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The efficacy of neutron radiation therapy in treating salivary gland malignancies

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ABSTRACT

Objectives: Radiation therapy is commonly used to treat head and neck malignancies. While there is abundant research regarding photon radiation therapy, literature on neutron radiotherapy (NRT) and oral complications is limited. This study aims to determine: (1) the 6-year and 10-year locoregional control and survival rates, (2) factors associated with locoregional control and survival and (3) the frequency of oral complications in patients undergoing NRT for salivary gland malignancies.

Materials and methods: This is a retrospective cohort study. The sample was composed of patients with salivary gland malignancies treated with NRT between 1997 and 2010. Data were extracted from patient charts, telephone surveys, and social security records. Multivariate competing risk and Cox regression models were used to assess predictors of locoregional control and survival.

Results: The sample was composed of 545 subjects with a mean age of 54.2 years (± 16). The predominant tumor and location were adenoid cystic carcinoma (47%) and the parotid (56%). Multivariate analysis indicated that positive surgical margins, biopsied/inoperable malignancies, neck involvement, and lymphovascular invasion were prognostic risk factors associated with decreased survival. The 6- and 10-year locoregional control rates were 84% and 79%. The 6- and 10-year survival rates were 72% and 62%. Osteoradionecrosis developed in 3.4% of subjects.

Conclusions: The 6- and 10-year locoregional control and survival rates compare favorably to rates reported for conventional photon radiation. Osteoradionecrosis rates were comparable to that of photon radiation treatment (2–7%). Given the potential benefits of NRT, healthcare professionals should be educated regarding its indications and oral complications.

Introduction

Salivary gland tumors are relatively infrequent, with an estimated incidence of 3:100,000 and account for approximately 3% of head and neck malignancies [1]. The diagnosis and treatment of these tumors presents a challenge to head and neck surgeons due to the variation in clinical presentation, diverse locations, histological appearance, and subtypes [2,3].

Radiation therapy is a mainstay as either primary or adjuvant treatment for head and neck malignancies. While there is extensive literature on conventional photon therapy, less is known about the role of high energy neutron radiotherapy (NRT) in the management of head and neck malignancy, including the oral manifestations, short- and long-term side effects, complications, management protocol, and

Abbreviations: NRT, neutron radiation therapy; UW, University of Washington; ORN, osteoradionecrosis; mPNI, microscopic perineural invasion; mLVI, microscopic lymphovascular invasion; BoS, base of skull; HR, hazard ratio; CI, confidence interval; RBE, relative biological difference; LET, linear energy transfer; ROS, reactive oxygenated species

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therapeutic efficacy. NRT is available in only a few centers throughout the world due to the relative rarity of unresectable salivary gland malignancies and the high maintenance cost of NRT facilities. Despite this, NRT has been shown to play an important role in treating oral salivary gland neoplasms [4].

The University of Washington (UW) is the only active center in the United States that offers NRT. The current facility has treated over 3000 patients since 1984. Recently Davis et al. published research on the efficacy of NRT on salivary gland malignancies [5]. The study was composed of 140 patients treated between 1997 and 2006 but excluded the parotid and base of tongue locations. The 6-year locoregional control and survival rates were 72% and 58% respectively. Osteoradionecrosis (ORN) was reported in 5.7% of patients. The current study is a continuation of the previous work on the therapeutic role of NRT in the management of salivary gland malignancies including parotid and base of tongue tumors.

This study seeks to determine the rates of locoregional control, survival, and oral complications among patients with head and neck salivary gland malignancies treated with NRT where the oral cavity is within the field of radiation and compare them with previously reported outcomes of conventional photon radiotherapy. Specifically, this study aims to (1) estimate 6-year and 10-year locoregional control and survival rates, (2) identify factors associated with locoregional control and survival and (3) measure the frequency of oral complications from neutron radiotherapy for head and neck salivary gland malignancies.

Materials and methods

Study design

This retrospective cohort study was approved by the local institutional review board (protocol number 6404). The study population included subjects with salivary gland malignancies (parotid, submandibular, sublingual, base of tongue, and minor salivary glands) treated with NRT at the UW Department of Radiation Oncology from 1997 to 2010. Specifically the NRT field must have involved the oral cavity.

