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Assessment of adjuvant therapy in resected head and neck cancer with high-risk features

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ABSTRACT

Objectives: Subgroup analysis from two randomized trials showed a survival benefit for adjuvant chemoradiation (CRT) over radiation alone (RT) in patients with extracapsular spread (ECS) of involved lymph nodes and/or positive margins (PM) in resected head and neck cancer (HNSCC). However, results were not analyzed separately for patients with ECS or PM and were not stratified by tumor subsite/HPV status. We therefore sought to determine whether adjuvant CRT is associated with a survival benefit, separately among patients with ECS or PM and stratified by subsite/HPV status.

Methods: Using the National Cancer Database (NCDB), we identified 6948 patients diagnosed with HNSCC between 2010 and 13 who underwent surgical resection and had either ECS or PM. The impact of adjuvant therapy on OS from surgery was evaluated using Cox proportional hazards regression adjusting for clinical and demographic factors.

Results: Adjuvant CRT was associated with a significant survival benefit over RT alone among patients with ECS (aHR 0.83, 95%CI 0.71–0.97) but not among those with PM (aHR 0.89, 95%CI 0.77–1.04). In patients with HPV-negative tumors, CRT was associated with a benefit over RT alone in the setting of ECS (aHR 0.83, 95%CI 0.70–0.98) but not PM (aHR 0.91, 95%CI 0.78–1.06). However, in patients with HPV-positive oropharynx tumors, CRT was not associated with a benefit over RT in ECS (aHR 0.94, 95%CI 0.47–1.88) but appeared beneficial in PM (aHR 0.54, 95%CI 0.32–0.90).

Conclusions: CRT appears beneficial over RT in ECS among patients with HPV-negative tumors, and beneficial in PM among patients with HPV-positive tumors.

Introduction

Patients with squamous cell carcinoma of the head and neck (HNSCC) may be managed with primary surgery when indicated. Those with locally advanced tumors, involvement of multiple lymph nodes or level IV/V nodes, extracapsular spread (ECS), positive resection margins (PM), and perineural or lymphovascular invasion are at high risk of local recurrence and may benefit from adjuvant radiation therapy (RT). Adjuvant RT has shown benefits in locoregional control and disease-specific survival, but not overall survival (OS), over surgery alone [1,2].

The addition of chemotherapy to adjuvant radiation regimens (CRT) has shown a survival benefit over adjuvant RT alone in high-risk HNSCC in the EORTC 22931 and RTOG 9501 trials [3,4]. Subgroup pooled analysis from these trials showed that this survival benefit was limited to patients with ECS and/or PM [5]. Guidelines subsequently changed to recommend adjuvant CRT for ECS or PM, and RT alone for other adverse features. However, long-term follow up of the RTOG 9501 trial did not find a survival advantage in patients treated with CRT when compared to RT alone [6].

In addition, the subgroup analysis of the two trials did not consider ECS and PM separately or stratify results by tumor subsite or human papilloma virus (HPV) status [5]. Recent observational studies have found that ECS is not a negative prognostic feature in HPV-positive tumors of the oropharynx [7–11], and institutional observational data suggests that CRT is not superior to RT alone in HPV-positive oropharynx tumors [8,12,13].

While PM has been consistently shown to be a negative prognostic factor across all head and neck subsites [14–19], some data suggests it may not be a negative feature in HPV-positive oropharynx tumors [11]. The impact of CRT in this setting alone has not been clearly studied using a large national dataset. Moreover, the pooled analysis across two trials did not separately evaluate ECS and PM—only 10% of the RTOG

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Table 1
Characteristics of patients with extracapsular spread or positive margins. Results presented as mean (continuous variables) or group% (categorical variables).

