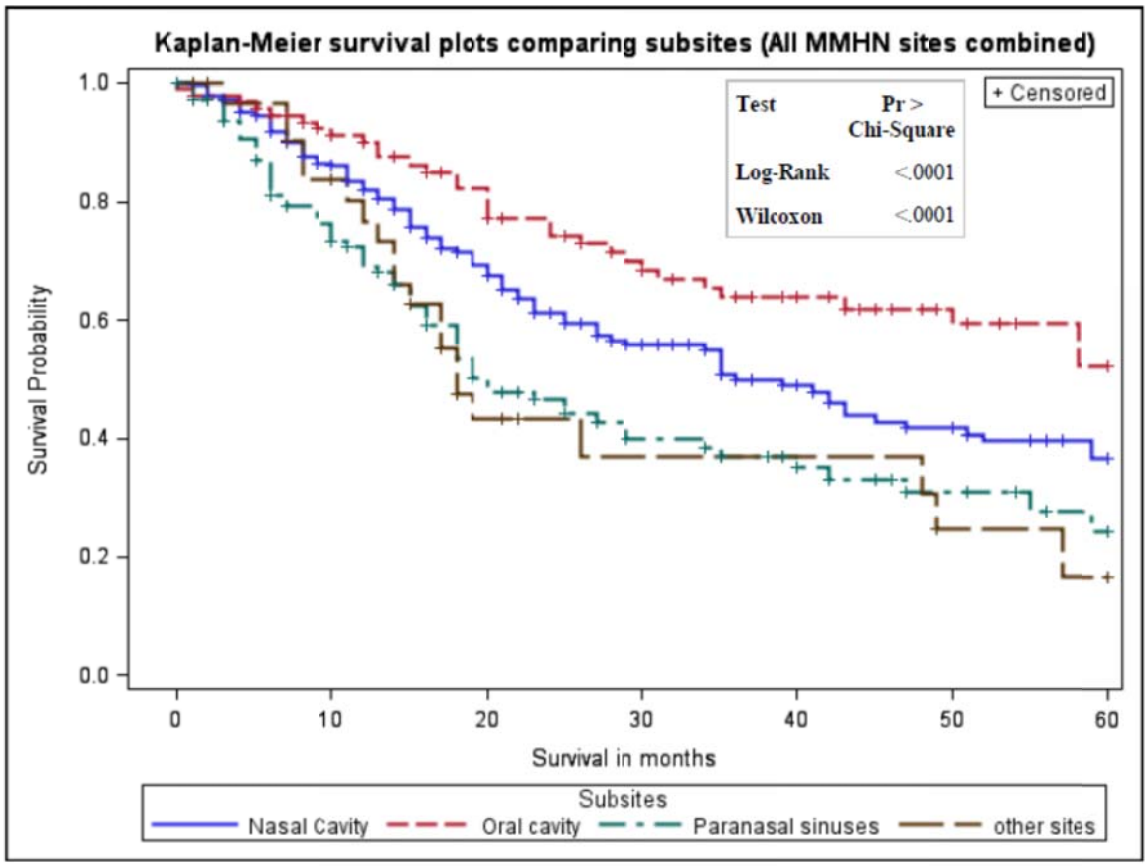

Figure 12 Kaplan-Meier survival plots comparing subsite level (All MMHN sites combined).