Variables

The primary outcomes were 6-year and 10-year locoregional control and overall survival rates. Secondary outcome variables included rates of distant metastasis, recurrence-free survival, progression-free survival, and oral complications of NRT, including ORN, xerostomia, mucositis, trismus (inability to open the mouth > 3 finger widths), oral pain, difficulty chewing, dysphagia, dysgeusia, and increase in dental decay.

Other variables in this study were: subject demographics and characteristics (age, sex, medical history, etc.); tumor initial treatment date, histological subtype, and location; prior surgical treatments; surgical margins; and existence of microscopic perineural invasion (mPNI), microscopic lymphovascular invasion (mLVI), and/or base of skull (BoS) invasion. Surgical margins of less than 1 mm were considered positive, 1–5 mm were considered close, and greater than 5 mm were considered negative.[6,7]

Data collection

The majority of study data was collected through medical chart review, including demographics, tumor characteristics, NRT dates, xerostomia and mucositis during NRT, and the timing of any recurrences and distant metastases. After reviewing each subject's medical chart history, the authors (MT, PD) attempted to contact every subject by telephone. Subjects who were contacted were given the UW quality-of-life survey for evaluation of oral clinical outcome variables including pain, difficulty chewing, dysphagia, dysgeusia, trismus, saliva decrease, speech changes, and any increase in dental caries after NRT. For survival data, if a subject or next of kin could not be contacted, then the primary care physician or general dentist was contacted. If no information was available, the authors accessed the resources of the US Social Security Office to determine survival status and date of death if deceased.

Data were collected independently by two calibrated members of the research team (MT, PD). Each medical record was reviewed for data-collection, and pertinent clinical outcome variables were documented on a de-identified Microsoft Excel workbook. Any discrepancies between data collectors were resolved by group review leading to a consensus decision. If there was a major discrepancy, the senior author (JD) reviewed the chart and made the final decision. Cause of death was not assessed.

Data analysis

All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Two-sided tests were used, with statistical significance defined as $p < 0.05$. Rates of locoregional control, freedom from distant metastasis, and freedom from tumor progression (i.e., freedom from both distant metastasis and local recurrence) were estimated using the cumulative incidence function with death treated as a competing risk. Overall survival rates, recurrence-free survival, and progression-free survival over 10-years were estimated using the Kaplan-Meier product-limit estimator. Time to recurrence and distant metastasis were censored by the last date in the medical charts. Overall survival was censored at the time of death record inquiry.

Fine & Gray competing risk regression models and Cox regression models were used to assess clinical and tumor characteristics as potential predictors of locoregional control and overall survival, respectively. Associations between predictors and outcomes were summarized using hazard ratios (HRs). Subjects were excluded from modeling if they were missing a value for any of the predictors included in the model. The multivariate model for locoregional control was constructed using variables where the Wald test of $HR = 1$ from the corresponding univariate model resulted in $p < 0.1$. The multivariate model for overall survival was constructed with all of the clinical and tumor factors considered, as there were > 3 times the number of deaths as recurrences [8].

Raw proportions of complications reported by subjects who responded to the phone survey were calculated without any adjustments or weighting for non-response. The incidence of ORN was determined through chart review and phone survey. ORN was right-censored by the last visit noted in the medical chart or the time of phone survey, whichever was later. ORN was also interval-censored when timing was uncertain based on the range indicated in the chart or phone survey response. If the subject could not provide any clear indication of timing, the censoring interval was defined as the last visit in the medical chart to the time of the phone survey. To account for right-censoring, interval-censoring, and the competing risk of death, the cumulative incidence of ORN was estimated using the multiple imputation approach of Delord and Génin [9] with the R package MIICD (version 2.2; Marc Delord, 2015; http://CRAN.R-project.org/package=MIICD). The nonparametric bootstrap was used to calculate 95% confidence intervals (CIs) for incidence of ORN.

Results

Demographics & tumor characteristics

Of the 559 subjects that met the inclusion criteria, 14 were excluded due to lack of follow-up data, leaving 545 available for the survival analysis. An additional 72 had no further medical visits within UW's network and could not be assessed for recurrence or distant metastases,

Table 1
Baseline demographics and clinical characteristics.

