

Scientific Article

# Hazards of sparing the ipsilateral parotid gland in the node-positive neck with intensity modulated radiation therapy: Spatial analysis of regional recurrence risk

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## Abstract

**Purpose:** The practice of deliberately sparing the ipsilateral parotid gland with intensity modulated radiation therapy (IMRT) in patients with node-positive head and neck cancer is controversial. We sought to compare the clinical outcomes among consecutive cohorts of patients with head and neck cancer who were treated with differing strategies to spare the parotid gland that is ipsilateral to the involved neck using IMRT.

**Methods and materials:** A total of 305 patients were treated with IMRT for node-positive squamous cell carcinoma of the head and neck. The first 139 patients were treated with IMRT whereby the ipsilateral parotid gland was delineated and intentionally designated as an avoidance structure during planning. The subsequent 166 patients were treated by IMRT without the deliberate sparing of the ipsilateral parotid gland.

**Results:** The 2-year estimates of overall survival, local-regional control, and distant metastasis-free survival were 84%, 73%, and 87%, respectively. The 2-year estimates of overall survival were 77% and 86% among patients who were treated by IMRT with and without the sparing of the ipsilateral parotid gland, respectively ( $P = .01$ ). The respective rates of 2-year regional control were 76% and 90% ( $P < .001$ ). A trend was observed between increased nodal burden in the ipsilateral cervical neck and the likelihood of regional failure for both groups. A spatial evaluation revealed a significantly higher incidence of marginal failures and true misses in the cohort of patients who underwent IMRT with the sparing of the ipsilateral parotid gland.

**Conclusion:** Caution is urged when using IMRT to spare patients' parotid gland on the involved side of neck disease. Our study showed a significantly higher preponderance of regional failure,

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Conflicts of interest: None.

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which highlights the need for careful patient selection and consideration of clinical and pathological factors that influence the likelihood of disease recurrence in the ipsilateral neck.

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## Introduction

The ability of intensity modulated radiation therapy (IMRT) to reduce xerostomia and improve health-related quality of life for patients with head and neck cancer has been well established.<sup>1</sup> Although these benefits, which are attributed to the creation of highly conformal dose distributions to desired targets while limiting radiation to the parotid gland, have led to the widespread adoption of IMRT in the management of head and neck cancer, they come at the expense of potentially underdosing areas at risk for disease recurrence and particularly those that are immediately adjacent to this designated organ at risk (OAR). Indeed, whether parotid gland-sparing IMRT can be safely performed (i.e., without placing patients at risk for marginal misses at the parotid gland-level II cervical nodal interface) on the involved, node-positive neck, especially in the setting of high-volume and/or bulky disease, is uncertain with limited data available to guide practice.

At our institution, the delineation and intentional sparing of both parotid glands was performed historically on all patients, even for those with node-positive disease. In August 2013, an unplanned interim review of data for all patients who were treated with IMRT was conducted and the practice of sparing the parotid gland on the involved side was abolished. The purpose of this study was to compare the patterns of failure and specifically regional recurrences among patients with positive nodes who were treated with IMRT for head and neck cancer based on whether the parotid gland on the side of the involved neck was attempted to be spared or not.

## Methods and materials

### Patients

This study was approved by the institutional review board at our institution prior to the collection of all patient information. The medical records of 305 consecutive patients who were treated with IMRT for stage III or IV squamous cell carcinoma of the oropharynx, oral cavity, larynx, and hypopharynx and that required unilateral or bilateral irradiation of the neck between April 2011 and January 2016 were included in this study. All patients were retrospectively staged in accordance with the 2009 American Joint Committee on Cancer staging classification. Positron

emission tomography (PET) scans were obtained at the time of diagnosis in 229 patients (75%) including all patients who were treated with primary IMRT.

A total of 157 patients (51%) were treated with IMRT by definitive intent. The remaining 148 patients (49%) were treated with IMRT after gross surgical resection. The type of surgery depended on the primary site, extent of disease, cosmetic considerations, and discretion of the surgeon. No definite policy existed with regard to adjunct therapy but in general, patients were referred for postoperative radiation when high-risk features were present such as pathological T3 to T4 disease, multiple lymph node involvement, extra-capsular extension, and perineural or lymphovascular space invasion, or when there was uncertainty about the completeness or adequacy of the excision on the basis of intraoperative and pathological findings. Because our intent was to analyze the regional recurrence patterns among patients who were and were not treated with parotid gland-sparing IMRT to a high-risk involved neck, only patients with clinically and/or pathologically node-positive cancer were included.

