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Sparing of high retropharyngeal nodal basins in patients with unilateral oropharyngeal carcinoma treated with intensity modulated radiation therapy

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Abstract

Background—The introduction of intensity modulated radiotherapy (IMRT) has facilitated dose painting and sparing of uninvolved/low-risk nodal basins in head and neck cancers. In oropharynx cancer (OPC), elective coverage of uninvolved high contralateral retropharyngeal (RP) nodes and the risk associated with sparing this region remain unclear. In this study, we examined outcomes of OPC patients treated with IMRT and omission of contralateral high RP coverage.

Methods and Materials—We identified 102 OPC patients with cN0-N2b disease treated with definitive IMRT +/- concurrent chemotherapy between 2010 and 2013. The contralateral RP nodal basins superior to the vertebral level of C1 were omitted from the elective IMRT field for all patients. Of the 67 patients (66%) with p16 status available, 63 (94%) were p16+. We used the Kaplan-Meier method to estimate overall survival (OS), as well as freedom from local failure (FFLR), regional failure (FFRF), distant failure (FFDF) and retropharyngeal failure (FFRPF).

Results—The median follow-up was 26.9 months (range: 3.0–59.9 months). There were no failures in the treated ipsilateral RP nodes or the spared contralateral high RP nodes in the entire cohort. In the p16+ cohort and the entire cohort, the 2-year rates of OS, FFLF, FFRF, FFDF and FFRPF were 98.0% and 95.1%, 98.1% and 97.7%, 96.4% and 96.7%, 98.1% and 95.1% and 100% and 100%, respectively.

Conclusion—Omission of contralateral high RP nodes in patients with p16+ OPC patients with unilateral disease is safe.

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Introduction

In the past decade, intensity modulated radiotherapy (IMRT) has emerged as the standard of care in head and neck squamous cell carcinoma (HNSCC) [1, 2]. Numerous prospective analyses have demonstrated excellent rates of locoregional control while simultaneously decreasing the incidence of both acute and late toxicities—including xerostomia and dysphagia—when compared with prior treatment approaches (conventional and 3D conformal radiotherapy) [3–5].

IMRT allows for selective irradiation of lymph node levels likely to be involved with subclinical disease while sparing structures with low risk of microscopic disease. The retropharyngeal nodes (RP)—first topographically described by Rouviere in 1932 [6] and currently considered part of level VII [7]—are often considered at risk of metastatic spread in oropharyngeal, nasopharyngeal, and hypopharyngeal cancers [8–11]. One single institution study of collective HNSCC patients of multiple primary subsites has demonstrated safe elimination of contralateral high RP nodal treatment from IMRT fields in the setting of post-operative irradiation [12] [12, 13], while another has suggested that bilateral RP nodal treatment is necessary. Improvements in quality of life metrics have been observed with RP nodal sparing [12].

The goal of this study is to explore the safety of contralateral high RP nodal sparing in the definitive setting in a cohort of contemporary, primarily p16+ patients with oropharynx cancer (OPC) with unilateral nodal disease. At our center, the majority of patients with locally advanced OPC undergo definitive concurrent chemoradiation [5] and patients with OPC (N0-N2b) and unilateral nodal disease have been treated at our center with sparing of the contralateral high RP nodal basin since the year 2010. Herein, we describe the outcomes of high contralateral RP nodal sparing and assess the safety of this approach.

Methods and Materials

This retrospective review was approved by the institutional review board at our center. We identified 102 consecutive cN0-N2b OPC patients who were treated with definitive IMRT in which the contralateral high RP nodes above C1 were not targeted in the IMRT treatment field.

Staging Workup

A complete medical history, physical examination with fiberoptic nasopharyngoscopy, computed tomographic (CT) and/or magnetic resonance imaging (MRI) scans of the head and neck were performed as part of the pretreatment evaluation. Additional imaging included a plain radiograph, CT of the chest or positron emission tomography (PET). All patients were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual. Immunohistochemical staining of p16 was performed on 66% of patients.

Treatment

For each patient, the recommended course of treatment was formulated with the input of a multidisciplinary team including a radiation oncologist, medical oncologist, head and neck surgeon, pathologist and radiologist. In the majority of cases, cisplatin was administered, delivered to a dose of 100mg/m² every 3 weeks or weekly at 30–40 mg/m². Alternatively, patients were treated with cetuximab given as an initial loading dose of 400 mg/m² followed by weekly cycles administered at 250 mg/m². Other concurrent systemic regimens are indicated in Table 1.

Radiation planning and treatment

A planning CT with a slice thickness of 3mm was obtained for all patients with the use of intravenous iodinated contrast when not contraindicated. Patients were simulated in the supine position with the use of an aquaplast mask for immobilization. All patients were treated with IMRT. Organs at risk and target volumes were delineated as described previously [XXX]. Briefly, primary gross tumor volume (GTV) included all gross disease discovered on clinical examination, nasopharyngoscopy and imaging. Primary nodal GTV included all proven or suspicious (>1 cm, necrotic, contrast enhancing, or FDG avid) lymph nodes. The high-risk clinical target volume (CTV_{59,4}), or subclinical disease, was defined as GTV plus a margin of 0.5 cm to 1.0 cm. In the node positive neck, CTV_{59,4} included levels II–V (though V was excluded at the discretion of the treating physician) and the entire RP chain extending from the skull-base to the hyoid bone. In the node negative neck, CTV₅₄ included levels II–IV and RP nodes from the hyoid to the level of the C1 vertebral body. The PTV₇₀ was defined as gross tumor plus a margin of 0.3-cm to 0.5 cm, and the PTV_{59,4} and PTV₅₄ were defined as their respective CTVs plus an identical margin.