Variable	No. (%)
Sex	
Male	258 (47.3)
Female	287 (52.7)
Age at NRT	
< 40 years	87 (16.0)
40–49 years	126 (23.1)
50–59 years	114 (20.9)
60–69 years	123 (22.6)
≥70 years	95 (17.4)
Tumor pathology	
Adenoid cystic carcinoma	258 (47.3)
Mucoepidermoid carcinoma	88 (16.1)
Adenocarcinoma	66 (12.1)
Acinic cell carcinoma	60 (11.0)
Pleomorphic adenoma	15 (2.8)
Carcinoma Ex pleomorphic adenoma	12 (2.2)
Epithelial/myoepithelial cell carcinoma	11 (2.0)
Other[a]	35 (6.0)
Tumor location	
Parotid	307 (56.3)
Submandibular	87 (16.0)
Base of tongue	64 (11.7)
Hard/soft palate	38 (7.0)
Retromolar	9 (1.7)
Buccal mucosa	9 (1.7)
Maxillary sinus	8 (1.5)
Other	23 (4.2)
Tumor extent[b]	
Microscopic perineural involvement	294 (55.3)
Base of skull involvement	84 (15.5)
Neck involvement	104 (20.1)
Microscopic lymphovascular invasion	164 (31.5)
Surgery status	
No surgery/biopsy only	145 (26.3)
Surgery	400 (73.7)
Margin status[b,c]	
Positive	316 (79.0)
Close	45 (11.3)
Negative	39 (9.8)

[a] Three subjects with unclear pathology were placed into the "Other" category.
[b] Subjects with missing values were excluded from the corresponding summary: microscopic perineural involvement (n = 13), base of skull involvement (n = 3), neck involvement (n = 28), microscopic lymphovascular invasion (n = 25) and surgery/margins (n = 2).
[c] Only subjects that underwent surgery had recorded margins (n = 400).

and were therefore excluded from analyses of those outcomes.

Of the 545 subjects, 258 (47%) were male with mean age of 54 (± 16). The distribution of cases by site and histology is shown in Table 1. The most common tumor locations were the parotid (56%) followed by the submandibular (16%) and base-of-tongue (12%). While 24 tumors types were identified through the pathology reports, the most common type of tumor histology was adenoid cystic carcinoma (47%) followed by mucoepidermoid carcinoma (16%), and adenocarcinoma (12%).

In terms of tumor extent, 55% had mPNI, 16% involved the BoS, 20% had neck involvement, and 32% had mLVI (Table 1). 400 (74%) of subjects underwent surgical resection and post-operative NRT, while 145 (26%) were inoperable (biopsy only) and underwent primary NRT. Of the 400 subjects resected with documented margins, 316 (79%) had positive margins, 45 (11%) had close margins, and 39 (10%) had negative margins.

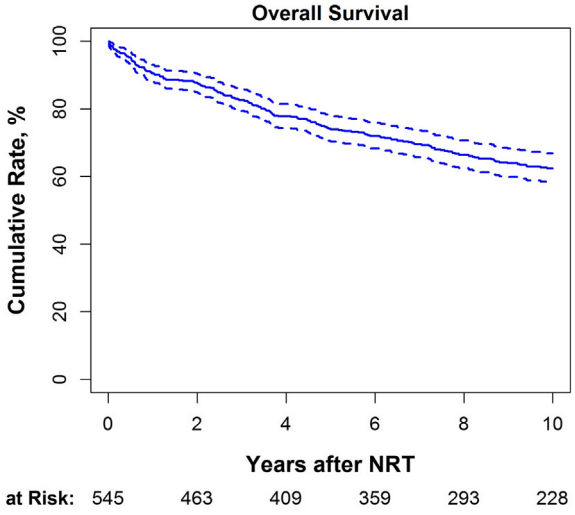

Fig. 1. Kaplan-Meier curve for overall survival. Error limits are shown as dotted curves.

Locoregional control, overall survival & other outcomes over 10 years

Over a period of 10 year follow-up, there were 58 locoregional recurrences and 70 first-time distant metastases. The 6- and 10-year locoregional control rates were 84% (95% CI: 80–88%) and 79% (95% CI: 74–84%), respectively. After 6 and 10 years, respectively, 80% (95% CI: 76–85%) and 77% (95% CI: 72–82%) of subjects were free of distant metastasis.