### Simulation and target volume delineation

At the time of simulation and prior to the daily treatment, the head, neck, and shoulders were immobilized in a hyperextended position by using a perforated, thermoplastic head mask with the neck supported on a Timo cushion (S-type; Med-Tec, Orange City, IA) that was mounted on a carbon fiber board (S-type; Med-Tec) that allowed patient positioning to be indexed. For some patients, the hyperextension of the neck was not possible because of discomfort and a neutral position was selected at the discretion of the physician.

At the time of computed tomography (CT) simulation, the isocenter was placed approximately at the center of the gross tumor volume (GTV). Axial images with a contiguous, 3-mm slice thickness were obtained for planning and transferred into a contouring workstation where a delineation of the target and normal tissue structures were performed. Intravenous contrast was not mandatory but routinely used during the time course of this study.

For the patients who were treated with definitive IMRT, the GTV was specified as the extent of the tumor as demonstrated by preoperative imaging and a physical examination including an endoscopy. Grossly positive lymph nodes were defined as lymph nodes that were greater than 1 cm, those with a necrotic center, or with a standardized

uptake value (SUV) greater than 3 on PET scans. The high-risk clinical target volume (CTV-H) was defined as the GTV plus a margin of 0.5 to 1 cm to account for microscopic disease spread. The low-risk clinical target volume (CTV-L) included all uninvolved areas in the cervical neck and supraclavicular fossa. In some cases, an intermediate-risk clinical target volume (CTV-I) was devised to include the ipsilateral neck. For patients who were treated with IMRT postoperatively, the CTV-H was defined as the surgical tumor bed that was at risk to harbor microscopic residual disease and the ipsilateral neck. The CTV-L in these cases encompassed the uninvolved contralateral neck.

The consensus guidelines that were endorsed by the Radiation Therapy Oncology Group, European Organization for Research and Treatment of Cancer, Danish Head and Neck Cancer Group, Groupe d'Oncologie Radiothérapie Tête et Cou, and National Cancer Institute of Canada were routinely used to assist in clinical target volume (CTV) delineation.<sup>2</sup> The planning target volume (PTV) contained an automated 0.3 to 0.5 cm expansion of the CTV surfaces to account for patient setup error. An extended-field IMRT technique was used for all patients. Decisions on margin expansions were made at the discretion and comfort level of the treating physician.

### Dose specification and intensity modulated radiation therapy planning

For patients who received definitive IMRT, treatment plans were designed to deliver a dose of 70 Gy to 95% or more of the PTV-H in 33 to 35 fractions. For postoperative patients, plans were designed to deliver a dose of 60 to 66 Gy to at least 95% of the PTV-H in 30 to 33 fractions. For patients who were both definitively and postoperatively treated, the PTV-L was specified to receive a prophylactic dose of 54 to 56 Gy with a simultaneous-integrated boost IMRT technique. The dose to the PTV-I ranged from 56 to 63 Gy.

The goal of IMRT planning was to deliver the prescription dose to 95% of the respective PTVs. Treatment goals were to generate a plan with the prescription isodose lines that conform to the defined PTVs while minimizing the dose that is delivered to the specified OARs including the spinal cord, brainstem, optic chiasm, cochlea, and parotid gland. Other OARs that were commonly delineated at the discretion of the physician included the oral cavity, pharyngeal constrictor muscles, cricopharyngeal inlet, larynx, and brachial plexus. IMRT planning was performed with heterogeneity corrections using a convolution/superposition-based dose calculation algorithm. Plans were normalized to achieve adequate target coverage without excessive dose inhomogeneity. Daily image guided radiation therapy images were acquired volumetrically using either kV cone beam or mV fan beam to assist with patient positioning.

### Parotid gland-sparing intensity modulated radiation therapy

Between April 2011 and August 2013, the parotid gland on the ipsilateral side was contoured and delineated as an OAR. This structure was spared with a constraint goal of mean < 26 Gy (and/or V30 < 50%) and 139 patients were deliberately treated with ipsilateral parotid gland-sparing IMRT. In most cases, underdosage of the region near the parotid gland was allowed to meet the constraint of this OAR even while maintaining a 95% coverage to the elective PTV areas.

Beginning in August 2013, an unplanned interim review of our data for those patients who were treated with IMRT was conducted and this policy was revised such that parotid gland-sparing was no longer performed on the ipsilateral side. The subsequent 166 patients were treated in accordance with this guideline. Notably, for patients with N2c disease that involved the level II lymph nodes, neither parotid gland was delineated and spared. Both the deep and superficial lobes of the parotid gland were included in the OAR when it was delineated.

