

CLINICAL INVESTIGATION

Head and Neck

## FREEDOM FROM LOCAL AND REGIONAL FAILURE OF CONTRALATERAL NECK WITH IPSILATERAL NECK RADIOTHERAPY FOR NODE-POSITIVE TONSIL CANCER: RESULTS OF A PROSPECTIVE MANAGEMENT APPROACH

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**Purpose:** To review the outcomes of a prospective management approach using ipsilateral neck radiotherapy in the treatment of node-positive squamous cell carcinoma of the tonsil with a well-lateralized primary lesion.

**Methods and Materials:** Between August 2003 and June 2007, 20 patients who presented with squamous cell carcinoma of the tonsil, without involvement of the base of the tongue or midline soft palate, and with Stage N1-N2b disease were prospectively treated with radiotherapy to the primary site and ipsilateral neck. In addition, 18 patients received concurrent chemotherapy. The actuarial freedom from contralateral nodal and in-field progression was determined. Acute and late toxicity were prospectively evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, and Radiation Therapy Oncology Group criteria.

**Results:** The nodal disease was Stage N1 in 4 patients, N2a in 3 patients, and N2b in 13 patients. At a median follow-up 19 months (range, 12–40), no in-field or contralateral nodal recurrences had been observed. The 2-year freedom from distant metastasis rate was 87.4%. The actuarial 2-year disease-free and overall survival rates were both 79.5%. Late Radiation Therapy Oncology Group grade 2 xerostomia occurred in 1 patient (5%). No late Grade 3 or greater toxicity was observed. No patient was feeding tube dependent at their last follow-up visit.

**Conclusion:** In carefully selected patients with node-positive, lateralized tonsillar cancer, treatment of the ipsilateral neck and primary site does not appear to increase the risk of contralateral nodal failure and reduces late morbidity compared with historical controls. Although the outcomes with ipsilateral radiotherapy in the present series were promising, these findings require longer follow-up and validation in a larger patient cohort. © 2009 Elsevier Inc.

Tonsil, Squamous cell carcinoma, Node-positive, Ipsilateral, Radiotherapy.

### INTRODUCTION

Because of the well-lateralized location of the tonsils compared with other head-and-neck mucosal sites, squamous cell carcinomas arising at this site tend to metastasize primarily to the ipsilateral cervical lymph nodes. Studies analyzing the patterns of failure in tonsillar cancer have suggested that regional failure in the contralateral neck is rare. In a series of 384 patients with cancer of the tonsil treated at Washington University with radiotherapy (RT) to the tonsil and bilateral neck alone or similar RT combined with surgery, contralateral neck failure occurred in 5.8% of patients treated with RT alone and 4.8% of patients treated with combined surgery and RT (1). Of patients treated with tonsillectomy and en bloc neck lymph node dissection followed by adjuvant RT, only 2.3% experienced contralateral regional failure. On the basis of these observations, it was hypothesized that ipsilateral RT

could decrease acute and late radiation toxicity by sparing the contralateral structures, without compromising locoregional control.

O'Sullivan *et al.* reported on the Princess Margaret Hospital experience using ipsilateral-only RT. The investigators reported contralateral neck failure in 3.5% of patients treated with RT to the primary site and ipsilateral neck only (2). The risk of contralateral failure was strongly associated with involvement of the base of the tongue and palate by the primary tumor. Node-positive disease was also associated with contralateral neck failure on univariate analysis; however, the patients with node-positive disease presented with more extensive primary lesions, potentially biasing the analysis. Because of an increased rate of contralateral failures observed with node-positive disease, these investigators (2) and others (3) have recommended against routine use of ipsilateral RT for these patients. Treatment to the bilateral neck

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has been the accepted standard of care for patients presenting with ipsilateral nodal disease, in particular Stage N2.

Several clinically relevant advances in RT delivery and imaging have occurred since the first studies of ipsilateral tonsil RT were reported. Intensity-modulated RT (IMRT) as a tool for normal tissue sparing and, in particular, parotid gland sparing, has been widely adopted in the United States in the management of head-and-neck cancer. One argument for the continued inclusion of the contralateral neck in high-risk tonsil cases with an ipsilateral node-positive presentation is that morbidity is low with IMRT and parotid sparing can be achieved (4). Although IMRT does decrease the incidence of high-grade late xerostomia compared with bilateral RT using conventional techniques, the incidence and severity of acute skin and mucosal toxicities are similar or, in many cases, greater than with conventional three-dimensional technique (5). Also, low-grade late xerostomia remains common (6). Additionally, advances in radiographic (magnetic resonance imaging) and nuclear (positron emission tomography [PET]) imaging have made staging and subsequent follow-up more accurate, allowing for better detection of occult contralateral lymph node metastases (7, 8).