Over 10 years, 191 deaths were recorded. Overall survival was 72% (95% CI: 68–76%) at 6 years and 62% (95% CI: 58–66%) at 10 years (Fig. 1). Recurrence-free survival was 68% at 6 years (95% CI: 63–74%) and 62% at 10 years (95% CI: 57–68%). The corresponding estimates of progression-free survival were 58% (95% CI: 53–64%) and 51% (95% CI: 45–57%) at 6 and 10 years, respectively.

Predictors of locoregional recurrence & overall survival

Univariate and multivariate analysis of potential predictors of locoregional recurrence are summarized in Table 2. The multivariate analysis consisted of 460 subjects with no missing values among the included predictors out of 473 with follow-up. After multivariate adjustment, subjects with BoS involvement had significantly higher risk of locoregional recurrence than those without (HR = 2.15, 95% CI: 1.13–4.10, p = 0.019). There was also a trend toward lower risk of recurrence for subjects that underwent post-operation NRT (HR = 0.57, 95% CI: 0.32–1.04, p = 0.066) compared to those that underwent primary NRT without resection (Table 2). Among tumors that underwent resection and post-operative NRT, the rate of recurrence did not differ significantly between those with positive and close or negative margins (p = 0.51). Despite this, we note that the actual recurrence rates were higher among subjects with positive margins when compared to those with negative or close margins. No other subject or tumor factors were significantly associated with recurrence, including tumor location (p = 0.15). Fig. 2 summarizes locoregional control rates by BoS involvement and surgery/margin status.

Univariate and multivariate analysis of potential predictors of overall survival are summarized in Table 3. The multivariate analysis consisted of 513 subjects without missing values among the included predictors out of 545 total subjects. After multivariate analysis, female sex (HR = 0.67, p = 0.014), age (p < 0.001), neck involvement (HR = 1.60, p = 0.025), mLVI (HR = 1.47, p = 0.033), and surgery/margin status (p < 0.001) were independently associated with survival. Those who underwent surgical resection had significantly better survival than those who did not (HR = 0.48, p < 0.001) and those

Table 2
Predictors of locoregional recurrence.

	Univariate models			Multivariate model[a]		
Variable	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Sex			0.54			
Male	(ref)					
Female	0.85	(0.51–1.42)				
Age at NRT			0.14			
< 40 years						
40–49 years	0.33	(0.13–0.81)				
50–59 years	0.68	(0.32–1.46)				
60–69 years	0.92	(0.46–1.85)				
≥70 years	0.66	(0.27–1.63)				
Tumor pathology			0.14			
Adenoid cystic carcinoma	(ref)					
Mucoepidermoid carcinoma	0.54	(0.25–1.17)				
Adenocarcinoma	0.31	(0.10–1.01)				
Acinic cell carcinoma	0.50	(0.20–1.26)				
Other	0.65	(0.29–1.48)				
Tumor location			0.15			
Parotid	(ref)					
Submandibular	0.98	(0.43–2.27)				
Base of tongue	2.43	(1.16–5.09)				
Hard/soft palate	1.33	(0.56–3.20)				
Other	1.75	(0.81–3.82)				
Tumor extent						
Microscopic perineural involvement	1.68	(0.98–2.87)	0.059	1.60	(0.86–3.01)	0.14
Base of skull involvement	2.45	(1.37–4.38)	0.002	2.15	(1.13–4.10)	0.019
Neck involvement	1.12	(0.64–1.98)	0.68			
Microscopic lymphovascular invasion	1.75	(0.66–2.44)	0.47			
Surgery/margins			0.042			0.15
None/biopsy only	(ref)			(ref)		
Positive	0.58	(0.32–1.03)		0.61	(0.33–1.12)	
Close/negative	0.33	(0.13–0.84)		0.45	(0.17–1.18)	
Surgery status[b]			0.033			0.066
No surgery	(ref)			(ref)		
Surgery	0.54	(0.31–0.95)		0.57	(0.32–1.04)	
Margin status			0.21			0.51
Positive	(ref)			(ref)		
Close/negative	0.57	(0.24–1.37)		0.73	(0.29–1.86)	

HR = hazard ratio for locoregional recurrence; CI = confidence interval.