### Endpoints and statistical analysis

Patients were asked to return for a follow-up visit 2 to 3 weeks after completion of the radiation therapy and then every 2 to 3 months for the first year, 4 to 6 months for the second year, and then annually thereafter. Local control was deemed to be attained if there was no evidence of a tumor at the primary site on the basis of clinical and radiographic findings at the time of the follow-up visit. Regional failure was recorded separately if there was evidence of a cervical or supraclavicular mass that was distinct from the primary site.

Patients who had persistent disease either clinically or radiographically after definitive IMRT were referred for salvage neck dissection. The salvage of recurrences was not taken into account in the evaluation of local-regional control. Patient follow-up was reported up to the date the patients was last seen at the clinic or up to the date of death. All events were measured from the last day of radiation therapy. The median follow-up time among patients who were treated with and without ipsilateral parotid gland-sparing was 30 months (Range, 6-60 months) and 22 months (Range, 4-37 months). Actuarial estimates of local-regional control, distant metastasis-free survival, and overall survival were calculated using the Kaplan-Meier method. A comparison of the proportion of patients in each baseline subgroup was performed using the  $\chi^2$  test.

To better characterize the spatial properties of each regional recurrence, the original IMRT plans were retrieved in Digital Imaging and Communications in Medicine format and deformable image registration was employed using MIM (MIM Software, Inc., Cleveland, OH) to fuse the PET scans

that were obtained at the time of recurrence to the pre-treatment planning CT datasets. The recurrent tumor volume ( $V_{\text{recur}}$ ) that represented each regional recurrence was subsequently identified on axial imaging using the 50%  $SUV_{\text{max}}$  threshold from the PET scan with the user blinded to the original target volumes and isodose distribution.

After  $V_{\text{recur}}$  was identified on the planning CT datasets, the dose of radiation that was received by  $V_{\text{recur}}$  was calculated and analyzed using dose-volume histograms. The criteria proposed by Dawson et al were used to classify recurrences into infield in which  $V_{\text{recur}} \geq 95\%$  was within the 95% isodose, marginal miss if 20% to 95% of  $V_{\text{recur}}$  was within the 95% isodose, or true miss if  $< 20\%$  of the  $V_{\text{recur}}$  was inside the 95% isodose.<sup>3</sup> For each  $V_{\text{recur}}$ , the mean dose, D90 (i.e., dose delivered to 90% of the  $V_{\text{recur}}$ ) and V100 (i.e., percentage volume encompassed by the prescription isodose line) were determined.

## Results

### Patients

Table 1 outlines the clinical and disease characteristics of the patient population that was treated with IMRT according to whether ipsilateral parotid-sparing was performed. There was no difference in the baseline characteristics between the two groups with the exception of concurrent chemotherapy usage ( $P < .001$ ). The median age was 60 years (Range, 22-96 years). Concurrent chemotherapy was administered to 183 patients (60%). For patients who were treated with definitive IMRT, the distribution of T stage was as follows: 11% of patients were T1, 26% were T2, 27% were T3, and 36% were T4. Clinical N stage was as follows: 12% of patients were N1, 28% were N2a, 30% were N2b, 25% were N2c, and 5% were N3. For patients who were treated with postoperative IMRT, the distribution of pathological T stage was as follows: 36% of patients were T1, 33% were T2, 21% were T3, and 10% were T4. The pathological N stage was as follows: 14% of patients were N1, 32% were N2a, 37% were N2b, 13% were N2c, and 4% were N3. A total of 369 hemi-necks with N-positive disease were used for this analysis.

### Survival and disease control

Of the 305 patients, 270 patients were alive at the time of the last follow-up, which yielded a 2-year estimate of overall survival of 84%. As illustrated in Figure 1a, the 2-year estimates of overall survival were 77% and 86% among patients who were treated by IMRT with and without parotid gland-sparing, respectively ( $P = .01$ ).

A total of 67 of 305 patients experienced local-regional recurrence, which yielded a 2-year estimate of local-regional control of 73%. The median time to local-regional recurrence for all patients who were treated with IMRT was

**Table 1** Clinical and disease characteristics

Characteristic	PS	(%)	No PS	(%)
Primary site ( $P = .60$ )				
Oropharynx	74	(53)	85	(51)
Oral cavity	41	(30)	55	(33)
Larynx/hypopharynx	24	(17)	26	(16)
T-classification ( $P = .56$ )				
T1	28	(20)	28	(17)
T2	39	(28)	46	(28)
T3	37	(27)	47	(28)
T4	35	(25)	45	(27)
N-classification ( $P = .41$ )				
N1	16	(12)	24	(15)
N2a	45	(32)	46	(44)
N2b	42	(30)	60	(36)
N2c	31	(22)	27	(16)
N3	5	(4)	9	(12)
Treatment intent ( $P = .57$ )				
Definitive radiation	69	(50)	88	(53)
Postoperative radiation	70	(50)	78	(47)
Concurrent chemotherapy ( $P \leq .001$ )				
Yes	97	(70)	78	(47)
No	42	(30)	88	(53)
Sex ( $P = .72$ )				
Male	90	(65)	111	(67)
Female	49	(35)	55	(33)
Human papillomavirus status ( $P = .55$ )				
Positive	43	(31)	55	(33)
Negative	40	(29)	51	(31)
Unknown	56	(40)	60	(36)