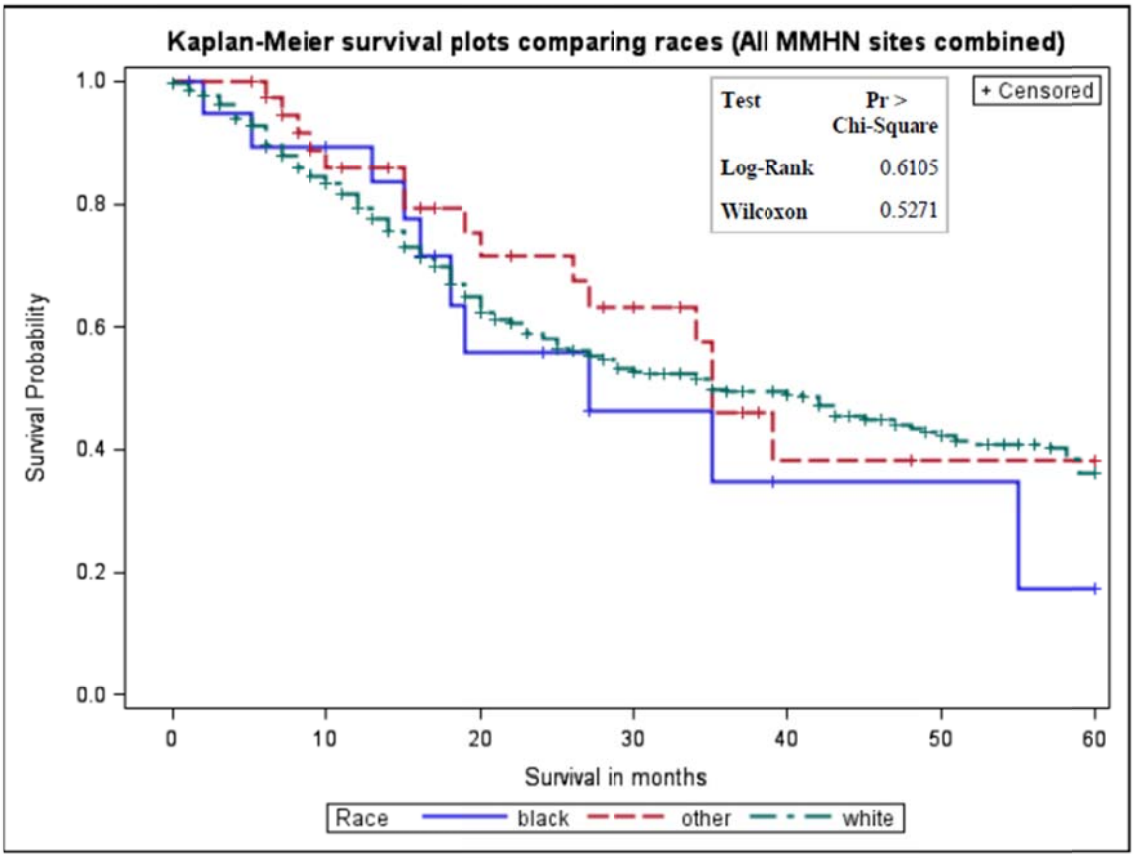

Figure 13 Kaplan-Meier survival plots comparing races (All MMHN sites combined).

Table 2: Multivariate analyses assessing 5-year cause specific survival by treatment type (surgery alone compared to radiation post-surgery) within head and neck cancer subsites.

	Multivariable analysis		
Sites	Hazard Ratio	95% CI	P-value
All sites	0.90	(0.68-1.18)	0.42‡
Oral cavity	1.33	(0.61-2.89)	0.47†
Nasal Cavity	0.94	(0.63-1.41)	0.78‡‡
Para Nasal Sinuses	0.69	(0.40-1.19)	0.18††
Other sites	1.31	(0.52-3.34)	0.57*

‡ Stratified cox model comparing the two treatment modalities, stratified on stage and adjusted for age, marital status, and subsite.

† Cox model comparing the two treatment modalities, adjusted for stage, age , marital status

‡‡ Stratified Cox model comparing the two treatment modalities, stratified on stage and adjusted for age and marital status.

†† Cox model comparing the two treatment modalities adjusted for stage, age , gender, marital status and race.

* Cox model comparing the two treatment modalities adjusted for stage, age , marital status, gender, year of diagnosis and race.

References:

1. Dahlgren, L., Schedvins, K., Kanter-Lewensohn, L., Dalianis, T., & Ragnarsson-Olding, B. K. (2005). Human papilloma virus (HPV) is rarely detected in malignant melanomas of sun sheltered mucosal membranes. [Research Support, Non-U.S. Gov't]. *Acta Oncol, 44*(7), 694-699. doi: 10.1080/02841860500247461
2. Lundberg, R., Brytting, M., Dahlgren, L., Kanter-Lewensohn, L., Schloss, L., Dalianis, T., & Ragnarsson-Olding, B. (2006). Human herpes virus DNA is rarely detected in non-UV light-associated primary malignant melanomas of mucous membranes. [Research Support, Non-U.S. Gov't]. *Anticancer Res, 26*(5B), 3627-3631.
3. Giraud, G., Ramqvist, T., Ragnarsson-Olding, B., & Dalianis, T. (2008). DNA from BK virus and JC virus and from KI, WU, and MC polyomaviruses as well as from simian virus 40 is not detected in non-UV-light-associated primary malignant melanomas of mucous membranes. [Research Support, Non-U.S. Gov't]. *J Clin Microbiol, 46*(11), 3595-3598. doi: 10.1128/JCM.01635-08
4. Axell, T., & Hedin, C. A. (1982). Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. [Research Support, Non-U.S. Gov't]. *Scand J Dent Res, 90*(6), 434-442.
5. Holmstrom, M., & Lund, V. J. (1991). Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. [Case Reports]. *Br J Ind Med, 48*(1), 9-11