[a] The multivariate model included all predictors with $p < 0.1$ during univariate analysis except surgery status, which was redundant when surgery/margins was included.

[b] In a separate multivariate model, surgery status was adjusted for the other factors with $p < 0.1$ during univariate analysis except surgery/margins and margin status.

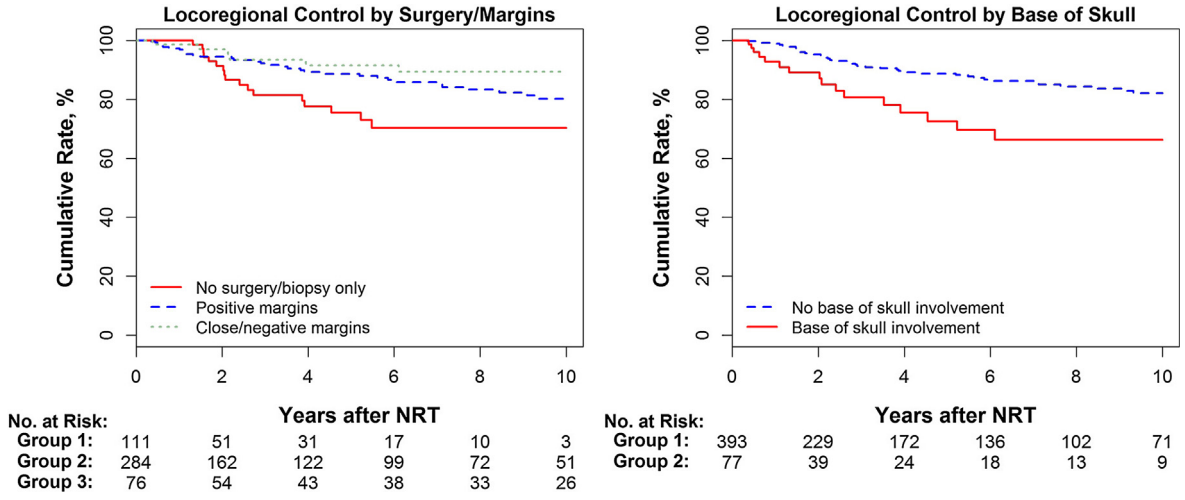

Fig. 2. Kaplan-Meier curves for predictors of locoregional control.

Table 3
Predictors of overall survival.

	Univariate Models			Multivariate Model[a]		
Variable	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Sex			0.009			0.014
Male	(ref)			(ref)		
Female	0.69	(0.52, 0.91)		0.67	(0.49–0.92)	
Age at NRT			< 0.001			< 0.001
< 40 years	(ref)			(ref)		
40–49 years	1.72	(0.90, 3.31)		1.78	(0.90–3.50)	
50–59 years	1.90	(0.99, 3.65)		1.67	(0.84–3.35)	
60–69 years	3.68	(2.01, 6.75)		3.67	(1.93–6.98)	
≥70 years	6.77	(3.73, 12.30)		5.73	(3.00–10.95)	
Tumor pathology			< 0.001			0.43
Adenoid cystic carcinoma	(ref)			(ref)		
Mucoepidermoid carcinoma	0.87	(0.57, 1.34)		0.78	(0.49–1.27)	
Adenocarcinoma	1.90	(1.30, 2.76)		1.06	(0.67–1.67)	
Acinic cell carcinoma	0.43	(0.23, 0.81)		0.68	(0.34–1.35)	
Other	0.74	(0.46, 1.18)		0.67	(0.39–1.17)	
Tumor location			0.10			0.21
Parotid	(ref)			(ref)		
Submandibular	1.41	(0.95, 2.08)		1.16	(0.74–1.82)	
Base of tongue	1.66	(1.10, 2.51)		0.62	(0.34–1.11)	
Hard/soft palate	1.11	(0.63, 1.95)		1.29	(0.70–2.35)	
Other	1.40	(0.86, 2.26)		1.19	(0.70–2.00)	
Tumor extent						
Microscopic perineural involvement	1.39	(1.03, 1.88)	0.030	1.19	(0.85–1.68)	0.31
Base of skull involvement	1.05	(0.71, 1.56)	0.79	0.90	(0.58–1.42)	0.67
Neck involvement	1.98	(1.42, 2.75)	< 0.001	1.60	(1.06–2.41)	0.025
Microscopic lymphovascular invasion	2.04	(1.51, 2.74)	< 0.001	1.47	(1.03–2.10)	0.033
Surgery/margins			< 0.001			< 0.001
None/biopsy only	(ref)			(ref)		
Positive	0.46	(0.34, 0.63)		0.54	(0.37–0.79)	
Close/negative	0.28	(0.16, 0.47)		0.32	(0.18–0.56)	
Surgery status[b]			< 0.001			< 0.001
No surgery	(ref)			(ref)		
Surgery	0.42	(0.32–0.56)		0.48	(0.33–0.69)	
Margin status			0.046			0.047
Positive	(ref)			(ref)		
Close/negative	0.59	(0.35–0.99)		0.58	(0.34–0.99)	