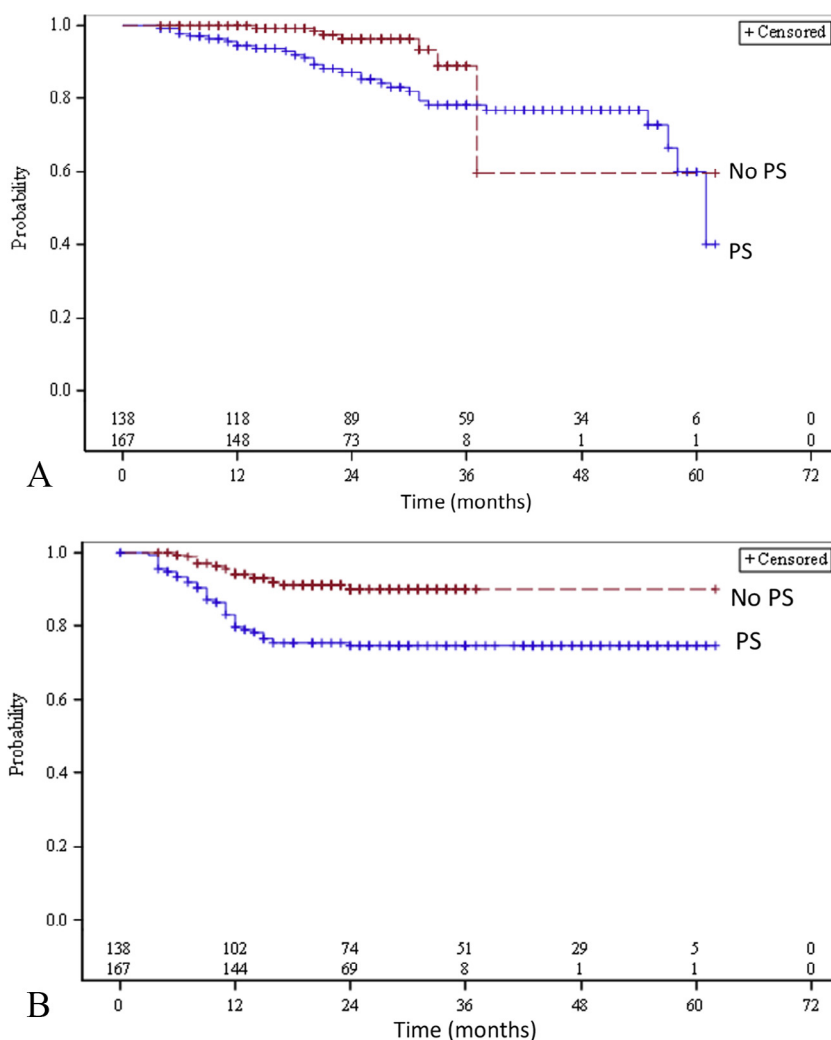
PS, parotid gland-sparing intensity modulated radiation therapy.

10 months (Range, 1-32 months). Fifty-seven of these patients with local-regional recurrences had first events of disease failure and the remaining 10 occurred subsequent to the development of distant metastasis. Thirty-one patients developed distant metastasis, which yielded a 2-year distant metastasis-free survival rate of 87%.

### Neck control

A total of 46 of 67 patients with local-regional recurrence had regional events. As illustrated in Figure 1b, there was a significant difference in 2-year regional control between patients who were treated with ipsilateral parotid gland-sparing and without parotid gland-sparing, respectively (76% vs 90%;  $P < .001$ ). In total, 32 of 139 patients (23%) who were treated with ipsilateral parotid sparing experienced regional failure compared with 14 of 166 patients (8%) who were treated without.

When limiting the analysis to regional recurrences in the nodal station that are immediately adjacent to the parotid gland, the 2-year freedom-from-level-II recurrence rates were 80% and 96% for patients treated with and without ipsilateral parotid gland-sparing IMRT for node-positive disease, respectively ( $P = .01$ ).



**Figure 1** (A) Overall survival according to use of ipsilateral parotid gland-sparing intensity modulated radiation therapy; (B) Local-regional control according to use of ipsilateral parotid gland-sparing intensity modulated radiation therapy.

