Oral Oncology 93 (2019) 96–100

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Occult contralateral nodal disease in oropharyngeal squamous cell carcinoma patients undergoing primary TORS with bilateral neck dissection

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ARTICLE INFO

Keywords:
Oropharynx
Oropharyngeal neoplasms
Lymph node dissection
Head and neck neoplasms

ABSTRACT

Background: Knowledge of the rate of occult contralateral nodal disease for oropharynx cancers (OPSCC) in the era of Human Papillomavirus-dominated disease would inform practitioners as to who may be a candidate for unilateral neck management. The objective of this study was to determine the rate of pathologic contralateral positive nodes in patients in OPSCC patients with pT1 and pT2 disease treated with TORS and bilateral neck dissections (BND).

Methods: Retrospective review of medical records was performed at Princess Margaret Cancer Center, Toronto; Icahn School of Medicine at Mount Sinai, New York City; and Montefiore Medical Center, New York City. Patients with pT1-2 N0-3 (AJCC 8th Edition) OPSCC disease treated with TORS and BND were included.

Results: Thirty-two patients met inclusion criteria. Twelve patients (37.5%) had a tonsil primary site, 19 (59.4%) patients had a base of tongue primary site, and 1 (3.1%) patient had a pharyngeal wall primary. Twenty-four (75%) patients were known to be p16+. Twenty-seven patients (84.4%) were radiographically negative in the contralateral neck preoperatively, and two of these patients had pathologic contralateral positive nodes. The occult pathologic contralateral nodal metastasis rate was 7.4% (2/27). The sensitivity, specificity, positive predictive value, and negative predictive value of suspicious contralateral nodes on preoperative imaging for pathologically positive nodes were 33.3%, 86.2%, 20% and 93% respectively. In the p16+ subgroup, the occult nodal positive rate in the contralateral neck was 5%.

Conclusions: pT1-2 OPSCC patients undergoing TORS and elective contralateral neck dissection have a low rate of pathologic contralateral nodal positivity.

Introduction

The occult rate of unilateral nodal metastases in oropharyngeal squamous cell carcinoma (OPSCC) is historically understood to be approximately 30%, warranting early elective treatment of the neck [1–4]. Further studies have investigated the risk of developing contralateral nodal metastases in patients treated with upfront surgical approaches and have demonstrated a risk of contralateral metastasis ranging from 16 to 29% [5–7]. These studies, however, included patients with advanced stages of OPSCC treated with more invasive approaches and also included patients treated well before the emergence of Human Papillomavirus (HPV) as the main etiologic agent in the

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https://doi.org/10.1016/j.oraloncology.2019.04.017
Received 5 February 2019; Received in revised form 18 March 2019; Accepted 24 April 2019
Available online 01 May 2019
1368-8375/

development of OPSCC. More recently, Kato et al. and Tritter et al. have described the incidence of contralateral or bilateral nodal adenopathy in the HPV era and reported an incidence of 14–26% [8,9]. These studies included patients treated with non-surgical modalities and identified the incidence of bilateral or contralateral disease by imaging or clinical exam only.

As many patients with OPSCC are treated with non-surgical modalities including radiation and chemotherapy, there has been limited reporting of the rate of pathologic nodal positivity in the contralateral neck. The incidence of occult *contralateral* neck nodal disease is not definitively known in this patient population, particularly in the era of HPV and the increased use of transoral approaches.

As the radiation treatment of patients with early T category, lateralized OPSCCs trends toward ipsilateral-only, it would be essential to know the contralateral nodal incidence in surgically treated patients, particularly in radiographically N0 cases. Imaging modalities have advanced, and the pathophysiologic nature of OPSCC has changed since the publication of occult contralateral nodal disease rates that currently guide surgical practice. The purpose of the current study is to determine the rate of contralateral neck nodal positivity for T1-2 OPSCC patients undergoing TORS and bilateral neck dissection in a multicenter population.