6. Curtin, J. A., Busam, K., Pinkel, D., & Bastian, B. C. (2006). Somatic activation of KIT in distinct subtypes of melanoma. [Research Support, N.I.H., Extramural]. *J Clin Oncol, 24*(26), 4340-4346. doi: 10.1200/JCO.2006.06.2984
7. Van Raamsdonk, C. D., Bezrookove, V., Green, G., Bauer, J., Gaugler, L., O'Brien, J. M., . . . Bastian, B. C. (2009). Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. [Research Support, N.I.H., Extramural
8. Cancer Facts & Figures 2012- American Cancer Society
9. McLaughlin, C. C., Wu, X. C., Jemal, A., Martin, H. J., Roche, L. M., & Chen, V. W. (2005). Incidence of noncutaneous melanomas in the U.S. [Comparative Study]. *Cancer, 103*(5), 1000-1007. doi: 10.1002/cncr.20866
10. Mihajlovic, M., Vlajkovic, S., Jovanovic, P., & Stefanovic, V. (2012). Primary mucosal melanomas: a comprehensive review. [Research Support, Non-U.S. Gov't]. *Int J Clin Exp Pathol, 5*(8), 739-753.
11. Lengyel, E., Gilde, K., Remenar, E., & Esik, O. (2003). Malignant mucosal melanoma of the head and neck. *Pathology Oncology Research, 9*(1), 7-12. doi: Paor.2003.9.1.0007
12. Chang, A. E., Karnell, L. H., & Menck, H. R. (1998). The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. [Comparative Study]. *Cancer, 83*(8), 1664-1678
13. Jethanamest, D., Vila, P. M., Sikora, A. G., & Morris, L. G. (2011). Predictors of survival in mucosal melanoma of the head and neck. [Research Support, N.I.H.,

Extramural]. *Ann Surg Oncol, 18*(10), 2748-2756. doi: 10.1245/s10434-011-1685-4

14. Papaspyrou, G., Garbe, C., Schadendorf, D., Werner, J. A., Hauschild, A., & Egberts, F. (2011). Mucosal melanomas of the head and neck: new aspects of the clinical outcome, molecular pathology, and treatment with c-kit inhibitors. [Evaluation Studies
15. Temam, S., Mamelle, G., Marandas, P., Wibault, P., Avril, M. F., Janot, F., . . . Luboinski, B. (2005). Postoperative radiotherapy for primary mucosal melanoma of the head and neck. [Comparative Study]. *Cancer, 103*(2), 313-319. doi: 10.1002/cncr.20775
16. Patel, S. G., Prasad, M. L., Escrig, M., Singh, B., Shaha, A. R., Kraus, D. H., . . . Shah, J. P. (2002). Primary mucosal malignant melanoma of the head and neck. *Head Neck, 24*(3), 247-257.
17. National Comprehension Cancer Network (NCCN), Clinical Practice Guidelines in Oncology (NCCN Guidelines)- Head and Neck Cancers, version 1.2012
18. Lee, S. P., Shimizu, K. T., Tran, L. M., Juillard, G., & Calcaterra, T. C. (1994). Mucosal melanoma of the head and neck: the impact of local control on survival. *Laryngoscope, 104*(2), 121-126. doi: 10.1288/00005537-199402000-00001
19. Yii, N. W., Eisen, T., Nicolson, M., A'Hern, R., Rhys-Evans, P., Archer, D., . . . Gore, M. E. (2003). Mucosal malignant melanoma of the head and neck: the Marsden experience over half a century. *Clinical Oncology (Royal College of Radiologists), 15*(4), 199-204.

20. Hoyt, D. J., Jordan, T., & Fisher, S. R. (1989). Mucosal melanoma of the head and neck. *Archives of Otolaryngology - Head and Neck Surgery, 115*(9), 1096-1099.

21. Loree, T. R., Mullins, A. P., Spellman, J., North, J. H., Jr., & Hicks, W. L., Jr. (1999). Head and neck mucosal melanoma: a 32-year review. *Ear, Nose, and Throat Journal, 78*(5), 372-375.

22. Manolidis, S., & Donald, P. J. (1997). Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. *Cancer, 80*(8), 1373-1386.

23. McLean, N., Tighiouart, M., & Muller, S. (2008). Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. Oral Oncology, 44(11), 1039-1046. doi: 10.1016/j.oraloncology.2008.01.014

24. Brandwein, M. S., Rothstein, A., Lawson, W., Bodian, C., & Urken, M. L. (1997). Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Archives of Otolaryngology - Head and Neck Surgery, 123(3), 290-296.

25. Lund, V. J., Howard, D. J., Harding, L., & Wei, W. I. (1999). Management options and survival in malignant melanoma of the sinonasal mucosa. *Laryngoscope, 109*(2 Pt 1), 208-211

26. Saigal, K., Weed, D. T., Reis, I. M., Markoe, A. M., Wolfson, A. H., & Nguyen-Sperry, J. (2012). Mucosal melanomas of the head and neck: the role of postoperative radiation therapy. *ISRN Oncol, 2012*, 785131. doi: 10.5402/2012/

27. Nakashima, J. P., Viegas, C. M., Fassizoli, A. L., Rodrigues, M., Chamon, L. A., Silva, J. H., . . . Araujo, C. M. (2008). Postoperative adjuvant radiation therapy in the treatment of primary head and neck mucosal melanomas. *ORL; Journal of Oto-Rhino-Laryngology and Its Related Specialties, 70*(6), 344-351. doi: 10.1159/000163029

28. Lutzky, J., Bauer, J., & Bastian, B. C. (2008). Dose-dependent, complete response to imatinib of a metastatic mucosal melanoma with a K642E KIT mutation. [Case Reports.

29. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.0.4

30. http://seer.cancer.gov/tools/ssm/SSSM2000-122012.pdf