A subset analysis of the failure rates by disease burden in the ipsilateral hemi-necks with and without parotid gland-sparing IMRT is provided in **Table 2**. There was no difference in 2-year regional control between patients who were treated with primary radiation versus postoperative radiation (84% vs 83%;  $P = .71$ ). There was no difference in 2-year regional control whether an upfront neck dissection was performed or not (85% vs 81%;  $P = .38$ ). The use of concurrent chemotherapy did not influence 2-year regional control (84% vs 85%;  $P = .53$ ). The multivariate analysis results for factors that are predictive of 2-year regional control are outlined in **Table 3**.

**Dosimetric analysis**

Among these 46 patients with regional failures, a total of 49 events were analyzed (3 patients with clinical N2c disease at the time of diagnosis had evidence of bilateral

**Table 2** Regional failures according to use of ipsilateral parotid gland-sparing intensity modulated radiation therapy categorized by disease burden in the node-positive hemi-neck

Hemi-Neck	Ipsilateral parotid-sparing		No ipsilateral parotid-sparing	
	N	Failures (%)	N	Failure (%)
<b>Clinically staged</b>				
1 node, ≤ 3 cm	21	2 (10)	24	1 (4)
1 node, 3-6 cm	30	5 (17)	39	1 (3)
>1 node, 3-6 cm	34	10 (29)	44	3 (7)
>6 cm node	2	2 (100)	6	1 (17)
<b>Pathologically staged</b>				
1 node, ≤ 3 cm	15	1 (7)	16	1 (6)
1 node, 3-6 cm	34	5 (15)	27	2 (4)
>1 node, 3-6 cm	33	11 (33)	38	3 (8)
>6 cm node	3	1 (33)	3	0 (0)

**Table 3** Multivariate analysis of potential factors for regional recurrence

Factor	Strata	2-yr regional control (%)	OR	95% CI	P-value
Age	≤ 60 years	85%	0.83	(0.79, 1.12)	.46
	> 60 years	82%			
Sex	Male	86%	0.80	(0.68, 1.15)	.27
	Female	83%			
T-stage	T0-T2	82%	0.79	(0.56, 1.27)	.39
	T3-4	85%			
Treatment intent	Definitive IMRT	84%	0.88	(0.65, 1.40)	.50
	Postoperative IMRT	83%			
Primary site	Oropharynx	80%	1.07	(0.67, 1.78)	.36
	Nonoropharynx	84%			
HPV status	Positive	89%	1.29	(0.55, 2.23)	.09
	Negative/unknown	81%			
Ipsilateral PS	Yes	76%	1.45	(0.70, 1.92)	.01
	No	90%			

CI, confidence interval; HPV, human papillomavirus; IMRT, intensity modulated radiation therapy; OR, odds ratio; PS, parotid gland-sparing.

recurrences) and classified as follows: 21 events were in-field recurrences (17 in the high-risk ipsilateral cervical neck, 4 in the low-risk contralateral or supraclavicular neck); 19 cases were marginal recurrences (14 in the ipsilateral level II neck and/or parapharyngeal space in the vicinity of spared parotid gland, 4 elsewhere in the ipsilateral cervical or supraclavicular neck; and 1 in the retropharyngeal area), and 9 cases were true misses (5 in the ipsilateral level II neck in the region of the retrostyloid space; 4 elsewhere in the ipsilateral cervical or supraclavicular neck).

Of these 49 regional failures, 40 (82%) occurred without evidence of a local recurrence. Notably, no patient recurred in the contralateral N0 neck in the vicinity of the spared parotid gland. Eighteen of 19 marginal recurrences as well as true misses occurred among the cases that were treated with ipsilateral parotid gland-sparing IMRT. The one case of marginal recurrence that occurred in a patient who was treated without parotid gland-sparing IMRT involved a failure that was lateral to the supraclavicular region. Forty of 49 regional recurrences (82%) were designed to be included in the CTV-I with the remaining 9 cases (18%) that were designed for the CTV-L.