Patients and methods

Study cohort

At each institution, institutional research ethics board approval was granted for the study (University Health Network: #16-5407; Icahn School of Medicine at Mount Sinai: #15-01091; Montefiore Medical Center: exempt from IRB). Patients were identified from each institution based on either prospectively or retrospectively collected databases. Patients with pT1-2 N0-3 M0 (AJCC 8th Ed.) who underwent transoral robotic surgery (TORS) for primary site resection and bilateral neck dissections were included in the analysis. Neck dissections could be performed either concurrently or in a staged fashion, with or without adjuvant therapy postoperatively. Patients who (a) had prior treatment for head and neck cancer, (b) had neoadjuvant therapy, (c) had an aborted TORS approach, (d) had a non-oropharyngeal primary site, (e) had non-squamous cell carcinoma pathology, or (f) did not have available imaging or medical records for review were excluded. Specific indications for bilateral neck dissections were not recorded as these were often not specified in the medical record. Bilateral neck dissction indication was not explicitly sought but presumed to be based upon clinical, radiographic and patient-specific factors.

Review of medical records for clinical, pathologic and radiographic information was performed at each institution and de-identified prior to transfer to the University of Toronto for compilation and statistical analysis.

Imaging

Preoperative scans were re-reviewed by a neuroradiologist at each individual site, and findings were documented on a de-identified data collection. Imaging studies for each patient varied and included a combination of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography with computed tomography (PET-CT). The CT findings were preferentially included for nodal disease status, and MRI findings were preferentially included for primary tumor characteristics. If PET-CT was available, the final preoperative radiographic staging incorporated these PET-CT findings. The final radiographic stage utilized for analysis in this study incorporated all available radiographic information.

A suspicious node on imaging had one or more of the following traits: retropharyngeal nodes ≥ 0.8 cm in the longest dimension in the axial plane; jugulodigastric chain and level 1b nodes ≥ 1.5 cm; nodes in all other levels ≥ 1.0 cm; nodes with cystic or necrotic components of any size; nodes with a rounded rather than ovoid shape of any size; asymmetric clustering of nodes, loss of fatty hilum [10]. Enhancement with intravenous contrast was not a definite consideration for suspicious adenopathy. Extranodal extension (ENE) was considered present with poorly defined peripheral margins, and/or matted nodes.

Pathology

Pathologic findings were collected from the surgical pathology reports generated at the time of surgery. In general, p16 positivity was defined as at least > 70% immunohistochemical staining.

Statistical analysis

The main outcome measure for this study was the rate of occult contralateral nodal disease on final pathology. Occult nodal disease was defined as the presence of contralateral pathologic nodal metastases when there was no pre-operative suspicion on imaging of contralateral nodal disease. Statistical analyses were conducted using SAS 9.3 and R. For categorical variables and continuous variables, the Fisher exact and Kruskal Wallis tests were respectively used. Sensitivity, specificity, negative predictive value and positive predict value including 95% CIs were calculated using the publically available MedCalc© software (MedCalc.org).

Results

Study population

In total, there were 32 patients who met inclusion criteria, including 27 men and 5 women. The average age for included patients was 62.5 years (SD 10.7 years). The clinical, radiographic, and pathologic characteristics for the study population are displayed in Tables 1 and 2**.** There were 12 (37.5%) tonsil primary and 19 (59.4%) base of tongue primary tumors. Seventy-five percent of patients were p16+. Regarding T category, 40.6% were pT1 and 59.4% were pT2. The average tumor size was 2.23 cm.

Occult contralateral nodal disease

In total, there were 2 patients of 27 with radiographically negative contralateral necks that had positive nodes on final pathology, with a subsequent occult nodal disease rate of 7.4%. One of these patients was a radiographically T2N1 p16+ tonsil cancer 7 mm from midline, and the other was a radiographically T4a (deep tongue muscle) N2b p16- base of tongue primary at the midline. The occult nodal disease rate in the p16+ cohort was 5% (1/20). Radiographic T category, pathologic T category, distance to midline and primary subsite were not significantly associated with occult contralateral nodes. radiographic T category, pathologic T category, and primary subsite (see Table 3).