The question posed in the present study was whether the contralateral neck can be safely spared in selected patients with well-lateralized tonsillar cancer presenting with ipsilateral node-positive disease. We reviewed our multidisciplinary treatment policy used in selected patients with node-positive tonsillar cancer, well-lateralized primary lesions, and no involvement of the base of the tongue or palate, who were treated with ipsilateral RT. We report the rates of contralateral neck failure and toxicity in patients undergoing this approach.

## METHODS AND MATERIALS

### *Patients*

Selected patients with Stage T1-T3 squamous cell carcinoma of the tonsil, without involvement of the base of the tongue or soft or hard palate, and with positive ipsilateral cervical lymph nodes (Stage N1-N2b) were treated with ipsilateral external beam RT. These patients had no evidence of contralateral cervical lymphadenopathy or distant metastatic disease on the pretreatment staging evaluation. Treatment was delivered between August 2003 and June 2007.

### *Staging evaluation*

The patients underwent evaluation and disease staging in a multidisciplinary head-and-neck clinic that included a surgeon, radiation oncologist, and medical oncologist. One patient was referred from a university hospital after undergoing tonsillectomy and ipsilateral neck dissection for postoperative management but was then seen in the multidisciplinary head-and-neck clinic for treatment recommendations. All patients had undergone computed tomography (CT) of the head and neck. Direct examination under anesthesia or flexible nasopharyngoscopy was performed to rule out involvement of the base of the tongue or midline palate. Pretreatment fluorodeoxyglucose-PET scans were obtained in all cases to rule

out occult contralateral neck lymphadenopathy and distant metastatic disease.

### *Radiotherapy*

The patients were treated using either three-dimensional conformal RT ( $n = 11$ ) or IMRT ( $n = 9$ ). The clinical target volumes (CTVs) were defined as follows: microscopic CTV included the sites of gross disease, with margins for microscopic disease extension and electively treated nodal volumes and the boost CTV included areas of gross disease. The planning target volume (PTV) was generated by uniformly expanding the CTV by 5 mm. In 19 patients, the microscopic PTV was treated to 50 Gy in 25 fractions. Subsequently, a cone-down boost was delivered to the PTV boost. The total dose to the primary tumor or tumor bed was 60–66 Gy for patients treated in the adjuvant setting and 66–70 Gy for patients treated to gross disease. The involved lymph node regions treated after neck dissection received a median of 60 Gy (range, 59.4–60). Those treated before neck dissection received a median of 56 Gy (range, 50–60). Patients treated to gross nodal disease received 65–70 Gy. One patient underwent IMRT with a simultaneous integrated boost to the PTV boost to a dose of 67.2 Gy in 2.1 Gy/fraction and 52.8 Gy in 1.65 Gy/fraction to the microscopic PTV. For patients treated using IMRT, the entire ipsilateral neck was treated using the IMRT plan. For patients treated using three-dimensional conformal RT, half-beam blocked lateral fields were used to treat the primary site and superior cervical lymph nodes and were matched inferiorly to a half-beam blocked anterior neck field.

The dose constraints were as follows: the contralateral parotid was limited to a mean dose <20 Gy, the spinal cord was limited such that 1% could not receive >50 Gy, and the mandible was limited to <1% receiving 75 Gy. The contralateral neck was limited to a maximal dose of <20 Gy. Axial CT images and coronal reconstructions for all RT plans were reviewed to ensure that the 20-Gy isodose did not extend into the contralateral neck. The dose to the ipsilateral parotid gland was not constrained.

### *Surgery*

Of the 20 patients, 16 (80%) were treated with tonsillectomy and 14 had undergone ipsilateral neck dissection before ipsilateral RT. Most patients treated with initial surgery had either positive microscopic margins ( $n = 16$ ) and/or extracapsular nodal extension ( $n = 9$ ). Patients with Stage N2a disease or large (>3 cm) Stage N2b disease underwent neoadjuvant chemoradiotherapy followed by planned selective neck dissection. Four patients were treated with this approach. One patient with a large Stage T3 primary tumor was treated with neoadjuvant chemoradiotherapy followed by tonsillectomy. No patients underwent surgery of the contralateral neck.

### *Chemotherapy*

Of the 20 patients, 19 received chemotherapy, with 18 receiving concurrent platinum-based chemoradiotherapy. Chemotherapy was included for high-risk features, including Stage N2 disease, positive microscopic margins after surgery, and/or extracapsular extension of lymph nodes. Concurrent chemotherapy involved either cisplatin every 3 weeks or weekly doublet chemotherapy with a platinum and taxane. Two patients received weekly cetuximab, in addition to concurrent chemoradiotherapy. Two patients were not considered medically fit for concurrent chemoradiotherapy. One received induction cisplatin chemotherapy (100 mg/m<sup>2</sup> every 3 weeks) followed by RT, and one was treated with RT alone.

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