Neutron therapy for high grade salivary gland carcinoma in the adjuvant and primary treatment setting

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Abstract

Introduction: Neutron radiotherapy is an attractive option for the treatment of salivary gland cancers (SGCs), which are relatively radio-resistant Neutrons inflict a higher proportion of irreparable double-stranded DNA damage within tumor cells compared to photon radiation. A prior randomized study has reported improved locoregional control of neutron over photon therapy for patients with unresectable salivary gland malignancy. Additional retrospective data shows good control rates in the post-operative adjuvant setting, but there has yet to be a large, multi-institutional study comparing photons versus neutrons in post-operative patients.

Objectives: Determine the differences in survival of patients undergoing neutron radiotherapy in comparison with patients treated with photon therapy for high-grade salivary malignancies using the National Cancer Database (NCDB). Compare differences of survival in patients treated with primary radiation.

Methods: Multicenter, retrospective population-based study of patients within the National Cancer Database (NCDB) from 2004-2014. 1,844 patients were selected on diagnosis of high-grade parotid and submandibular malignancies. 1,777 patients receiving photon and 67 patients receiving neutron therapy were identified who met inclusion criteria. Patients were then categorized as having primary surgery with adjuvant radiation or primary radiation without prior surgery. Bivariate analysis was performed to assess for differences between groups, and restricted mean survival time (RMST) analysis was performed at 1-, 2-, and 5-year timepoints with controlling for available covariate data.

Results: There was no significant difference in RMST for patients receiving neutrons over photons at 1-, 2-, and 5-years in the adjuvant setting. Among patients undergoing primary radiotherapy, there was a difference in RMST of 2.29 months at 1-year and 5.05 months at 2-years for neutrons over photons, though this benefit was not observed at 5-years post-therapy.

Conclusions: For patients with high grade SGCs undergoing adjuvant photon versus neutron radiotherapy, there was no difference in RMST. There was observed to be a significant difference in RMST at 1 and 2 years among patients undergoing primary neutron therapy of up to 5 months. Given the benefit observed with primary neutron therapy, it should be considered in the both the primary and adjuvant treatment setting.

Introduction

Salivary gland malignancies, although rare, pose a unique challenge due to the heterogeneous nature of their pathologies. While initial studies suggested a relative radio-resistant phenotype to these cancers, further investigation has shown that post-operative radiotherapy (RT) provides a significant benefit in locoregional control (LRC). Treatment has traditionally been accomplished with the use of photon RT, but more recent comparisons of treatment for unresectable disease has revealed a slight benefit of neutron versus standard photon RT (2-year LRC of 67% vs 17%). This difference seems to coincide with what is known regarding the biological advantages of neutrons over photons, mainly: increased DNA damage and minimal exit dose through normal surrounding tissues.

Through utilization of the NCDB, we were able to perform the largest study to date comparing neutron to photon therapy for high grade SGCs. Our primary outcomes were to assess for differences in survival time for patients treated with standard photon versus neutron RT after surgery. Secondarily, we aimed to determine if there were any differences in patients receiving these therapies who had inoperable disease.

Methods

- NCDB data from 2004-2014 was filtered for patients with carcinoma of the parotid or submandibular gland and relevant cases selected as shown in Figure 1.
- Patients were divided based on whether they received primary surgery with adjuvant radiation or primary radiation without surgery. Comparison between neutron and photon radiotherapy within these groups was undertaken
- Kaplan-Meier analysis as well as restricted mean survival time analysis were performed