	Extracapsular Spread (n = 3245)	Positive Margins (n = 4096)
Age (mean, yrs)	59.5	61.3
Sex (%)		
Male	73.5	73.9
Female	26.5	26.1
Race/ethnicity (%)		
White	82.8	84.6
Black	9.4	8.1
Hispanic	3.9	3.8
Asian/Pacific Islander	2.4	2.0
Other/unknown	1.5	1.5
Insurance status (%)		
Private	44.5	44.4
Medicare	32.2	36.3
Medicaid	14.5	10.7
Other/none/unknown	8.8	8.7
Socioeconomic status (%)		
Low	36.5	33.4
Middle	31.6	33.9
High	31.4	32.2
Unknown	0.6	0.5
Comorbidity index (%)		
0	74.8	76.1
1	19.4	18.2
≥2	5.8	5.7
Primary site (%)		
Oral cavity	49.1	37.5
Oropharynx, HPV-negative	6.0	8.5
Oropharynx, HPV-positive	23.7	27.3
Hypopharynx	4.5	2.7
Larynx	16.7	24.0
Grade (%)		
1	5.3	9.7
2	51.1	49.9
3	36.2	31.0
Unknown	7.4	9.3
Pathologic T Stage (%)		
1	20.1	23.6
2	27.6	25.4
3	16.5	10.3
4	31.8	19.8
X	4.0	20.9
Pathologic N Stage (%)		
0	0.5	19.5
1	15.0	10.1
2	77.3	28.5
3	4.0	1.2
X	3.2	40.7
Lymphovascular invasion (%)		
Absent	42.7	49.2
Present	40.7	20.0
Unknown	16.6	30.7
Level IV or V Node involvement (%)		
Absent	68.5	82.9
Present	25.8	11.7
Unknown	5.7	5.4
Adjuvant treatment (%)		
None	18.6	24.2
RT alone	15.1	26.8
Chemo-RT	66.2	49.0

9501 group and 29% of the EORTC 22931 group had PM, while 53% and 57% had ECS in each group, respectively [5]. Thus, there remains a lack of comprehensive data evaluating the potential role of CRT in the setting of PM separately from ECS.

Therefore, we sought to evaluate the impact of adjuvant CRT over RT on survival in resected HNSCC separately for patients with ECS or PM using the National Cancer Database (NCDB). Our hypothesis is that the addition of CRT to RT will be associated with an OS benefit for both ECS and PM, but that this benefit will be limited to HPV-negative tumors.

Table 2
Predictors of receipt of adjuvant chemoradiation (CRT), among patients with extracapsular spread or positive margins. Results presented as% of each group receiving adjuvant CRT. P values from corresponding chi-square tests.

	Extracapsular spread		Positive margins	
	Receipt of CRT (%)	P value	Receipt of CRT (%)	P value
Age		< 0.001		< 0.001
< 50	77.0		59.9	
50–64	69.5		57.7	
≥65	54.8		32.3	
Sex		0.011		< 0.001
Male	67.5		51.5	
Female	62.7		41.7	
Race/Ethnicity		0.294		0.935
White	66.6		48.9	
Black	61.8		49.2	
Hispanic	67.2		48.1	
Asian/Pacific Islander	71.8		53.0	
Other/unknown	60.0		46.0	
Insurance status		< 0.001		< 0.001
Private	74.7		58.3	
Medicare	55.2		35.4	
Medicaid	66.7		55.3	
Other/none/unknown	63.1		50.4	
Socioeconomic status		< 0.001		0.178
Low	64.6		48.6	
Middle	62.6		48.6	
High	71.6		49.4	
Unknown	72.2		73.7	
Comorbidity index		< 0.001		0.005
0	68.4		50.2	
1	61.1		46.2	
≥2	55.6		40.8	
Primary site		< 0.001		< 0.001
Non-HPV	63.6		40.3	
Oropharynx, HPV-positive	74.5		72.0	
Grade		< 0.001		< 0.001
1	56.4		23.1	
2	64.2		46.7	
3	70.7		60.9	
Unknown	65.6		48.4	
Pathologic T Stage		0.004		< 0.001
1	68.4		38.0	
2	68.7		52.1	
3	62.4		60.3	
4	63.6		53.1	
X	75.2		48.0	
Pathologic N Stage		< 0.001		< 0.001
0	56.2		27.0	
1	55.4		54.2	
2	67.8		67.7	
3	70.0		67.3	
X	76.2		44.5	
Lymphovascular Invasion		0.910		< 0.001
Absent	66.4		43.9	
Present	65.8		63.3	
Unknown	66.7		47.7	
Level IV or V Node Involvement		0.456		< 0.001
Absent	65.8		45.7	
Present	67.9		69.7	
Unknown	64.3		54.5	