HR = hazard ratio for death by any cause; CI = confidence interval.
[a] The multivariate model included all predictors except surgery status, which was redundant when surgery/margins was included.
[b] In a separate multivariate model, surgery status was adjusted for the other factors except surgery/margins and margin status.

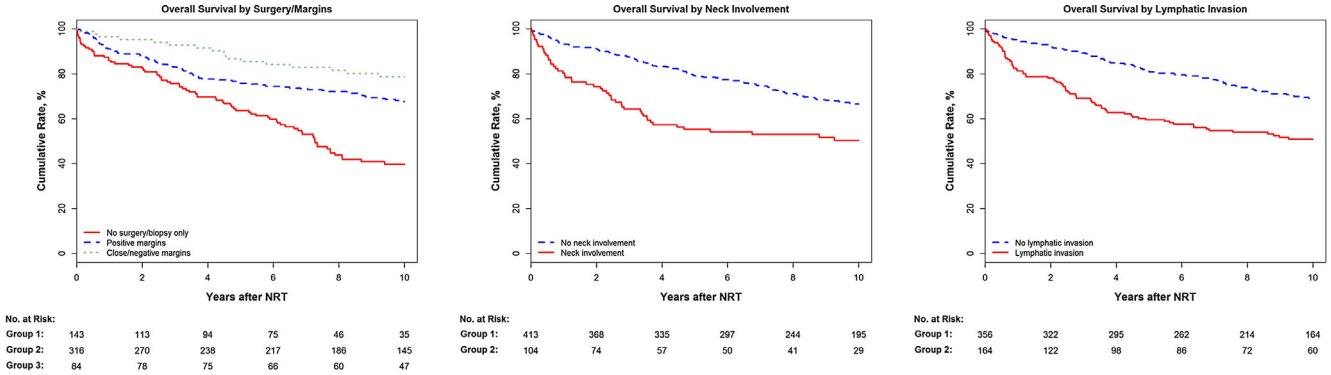

Fig. 3. Kaplan-Meier curves for predictors of overall survival.

whose margins were close or negative had significantly better survival than those with positive margins (HR = 0.58, p = 0.047). Tumor pathology (p = 0.43), tumor location (p = 0.21), mPNI (p = 0.31), and BoS involvement (p = 0.67) were not significantly associated with survival after adjusting for all factors in Table 3. Fig. 3 summarizes overall survival rates by surgery/margin status, neck involvement, and mLVI.

Oral complications

The oral side effects that subjects experienced during NRT treatment were xerostomia (89%) and mucositis (79%). Despite the majority of subjects having completed their treatment 10 or more years ago, 78 of 545 (14%) subjects were contactable and completed the quality-of-life survey provided by the researchers via telephone. Table 4 presents a

Table 4
Results of phone survey on neutron radiotherapy complications.

Complication	Value
Saliva decrease	56 (71.8)
Trismus	48 (61.5)
Dysgeusia	36 (46.2)
Dysphagia	34 (43.6)
Difficulty chewing	30 (38.5)
Increased tooth decay	28 (35.9)
Pain	27 (34.6)
Speech changes	25 (32.1)

Values are no. (%) out of 78 responses.

summary of the survey results indicating the frequency of secondary outcome variables. Of the subjects that completed the survey, 56 (72%) still experienced xerostomia, 48 (62%) reported trismus and 28 (36%) had an increase in tooth decay after treatment.