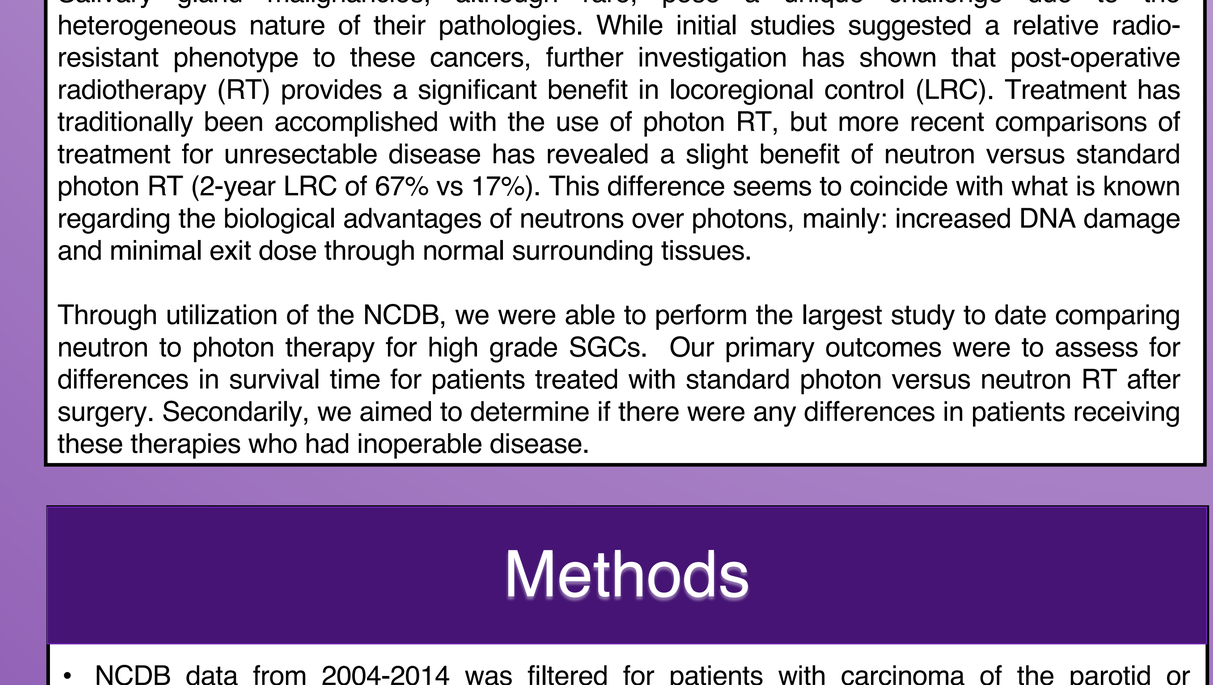


Figure 1. Flow diagram for patient selection.

Results

Table 1
Characteristics of patients undergoing primary surgery with adjuvant radiation therapy.

Variable		Treatment Group† All (N = 1,578)	Photon (n = 1,526)	Neutron (n = 52)	P-value
Age, median (SD)		63 (15.9)	64 (15.9)	59.5 (16.5)	0.0024*
Gender					
	Male	991 (62.8)	969 (63.5)	22 (42.3)	0.002*
	Female	587 (37.2)	557 (36.5)	30 (57.7)	
Race/ethnicity					
	White	1,330 (84.3)	1,301 (85.3)	29 (55.8)	<0.001*
	Black	142 (9.0)	139 (9.1)	3 (5.8)	
	Asian/Pacific Islander	54 (3.4)	53 (3.5)	1 (1.9)	
	Other or unknown	52 (3.3)	33 (2.2)	19 (36.5)	
Charlson-Deyo comorbidity score‡					
	0	1,358 (86.1)	1,309 (85.8)	49 (94.2)	0.192
	1	178 (11.3)	175 (11.5)	3 (5.8)	
	2	42 (2.7)	42 (2.7)	0 (0.0)	
T stage					
	T1-3	1,321 (83.7)	1,276 (83.6)	45 (86.5)	0.575
	T4	257 (16.3)	250 (16.4)	7 (13.5)	
N stage					
	0	655 (41.5)	623 (40.8)	32 (61.5)	0.874
	1	120 (7.6)	116 (7.6)	4 (7.7)	
	2	192 (12.2)	182 (11.9)	10 (19.2)	
	3	1 (0.1)	1 (0.1)	0 (0.0)	
	Unknown	610 (38.7)	604 (39.6)	6 (11.5)	
Histologic type§					
	Non-high risk subtype	872 (55.3)	846 (55.4)	26 (50.0)	0.347
	High risk subtype	706 (44.7)	680 (44.6)	26 (50.0)	
Common cellular morphologies					
	Mucoepidermoid carcinoma	301 (19.1)	295 (19.3)	6 (11.5)	0.033*
	Adenocarcinoma	265 (16.8)	258 (16.9)	7 (13.5)	
	Acinar cell carcinoma	234 (14.8)	218 (14.3)	16 (30.8)	
	Carcinoma, NOS	178 (11.3)	170 (11.1)	8 (15.4)	
	Carcinoma ex pleo	100 (6.3)	94 (6.2)	6 (11.5)	
	Other	500 (31.7)	491 (32.2)	9 (17.3)	
Radiation dose received (Gy), median (SD)¶		60.0 (10.1)	60.0 (10.2)	18.4 (15.0)	
Travel to care (miles), mean (SD)		40.5 (182.0)	28.7 (107.8)	378.4 (737.2)	< 0.001*