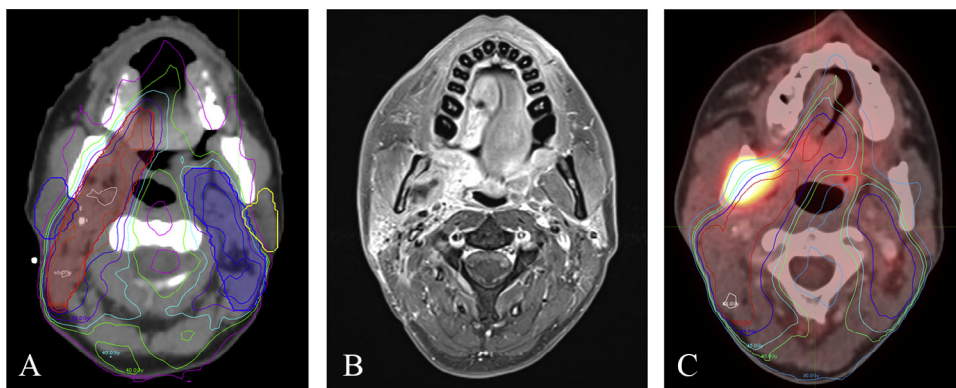
The average mean dose to  $V_{\text{recur}}$  for in-field, marginal, and true misses was 63 Gy, 52 Gy, and 37 Gy, respectively. These values represented 102%, 84%, and 55% of the prescription dose, respectively. Among the 19 marginal recurrences, the mean D90 and V100 were 46 Gy (Range, 39-55 Gy) and 83% Gy (Range, 30%-93%), respectively. Among the 9 true misses, the mean D90 and V100 were 33 Gy (Range, 19-42 Gy) and 11% (Range, 6%-19%).

## Discussion

The results of the present study illustrate the hazards of purposely sparing the parotid gland when disease is located

in the ipsilateral neck. Indeed, the rate of regional recurrence was reduced three-fold (from 23% to 8%) when this practice was abolished after an unplanned interim review at our institution. While our departmental standard has historically been to contour and deliberately spare both parotid glands regardless of the N stage, the recognition that node-positive patients are at a high risk for regional failure in the area of the ipsilateral parotid gland level II cervical interface as illustrated in [Figures 2-4](#) warranted a dramatic shift in practice policy. This was also partly due to an increased awareness that the analysis of dose-volume histogram data fails to provide information with regard to where cold spots may lie spatially in the PTV, even when at least 95% was covered, in accordance with the departmental guidelines. The data presented herein validates the effectiveness of this decision and highlights the importance of careful selection criteria for parotid gland-sparing IMRT.

Of note, early experiences that established the acceptability of parotid gland-sparing IMRT were fairly conservative and generally excluded patients with bilateral nodal involvement due to concerns of underdosing areas in the high level II neck that was adjacent to the parotid gland. In fact, landmark studies by the University of Michigan and the University of Florida limited parotid gland-sparing to the node-negative neck, which likely contributed to the low incidence of marginal misses.<sup>3,4</sup> Moreover, in their early IMRT experience, investigators from Washington University excluded the deep lobe of the parotid gland from the OAR due to concerns for potential failure in the vicinity of the deep lobe at the junction with the level II cervical lymph nodes.<sup>5</sup> In the only randomized study that has been published to date, Nutting et al showed equivalent rates of local-regional control between patients who were treated with IMRT and non-IMRT techniques for head and neck cancer.<sup>6</sup> Notably, none of the patients who were



**Figure 2** Case illustration: (A) A 40 year-old female patient status postpartial glossectomy and right, modified radical neck dissection for pathological T2N2a squamous cell carcinoma of the oral tongue. The patient was treated with postoperative intensity modulated radiation therapy to a dose of 60 Gy with intentional sparing of both parotid glands; (B) Nine months after completion of the adjuvant therapy, the patient palpated a right level II lymph node at the angle of the mandible and a magnetic resonance imaging scan revealed a heterogeneously enhancing lesion that was adjacent to the deep lobe of the ipsilateral parotid gland in the parapharyngeal space; (C) Registration of a positron emission/computed tomography scan that was obtained at the time of the recurrence to her original computed tomography plan confirmed a marginal miss with approximately 30% of the delineated recurring tumor volume within the 95% isodose line.

treated with IMRT had N2c disease and only the contralateral parotid gland was used as an OAR for IMRT optimization purposes with a constraint of < 24 Gy for planning.