Dose was prescribed in one of two ways: either with 2.12 Gy, 1.8 Gy, and 1.64 Gy daily fractions over a course of 33 days to the PTV₇₀, PTV_{59,4}, and PTV₅₄, respectively, or with a cone-down technique with 2 Gy daily fractions to PTV₇₀ and PTV₆₀ and 1.8 Gy daily fractions to PTV₅₄ for 30 days followed by 5 additional 2 Gy fractions to PTV₇₀. The lower neck was either included in the IMRT fields or included in a low anterior neck field matched to the IMRT fields. Treatment planning was performed using an in-house treatment planning software. An example plan of a patient treated with contralateral high RP nodal sparing is shown in figure 1 with representative sagittal, coronal and axial slices.

Follow up

Patients were evaluated weekly during the course of radiotherapy and every 2–4 months for the first 2 years following treatment. Subsequently, evaluations were performed every 4–6 months from years 3–5, and yearly thereafter. Follow up visits consisted of physical examination, flexible fiberoptic endoscopy, and neck palpation. Three months after treatment, a PET scan as well as CT or MRI of the neck were performed to assess response. Afterwards, imaging studies were typically performed as clinically indicated. Chest radiographs or other imaging was performed annually to assess for distant metastases as indicated.

Event definitions

Locoregional or distant recurrences were confirmed pathologically unless there was clear evidence of metastatic disease on CT or PET/CT scan. Local failure was defined as recurrence at the original site of gross disease within the oropharynx. Regional failure was defined as recurrence in any cervical lymph node. Retropharyngeal failure was defined as recurrence in either RP nodal chain. Distant failure was defined as metastatic failure in any organ outside of the head and neck.

Statistical Analysis

We used the Kaplan-Meier method and SPSS software (SPSS version 24, IBM) to estimate overall survival and recurrence outcomes.

Results

Table 1 shows the baseline patient and tumor characteristics. 67 patients (66%) had p16 status available and of those, 63 (94%) were found to be p16+. The majority (95.1%) of patients were treated with concurrent systemic therapy, most commonly cisplatin. The median follow-up was 26.9 months (range 3.0–59.9 months).

No failures were observed in the treated ipsilateral RP nodes or the spared contralateral RP nodes in the entire cohort. In the p16+ cohort and the entire cohort, the 2-year rates of overall survival, freedom from local failure, freedom from regional failure, freedom from distant metastasis and freedom from RP nodal failure were 98.0% and 95.1%, 98.1% and 97.7%, 96.4% and 96.7%, 98.1% and 95.1% and 100% and 100%, respectively (Figure 2).

Three regional nodal failures occurred, all of which were in-field: a 62 year old woman with p16+ T2N2b tonsillar carcinoma with multilevel nodal progression (ipsilateral levels II,III,IV) three months following IMRT, a 48 year old man with p16+ T3N2b tonsillar carcinoma who developed bilateral level II nodal progression in conjunction with local failure six months following IMRT and a 62 year old man with T3N2b disease (p16 unknown) who developed bilateral level II/III progression 6 months after IMRT. All three of these patients were treated with concurrent systemic therapy, two with cisplatin and one with cetuximab.

Discussion

In this contemporary cohort of 102 OPC patients with N0-N2b disease, we have demonstrated excellent rates of locoregional control and no failure in the contralateral high RP nodes in the uninvolved neck when not targeted electively with IMRT. These results corroborate those previous reports of successful contralateral RP sparing [12, 13] and extend this finding to a uniform group of mostly p16+OPC patients treated with definitive IMRT using modern staging and treatment techniques. For one third of the patients, p16 status was not available.

Eisbruch et al. reported on 133 primarily locally advanced HNSCC patients (60% OPC) treated with a combination of 3D conformal RT and IMRT, most of whom were treated with

postoperative radiation in which high RP nodal sparing was attempted. Within this cohort, three RP nodal failures were observed, all of which occurred in OPC patients prior to 1999 and only one of which was high contralateral and in the spared region near the base of skull in a patient with T3N3 tonsillar cancer. As a result, they recommended elective nodal coverage to include bilateral RP basins up to the base of skull in all locally advanced OPC cases.