A total of 16 subjects experienced ORN after NRT based on chart review (n = 12) and the phone survey (n = 4). There were 474 subjects that either had follow-up medical charts or completed the phone survey, so the crude overall rate of ORN was 3.4% (95% CI: 1.9–5.4%). After accounting for variable follow-up, uncertainty in the date of ORN diagnosis, and the competing risk of death, the actuarial estimates of ORN were 3.0% (95% CI: 1.0–5.3%) by 6-years and 7.2% (3.1–11.5%) by 10-years.

Discussion

The aim of this study was to (1) estimate 6-year and 10-year locoregional control and survival rates, (2) identify factors associated with locoregional control and survival and (3) measure the frequency of oral complications from NRT for all head and neck salivary gland malignancies from 1997 to 2010. Specifically the NRT field must have involved the oral cavity.

Therapeutic outcomes

The overall 6-year locoregional control rate was found to be 84%, which was higher than the 6-year locoregional control rate of 72% reported by Davis et al. [5]. This increase is likely related to the expanded inclusion criteria increasing the sample size by including salivary gland neoplasms of the parotid and base of tongue. Most parotid tumors arise from the superficial lobe with 10% to 20% involving the deep lobe and approximately 1% affecting the accessory lobe [1]. As such, these tumors will present as an obvious mass, generally resulting in earlier detection and better prognosis compared to other oral salivary gland tumors [10]. The results in this study further suggest that NRT provides favorable locoregional control rates when compared conventional photon radiotherapy [4,11].

The 6-year survival rate was found to be 72% in this study compared to the rate of 58% found by Davis et al. [5]. Similar to the increase in locoregional control rates; this increase is likely due to an expansion in the inclusion criteria. The 6-year survival rate in this study is analogous to the 6-year survival rate of 67% that was reported by the Douglas et al. 2003 study [11], and compares favorably to the five year survival rates of 51% to 71% previously reported for patients that underwent conventional radiation therapy for locally advanced salivary gland tumors [12–14]. Further, the 6-year survival rate for inoperable tumors (biopsy only) in this study was 59%, which is comparable to the 5-year survival rate for inoperable parotid gland tumors of 65% found in a previous study conducted by Wang et al. [15].

Positive surgical margins is a known prognostic risk factor associated with both locoregional control and survival [6,7,16]. A study conducted in 2015 by Dillon et al. found that a clear surgical margin (> 5 mm) was associated with the highest disease-free and overall survival rate (78%) when compared to a close (1–5 mm) and involved (< 1 mm) surgical margins with disease-free survival rate of 52% and 50%, respectively [6]. Although the authors did not find a statistically significant difference in recurrence by margin status among patients who underwent resection, we found that survival rates were significantly higher for those with close or negative margins compared to those with positive margins, even after adjustment for other factors. Using multivariate analysis, we found that mortality was greatest in patients with inoperable cases when compared to patients with positive surgical margins (HR = 0.54) and close or negative margins (HR = 0.32).

Douglas et al. [17] found skull base involvement to be an adverse factor for patient survival due to the lower neutron dose that could be safely given to the skull base portion of the tumor. With additional "boost" adjunctive treatment local control at 40 months improved from 39% to 82%. Currently all patients with skull base tumor extension are offered a "boost" with either gamma knife or photon radiotherapy. The current study did not find skull base involvement to be a statistically significant factor for survival likely reflective of this practice.

Oral complications

While previous literature reported that neutrons may cause more toxicity than photons, the frequency of oral complications due to NRT in this study appeared comparable to that of conventional radiation therapy. [18]. Long-term NRT-induced toxicities have been associated with xerostomia (60–90%), dysphagia (15–30%) and sensorineural hearing loss (40–60%) [1]. In the current study, 89% and 79% of the subjects experienced xerostomia and mucositis during treatment. Additionally, xerostomia and mucositis have been identified as common and expected complications associated with conventional radiotherapy [18]. The quality-of-life survey provided by the researchers via telephone was completed by a total of 78 subjects (14%), which is a uniquely large sample size compared to previous studies [5,18]. Among the oral complications surveyed, trismus (62%) and decreased saliva (72%) were the two most significant oral complications associated with NRT treatment.