Table 2. Restricted mean survival times of patients receiving primary surgery with adjuvant radiation therapy and adjusted for age, sex, Charlson-Deyo comorbidity score, and T stage.

	Cumulative number of cases		Adjusted mean time to death (95% CI)		Difference in mean time to death (95% CI)	
Years of follow-up	Neutron	Photon	Neutron	Photon	Crude	Adjusted
1 year	8	286	11.5 (11.2, 11.8)	11.5 (11.4, 11.6)	0.10 (-0.22, 0.41)	-0.01 (-0.32, 0.30)
2 year	10	387	21.3 (19.9, 22.7)	21.7 (21.3, 22.1)	0.05 (-1.35, 1.45)	-0.36 (-1.73, 1.00)
5 year	19	553	46.6 (41.6, 51.6)	46.6 (45.2, 48.0)	2.13 (-3.04, 7.30)	0.05 (-4.95, 5.04)

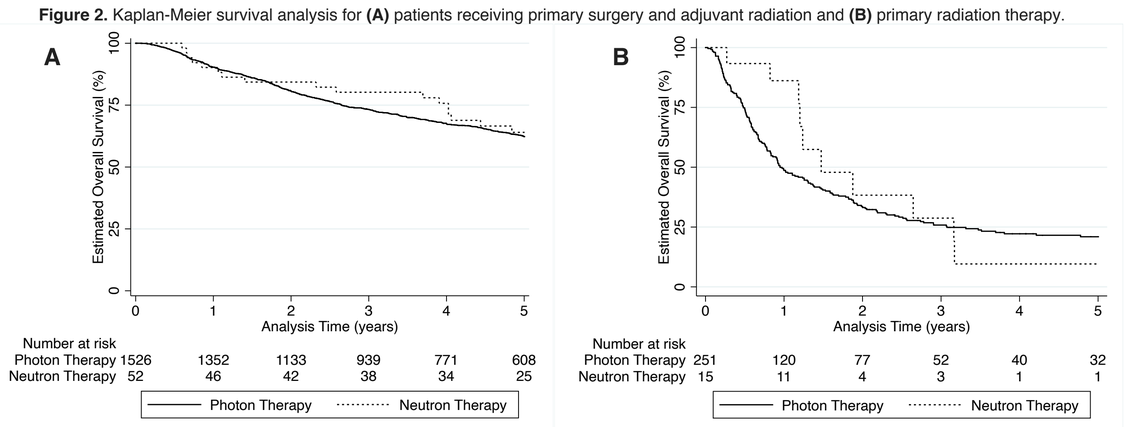
Table 3
Characteristics of patients undergoing primary radiation therapy without surgery.