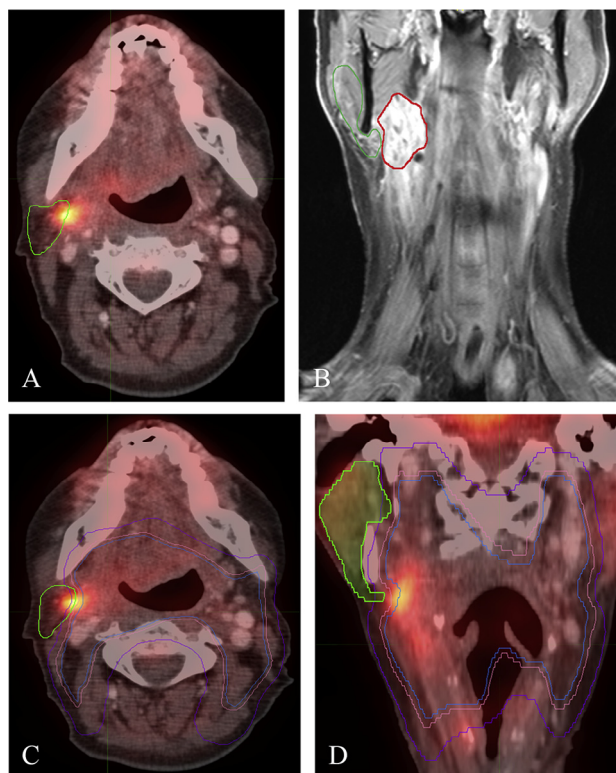
Given the failure patterns that were observed in our study, the importance of designating the CTV in a consistent and reproducible fashion is paramount. Although the consensus guidelines have been utilized to delineate the CTV at the time of IMRT treatment planning, these contouring recommendations are applicable only for patients with N0 low-risk necks.<sup>2</sup> For patients with node-positive disease either upfront or during the postoperative setting, guidelines are sparser but have been proposed by Gregoire et al.<sup>7</sup> A common recommendation is to extend the level II nodal station superiorly to cover the retro-styloid space up to the base of skull in the case of nodal involvement because the ipsilateral parotid gland often overlaps the CTV, which results in anatomical challenges with effective sparing of this OAR. This contrasts to the node-negative neck where the superior extent of the CTV typically ends at the caudal aspect of C1 and results in much more robust sparing of the parotid gland.

In all cases, consensus guidelines recommend the use of the medial edge of the sternocleidomastoid muscle, which is another region in close spatial proximity to the parotid gland, as the lateral border of the levels II, III, and IV lymph nodes. From an anatomical standpoint, aggressive sparing of the parotid gland on the node-positive neck may potentially lead to a compromise of coverage to areas at a high-risk for microscopic disease. This is especially the case given that the tail of the parotid gland essentially abuts to the level II cervical lymph node region near the angle of the mandible, which is an area that is well-known to be the first-echelon drainage site for many tumors of the mucosal

axis. Indeed, the classically defined anatomical boundaries of the parotid gland including the mastoid/styloid processes (posteriorly), masseter muscle (anteriorly), parapharyngeal space (medially), skin surface (laterally), external acoustic meatus (superiorly), angle of the mandible/posterior belly of digastric muscle (inferiorly) all come into close contact with the level II cervical lymph nodes.

The preeminent concern with the aggressive implementation of IMRT at the clinic is the possibility of a geographical miss in regions that are at a high risk for recurrence. Although the published literature to date on IMRT to the head and neck has suggested that marginal recurrences and misses are relatively rare, caution has been raised by some authors with regard to the possibility of overzealous parotid sparing.<sup>8-10</sup> Cannon and Lee documented 3 failures in the vicinity of the spared parotid gland in the involved neck among patients who underwent IMRT.<sup>11</sup> Eisbruch et al similarly reported that nearly all regional recurrences that were observed after IMRT occurred in the ipsilateral neck in the vicinity of level II or III.<sup>12</sup> Bussels et al also reported 6 patients who failed in level II or the parapharyngeal space in the ipsilateral neck after parotid gland-sparing IMRT for head and neck cancer.<sup>13</sup>

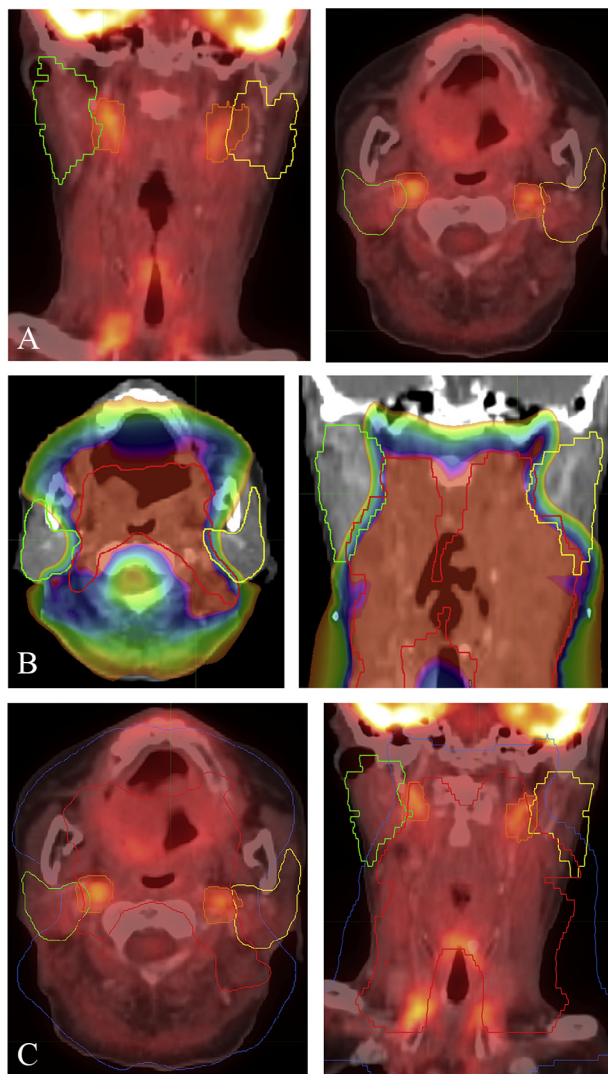
Despite attempts to provide guidelines to improve safety and documentation with respect to the use of IMRT, multiple aspects of IMRT planning are non-standardized.<sup>14</sup> This is particularly the case in the setting of head and neck IMRT where many processes are user-dependent including target delineation, CTV/PTV margin selection, beam angle design, constraint adoption, and prioritization of OAR and PTV coverage. Given that inverse planning typically refers to a computerized optimization scheme, tradeoffs are instituted at multiple levels so that parotid gland sparing can