Contralateral nodal disease

The overall incidence of pathologically positive contralateral nodes was 3/32 (9.4%). For tonsil and base of tongue primary respectively, there were 1/12 (8.3%) and 2/19 (10.5%) positive contralateral nodes. One patient with preoperatively predicted contralateral nodal disease confirmed on pathology had p16+ BOT radiographically T1N2 disease 5 mm from the midline (single contralateral node only on final pathology). Distance to midline was only available for 19/32 patients (59%). Of those with available data, the average distance to midline was 3.3 mm (range 0–8 mm) with 9 of 19 tumors located at the midline. Five patients had preoperatively radiographically suspicious nodes in the contralateral neck, but only one of these patients had pathologically positive contralateral nodes. The sensitivity, specificity, positive

Table 1
Study population patient characteristics and radiographic features. SD = standard deviation; ENE = extranodal extension; CT* = CT neck with contrast.

Patient characteristics	N = 32 (%)
Gender	
Female	5 (16)
Male	27 (84)
Age surgery	
Mean (SD)	62.5 (10.7)
Median (Min-Max)	62 (39–87)
Smoking status	
Active smoker	7 (22)
Ex-smoker	15 (47)
Never smoker	10 (31)
Primary subsite	
Base of tongue	19 (59)
Pharyngeal wall	1 (3)
Soft palate	0 (0)
Tonsil	12 (38)
p16 status	
Negative	6 (20)
Positive	24 (80)
Not reported	2
Radiographic (r) characteristics	N = 32 (%)
rT	
not visible	0 (0)
T1	9 (29)
T2	17 (55)
T3	1 (3)
T4a	4 (13)
Not reported	1
rN	
rN0	2 (6)
rN1	20 (62)
rN2	4 (12)
rN3	1 (3)
rN3b	5 (16)
Distance to midline	
Mean (sd)	0.3 (0.3)
Median (Min, Max)	0.5 (0,0.8)
Not reported	13
rENE	
No	9 (28)
Yes	23 (72)
Modalities	
PETCT alone	2 (6)
PETCT + CT*	13 (41)
PETCT + MRI	1 (3)
CT alone	16 (50)

Table 2
Pathologic findings. PNI = perineural invasion, LVI = lymphovascular invasion; ENE = extranodal extension.

Pathology	N = 32 (%)
PNI	
No	19 (90)
Yes	2 (10)
Missing	11
LVI	
No	17 (81)
Yes	4 (19)
Missing	11
pT	
0	0 (0)
1	13 (41)
2	19 (59)
pN	
pN0	5 (16)
pN1	19 (59)
pN2	4 (19)
pN2b	1 (3)
pN3b	3 (9.4)
pENE	
No	19 (61)
Yes	12 (39)
Not reported	1
pN laterality	
N0	5 (16)
Ipsilateral only	24 (75)
Bilateral	2 (6)
Contralateral only	1 (3)

Table 3
Sensitivity, Specificity, Negative Predictive Value (NPV) and Positive Predictive value (PPV) of preoperative imaging for contralateral nodal disease in oropharyngeal carcinoma patients treated with transoral robotic surgery and bilateral neck dissections.

	Sensitivity	Specificity	NPV	PPV
Entire cohort (32)	33.3%	86.2%	93%	20%
p16+ cohort (24)	50%	86%	95%	25%

predictive value, and negative predictive value of imaging for contralateral nodes were 33.3% (95% CI 0.84% to 90.6%), 86.2% (95% CI 68.3% to 96.1%), 20% (95% CI 3.8% to 61.2%) and 93% (95% CI 84.72% to 96.57%), respectively (Table 2). In the subgroup of patients that were p16+, there were 2/24 (8.3%) patients with positive contralateral nodes. The sensitivity, specificity, positive predictive and negative predictive values of imaging for contralateral nodes in the p16+ population was 50% (95% CI 1.3% to 98.7%), 86% (65.1% to 97.1%), 25% (5.5% to 65.5%) and 95% (82.5% to 98.7%), respectively.