A total of 16 study subjects were diagnosed with ORN, 12 of which were diagnosed through chart documentation and 4 of which were identified through the telephone survey. Historically, the risk of developing ORN of the head and neck ranges from 4.74% to 37.5% [19]. However, the incidence of ORN has declined over time due to improved radiation treatment, notably intensity modulated therapy and medical technological advances that enable improved targeting whilst limiting exposure to the mandible and maxilla [19]. A more recent review based on data collected from 1985 to 2010 reported that the risk of developing ORN is approximately 2–7% from post-operative conventional photon radiotherapy, depending on whether the patient has post radiotherapy tooth extractions [19,20]. Using a multiple imputation-based approach, our best estimate of the ORN rate after receiving NRT was 3–7%. Thus, the ORN rate in the current study appears to be comparable to the rate for conventional radiotherapy.

Pertinent literature

Neutron radiotherapy has been shown to play an important role in treating salivary gland neoplasms of the head and neck [4,21]. Stone introduced fast neutron beam radiotherapy in the 1930s as a clinical trial treating patients with varying malignancies, but the study was prematurely terminated due to devastating side effects [22]. It was only decades later that further understanding showed that the effective dose of neutron radiation was 3–4 times the intended dose, which led to the adverse effects [23]. Subsequent clinical trials that took into account the effective dose of NRT have shown improved clinical results for salivary gland tumors as compared to conventional radiation therapy.

The first radiobiological evidence that neutrons offered a therapeutic advantage compared to photons is attributed to Batterman et al in the 1970s [24]. They found the highest relative biological difference (RBE) of 8 occurred for adenoid cystic carcinoma compared to 3–3.5 for most normal tissues. This discovery was followed by many non-randomized neutron clinical trials that supported this conclusion [25,26]. Additional work has indicated that NRT has much higher linear energy transfer (LET) than conventional photon radiotherapy. The higher LET of NRT results in more unrepairable double-stranded DNA breaks within the cell directly; whereas, conventional radiotherapy relies on the formation of free-radicals and reactive oxygenated species (ROS) that damage DNA indirectly [27]. Generally, salivary gland tumors are slow growing with reduced metabolic activity [28]. This may result in sub-therapeutic effects of conventional photon radiotherapy due to the dependence of ROS formation inducing tumor cell death. Therefore, NRT uses higher LET to treat salivary glands malignancies that may be dormant or more resistant to conventional photon radiotherapy [5].

A retrospective study conducted in 2001 by Huber et al. compared radiotherapy with neutrons, photons, and mixed (photon/neutron) beam in 75 patients with advanced adenoid cystic carcinoma of the head and neck by analyzing locoregional control, survival, and complications. This study found that the 5-year locoregional control rate was 75% for neutron radiotherapy and 32% for both mixed and photon radiotherapy. The study found that survival for patients that underwent NRT was not significantly better when compared to traditional photon therapy [29].

Limitations

There are several limitations in this study: The intrinsic bias that accompanies a retrospective study, the geographically diverse population base, with patients seeking treatment from around the globe, made follow-up outcomes challenging to track. Additionally, due to the amount of time that had passed since the initial treatment, only 78 out of the 545 subjects (14%) completed the quality-of-life survey introducing the risk of recall bias. We used a multiple imputation approach to account for sources of bias, but we cannot rule out possibilities such as inadequate documentation or identification in the medical records. The study is also limited by the lack of a directly comparable control group of patients treated with conventional photon radiation. Therefore, comparisons were formulated from statistics found in previously published literature. In addition, due to the heterogeneity of this study, cancer related outcomes might be difficult to interpret.

Despite these limitations, this is currently the largest study assessing the long term survival, recurrence, and oral complications associated with NRT treatment of salivary gland malignancies.

Conclusions

This study found that NRT has a favorable locoregional control rate and comparable survival rate to that reported in literature for conventional photon radiotherapy when treating salivary gland malignancies. The rate of ORN and other oral complications resulting from NRT appear to be comparable to that reported for conventional photon radiotherapy. NRT is an appropriate form of treatment for patients with inoperable salivary gland tumors or those with high risk features following surgery, such as positive surgical margins.

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Conflicts of interest statement

The authors declare that there is no conflict of interest.

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