Variable		Treatment Group† All (N = 266)	Photon (n = 251)	Neutron (n = 15)	P-value
Age, median (SD)		73.5 (15.0)	74 (15.1)	66 (12.9)	0.511
Gender					
	Male	168 (63.2)	157 (62.6)	11 (73.3)	0.4
	Female	98 (36.8)	94 (37.4)	4 (26.7)	
Race/ethnicity					
	White	226 (85.0)	218 (86.9)	8 (53.3)	< 0.001*
	Black	24 (9.0)	24 (9.6)	0 (0.0)	
	Asian/Pacific Islander	9 (3.4)	3 (1.2)	6 (40.0)	
	Other or unknown	7 (2.6)	6 (2.4)	1 (6.7)	
Charlson-Deyo comorbidity score‡					
	0	215 (80.8)	201 (80.1)	14 (93.3)	0.424
	1	39 (14.7)	38 (15.1)	1 (6.7)	
	2	12 (4.5)	12 (4.8)	0 (0)	
T stage					
	T1-3	260 (97.7)	245 (97.6)	15 (100.0)	0.545
	T4	6 (2.3)	6 (2.4)	0 (0.0)	
N stage					
	0	91 (34.2)	85 (33.9)	6 (40.0)	0.665
	1	36 (13.5)	34 (13.5)	2 (13.3)	
	2	72 (27.1)	65 (25.9)	7 (46.7)	
	3	9 (3.4)	9 (3.6)	0 (0.0)	
	Unknown	58 (21.8)	58 (23.1)	0 (0.0)	
Histologic type§					
	Non-high risk subtype	167 (62.8)	159 (63.4)	8 (53.3)	0.436
	High risk subtype	99 (37.2)	92 (36.6)	7 (46.7)	
Common cellular morphology					
	Adenocarcinoma	73 (27.3)	70 (27.9)	3 (20.0)	0.003*
	Carcinoma, NOS	66 (24.7)	63 (25.1)	3 (20.0)	
	Mucoepidermoid carcinoma	44 (16.5)	41 (16.3)	3 (20.0)	
	Small cell carcinoma	18 (6.7)	18 (7.2)	0 (0.0)	
	Acinar cell carcinoma	13 (4.9)	9 (3.6)	4 (26.7)	
	Other	52 (19.5)	50 (19.9)	2 (12.3)	
Radiation dose received (Gy), median (SD)¶		45.0 (16.2)	48.6 (15.6)	12.7 (12.8)	
Travel to care (miles), mean (SD)		63.6 (310.8)	18.0 (41.7)	872.0 (1078.7)	< 0.001*

Table 4. Restricted mean survival times of patients receiving primary surgery with adjuvant radiation therapy and adjusted for age, sex, Charlson-Deyo comorbidity score, and T stage.

	Cumulative number of cases		Adjusted mean time to death (95% CI)		Difference in mean time to death (95% CI)	
Years of follow-up	Neutron	Photon	Neutron	Photon	Crude	Adjusted
1 year	7	164	11.3 (9.1, 13.5)	9.0 (7.4, 10.6)	2.37 (1.16, 3.59)	2.29 (0.65, 3.92)
2 year	8	181	18.6 (13.4, 23.8)	13.5 (9.9, 17.2)	4.69 (1.42, 7.95)	5.05 (0.95, 9.15)
5 year	10	196	29.3 (15.1, 43.4)	24.2 (13.4, 34.9)	3.99 (-4.29, 12.26)	5.08 (-4.99, 15.15)

Figure 2. Kaplan-Meier survival analysis for **(A)** patients receiving primary surgery and adjuvant radiation and **(B)** primary radiation therapy.



Conclusions

- Restricted mean survival times were significantly greater at 1- and 2-years following treatment for patients who did not receive primary surgery, but no difference was observed in the primary surgery group
- Travel distances were much greater for patients receiving neutron as opposed to photon RT
- Neutron therapy has a clear benefit in cases of unresectable disease but differences for patients receiving primary surgery followed by neutrons were not clearly identified