Discussion

The current study aims to determine the rate of occult contralateral nodal disease in pT1-T2 oropharyngeal cancers treated with TORS and bilateral neck dissections. Few studies have been published in the era of HPV+ OPSCC describing the rate of nodal disease in the contralateral neck, and fewer still the occult contralateral nodal disease rate. The rates in available studies are variable and methodologies are heterogeneous.

Shoustari et al. examined 41 T1-2 tonsil cancers treated from 2002 to 2009. They found that of the 41 patients, 7 (17.0%) presented with contralateral cervical nodal disease, all of which were p16+. They also reported that the rate of contralateral nodal disease was 25% for p16+ tumors and 0% for patients with p16- tumors [11]. In 2006, Lim et al. examined 52 patients undergoing elective contralateral neck dissections for oropharyngeal cancers, including all subsites and T category. They reported a 21% occult contralateral nodal disease rate (11/52) [3]. Patients were treated between 1992 and 2003, predating the emergence of HPV as the predominant causative agent, and they included tumors resected through both transoral and mandibulotomy approaches. The occult rate of contralateral nodal disease was significantly higher in their population compared to the cohort in the current study, which could be attributed to their inclusion of a significant portion of T3/T4 tumors.

More recent studies included HPV positivity as a distinguishing factor when examining rates of bilateral/contralateral nodal metastases in OPSCC. Tritter et al. examined 178 patients retrospectively with OPSCC and reported that there was no difference in the incidence of bilateral/contralateral nodal disease between HPV+ and HPV−

patients (24.6% vs. 29.1%, P = 0.53). They also reported, similar to other authors, that T4 disease and base of tongue primary have an increased the risk of bilateral/contralateral nodal disease [9]. This study determined nodal positivity mostly by imaging and only had minority of patients with pathologic confirmation.

A recent study of the National Cancer Database by Kato et al. evaluated 15,517 patients with oropharyngeal cancer for predictors of contralateral or bilateral nodal disease. They reported that there was no significant difference between HPV+ and HPV− patients in the incidence of bilateral/contralateral nodal disease (14.2% vs. 14.5%, p = 0.769) in univariable analysis. However, after adjusting for other baseline differences between HPV positive and negative cohorts, HPV positive status emerged as a an independent predictor of bilateral/contralateral nodal disease (OR 1.26 99% CI 1.1–1.44); along with base of tongue primary site (OR 2.15 99% CI 1.88–2.45); poorly differentiated tumor (OR 1.72 99% CI 1.2–2.46) and T4 classification (OR 6.65 99% CI 5.24–8.28) [8]. Overall, they reported rate of contralateral or bilateral nodal disease in 14.2% and 14.5% of HPV+ and HPV− patients, respectively, excluding N3 disease.

Variable methodology amongst studies may also explain the differences in reported rates of bilateral/contralateral nodal disease, including lack of pathologic confirmation and variations in choice of imaging modality utilized. The radiographic positivity rate for the contralateral neck was 15.6%, higher than the pathologic contralateral positive nodal rate (9.4%) in the current study, illustrating the difficulty in determining the true contralateral nodal disease rate in patients who receive non-surgical treatment. This is the first study to the authors' knowledge specifically examining occult contralateral nodal disease rates in patients with early pT category OPSCC of all subsites undergoing exclusively TORS with pathologic confirmation.