More recently, Spencer et al. reviewed a cohort of 234 patients with HNSCC of various sub-sites (50% OPC) in which contralateral high RP nodal sparing was performed in the clinically uninvolved neck. Most patients were treated with IMRT post-operatively (63%) and no failures were observed in the spared region. They were able to show that quality of life was improved with RP sparing when compared to an earlier cohort of patients in which high level II and RP nodes were not spared [12]. A recent series of nearly 1000 patients demonstrated that the RPLNs are radiographically involved in approximately 10% of OPC, and more commonly associated with tumors of the pharyngeal wall [14], which has been shown in other reports [11]. However, the data regarding radiographically uninvolved RPLNs is mixed. While some authors believe that the risk of subclinical involvement is sufficient to justify elective irradiation of the RPLNs, these same authors and others found that isolated contralateral RPLN disease is extraordinarily rare [9, 14].

Importantly, it must be recognized that despite not targeting the RP nodes explicitly, the spared volume can receive fall-off low scatter doses, which may be sufficient to control sub-clinical microscopic disease, particularly for radiosensitive HPV-associated disease. As more conformal therapies continue to be refined and investigated—intensity modulated proton beam therapy in particular—this effect and possible repercussions on disease control will become more clear.

The ultimate goal of eliminating nodal volumes and thereby decreasing the overall volume of irradiated tissue is to improve toxicity profile without sacrificing treatment outcomes. While toxicity rates were not explored in this study, it has been demonstrated that sparing of contralateral high level II and RP nodes is associated with improvement in quality of life [12]. Of note, the toxicity benefit of contralateral RP sparing alone has not yet been established. However, the dose to the pharyngeal mucosa and pharyngeal constrictors may be expected to be reduced, potentially resulting in decreased risk of mucositis and dysphagia.

The epidemiology of OPC has changed significantly in the last two decades with the epidemic of HPV-associated disease, which has been demonstrated to be prognostically and molecularly distinct from non-HPV related disease classically caused by tobacco and alcohol [15–17]. In our study, 94% of patients with available p16 testing were p16 positive, reflecting the modern landscape of OPC. Our study provides evidence that contralateral high RP sparing is safe in p16+ OPC patients treated with modern IMRT techniques, despite the highly lymphotropic nature of the disease.

Our study is limited by its retrospective nature and inherent biases associated with single institution studies. In the future, we hope to more directly address the question of how

sparing high RP nodal basins may affect toxicity. Our study population is relatively uniform, consisting of mostly p16+ OPC patients treated in the definitive setting. As such, these findings may not be generalizable to tumors of other HNSCC sub-sites or treatment in the post-operative setting, particularly after neck dissection where lymphatic drainage can be affected and may result in retrograde lymphatic flow and alternative patterns of spread. Furthermore, our study did not include patients with N2c disease, for whom bilateral prophylactic inclusion of RP nodal basins may be needed and only included two patients with tumors of the posterior pharyngeal wall who may be at higher risk of RP nodal metastasis but represent a minority of OPC. Lastly, the followup of patients in this study is primarily clinical with most patients being imaged at only a single time point following treatment. As such, the presence of subclinical recurrent RP nodal disease remains a possibility though no clinically relevant RP nodal recurrences were detected. Despite these limitations, we are able to show that, in the important and increasingly prevalent population of N0-N2b OPC patients, contralateral high RP nodal sparing in the uninvolved neck appears safe and should be strongly considered.

Acknowledgments

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Figure 1.

63 year old woman with T2N2a p16+ squamous cell carcinoma of the left base of tongue treated with definitive chemoradiation. Shown are (A) sagittal and (B) coronal images of the radiation plan demonstrating the superior extent of the retropharyngeal nodal contours. Shown in (C) is the superior-most axial slice with contralateral retropharyngeal nodal coverage (red contour). Dose range displayed is 30–75 Gy.

Figure 2.

Kaplan-meier estimates of (A) overall survival, (B) freedom from local failure, (C) freedom from regional failure, (D) freedom from distant metastasis and (E) freedom from retropharyngeal failure in N0-N2b oropharyngeal carcinoma patients treated with definitive intensity modulated radiotherapy and sparing of contralateral high retropharyngeal nodal basins.

Table 1

Baseline patient and tumor characteristics.

N=102			
Median age (range)		57 (25–82)	
Gender	Male	91	89.2%
	Female	11	10.8%
KPS	80	10	9.8%
	90	73	71.6%
	100	19	18.6%
T-stage	1	31	30.4%
	2	45	44.1%
	3	18	17.6%
	4	5	4.9%
N-stage	0	7	6.9%
	1	13	12.7%
	2a	8	7.8%
	2b	74	72.5%
	2c	0	0.0%
AJCC stage	1	2	2.0%
	2	3	2.9%
	3	13	12.7%
	4	84	82.4%
Concurrent Chemotherapy	None	5	4.9%
	Cisplatin	68	66.7%
	Cetuximab	14	13.7%
	Carboplatin + 5-FU	2	2.0%
	Cisplatin + cetuximab + bevacizumab	10	9.8%
	Cetuximab + albumin bound paclitaxel	1	1.0%
Induction chemotherapy	Yes	91	89.2%
	No	11	10.8%
p16 status	Positive	63	61.8%
	Negative	4	3.9%
	Unknown	34	33.3%
Oropharynx sub-site	Base of tongue	51	50.0%
	Tonsil	48	47.1%
	Posterior pharyngeal wall	2	2.0%
	Soft palate	1	1.0%