As a surrogate for contralateral nodal positivity in OPSCC patients undergoing non-surgical therapy, one may examine contralateral failure rates in OPSCC patients treated with ipsilateral only radiation. Very low contralateral failure rates have been reported in a number of studies where ipsilateral-only radiation therapy was used to treat lateralized OPSCC. Hu et al performed a prospective phase II trial for ipsilateral only radiation for well-lateralized T1-3 OPSCCs (excluding tongue base), including N2b patients. Of great clinical significance, they reported a 0% contralateral neck failure rate at 3 years [11]. They also performed a thorough review of the literature demonstrating a contralateral failure rate of 0–2% for most studies including T1-T2N0-N2b patients undergoing ipsilateral only treatment [12]. As a precursor to that clinical trial, O'Sullivan et al published a contralateral regional failure rate of 3.5% for ipsilateral only radiation for T1-2 tonsil cancers. Patients were excluded if the tumor was < 1 cm from the midline, involved > 1 cm depth of invasion into the tongue base, had advanced T category disease, and greater than N1 disease. They found that lesions involving both the soft palate and tongue base had a 20% risk for contralateral nodal failure, and should not be considered for ipsilateral only treatment in the future [13]. Dan et al. in 2015 reported 1 contralateral failure that was successfully salvaged in 61 T1-3 N0-3 well lateralized tonsil cancers [14]. Though many of the patients included in these studies also received systemic chemotherapy, the overall very low rate of contralateral failures in ipsilateral-only radiation tonsil cancers reflects the low occult nodal disease rate reported in the current study.

Occult nodal disease rates are predicated on the sensitivity and specificity of preoperative imaging. In the current study, the sensitivity, specificity, positive predictive value, and negative predictive value of preoperative imaging for contralateral nodes were 33.3%, 86.2%, 20% and 93%, respectively, and were slightly higher in the p16+ subgroup. As noted previously, the confidence intervals for those values are quite broad, reflecting the difficulty of precise calculations with such a small number of occult contralateral nodes. In previously published reports, the sensitivities and specificities of PETCT in the per-neck-side diagnosis of nodal disease in head and neck cancers are also variable, from 65% to 95% respectively each [15–20]. Few studies have explicitly examined the effectiveness of detecting *contralateral* nodes. The sensitivity is potentially significantly lower than previous reports due to a very low number of patients in the current study with positive contralateral disease. The current study included heterogeneous imaging modalities, but this often reflects the realistic nature of clinical practice.

There are a number of limitations to the current study, including the relatively small patient population and retrospective nature of the study. Indications for bilateral neck dissections were not specifically sought. Depending on a surgeon's clinical practice, indications for contralateral neck management may include radiographically suspicious contralateral nodes, presence or burden of ipsilateral nodal disease, base of tongue primary, soft palate involvement, proximity to midline and other patient and tumor specific factors. Base of tongue tumors were included with other well-lateralized sites. Base of tongue has bilateral lymphatic drainage similar to supraglottic cancers, and therefore most centers tend to manage bilateral necks early in these cases. Most studies that have examined outcomes for ipsilateral radiation alone excluded base of tongue primary sites for these reasons. Lastly, given the small sample size, there is a relative lack of precision around the estimates for diagnostic test properties (sensitivity, specificity, negative predictive value and positive predictive value). As we expected the sensitivity for axial imaging to predict occult disease was low and the specificity was high. These data suggest that axial imaging are not useful as a rule out test, but may be useful as a rule in test. However, to have a precise estimate for these values would require much larger sample size that is beyond the scope of this study.[21] For precise estimates of these values a larger study evaluating diagnostic test properties would be needed.

Bilateral neck irradiation had traditionally been employed for patients with advanced stage OPSCC [22,23], but given the above findings, the paradigm may be shifting towards more selective treatment fields to the ipsilateral neck only, even in N2b (AJCC 7th Ed.) disease. [12] The current study illuminates that the *occult* contralateral nodal disease rate in a surgically treated population including all subsites of OPSCC is < 10%, and < 5% in p16+ cases. Given such low rates of occult nodal disease in the contralateral neck in the current report, ipsilateral-only treatment could potentially be considered in select cases. Larger patient population studies are warranted.

Conclusion

The occult contralateral nodal metastatic rate and the overall contralateral metastatic rate were very low in this multicenter population with pT1-2 OPSCC undergoing TORS/bilateral neck dissections. This study examined a limited number of patients, and greater numbers are warranted prior to de-escalation of contralateral neck management in surgically-treated OPSCC.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding

NO funding sources were obtained for this publication.

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