**Figure 3** Case illustration: (A) A 55-year-old male patient status postchemoradiation to 70 Gy for T3N1 squamous cell carcinoma of the right tonsil who subsequently developed regional recurrence in the ipsilateral neck as shown by positron emission tomography (PET)/computed tomography (CT); and (B) magnetic resonance imaging scan. Notably, the gross tumor volume, situated adjacent to the deep lobe of the ipsilateral parotid gland, at the time of the recurrence (12 months after initial therapy) is shown in maroon and the parotid gland is outlined in green. (C) The original intensity modulated radiation therapy plan that was registered to the PET/CT at the time of recurrence with the blue, pink, and purple lines, which represent the 95%, 90%, and 85% isodose lines, respectively, confirms a marginal miss and the 95% isodose line encompasses approximately 60% of the delineated recurring tumor volume as shown on axial (D) and coronal sections. The ipsilateral parotid gland is delineated in green.

be achieved while maintaining a reasonable degree of coverage to the PTV.

However, as our findings demonstrate, these decisions can have profound consequences with respect to disease outcome. Although the conformity to the CTV of the neck is summarily reviewed through isodose distribution and dose-volume histogram data, the present study shows that aggressive sparing of the ipsilateral parotid gland OAR may come at the expense of inappropriately reduced coverage to the CTV to fulfill the constraints for the parotid gland OAR. Notably, the same aforementioned variabilities in planning and delivery contributed to the primary limitation of this study because elements that are subjected to physician discretion including the choice of expansion margins



**Figure 4** Case illustration: (A) A 67-year-old male patient with disease recurrence at bilateral level II in the cervical neck adjacent to the deep lobes of the parotid glands after previous completion of chemoradiation to 70 Gy approximately 10 months prior for T4N2C squamous cell carcinoma of the base of tongue. (A) A positron emission tomography (PET)/computed tomography (CT) at the time of recurrence illustrates the gross tumor in orange and the right and left parotid glands in green and yellow, respectively. (B) A review of the original intensity modulated radiation therapy plan revealed that bilateral parotid gland sparing was attempted and the red contour illustrates the PTV70 while the parotid glands are depicted in green and yellow. (C) The red, blue, aqua, and orange color washes represent the 100%, 95%, 80%, an 50%, isodose distributions, respectively. Deformable image registration of the original intensity modulated radiation therapy plan onto the PET/CT scans at the time of the recurrence with the red and blue lines represents the 95% and 50% isodose distributions and confirm the marginal misses bilaterally with approximately 90% and 92% of the delineated recurring tumor volume encompassed by the 95% isodose line, respectively, in the vicinity of the spared right and left parotid glands, respectively.



used to create target volumes are impossible to control for. We acknowledge that the heterogeneity of the population with respect to patient, disease, and treatment-related characteristics makes drawing definitive conclusions difficult but our findings are worthy of further hypothesis generation.

Lastly, it is uncertain how much additional clinical gain occurs when both parotid glands are attempted to be spared as opposed to only one. Although studies have clearly shown that minimizing doses to the parotid glands results in clinical gains with respect to xerostomia and quality of life, numerous questions persist with regard to the relationship between these outcomes and dosimetric parameters.<sup>15,16</sup> The published guidelines for the quantitative analyses of normal tissue effects in the clinic assert that severe xerostomia (defined as long-term salivary function of < 25% of baseline) is usually avoided if at least 1 parotid gland is spared to a mean dose of less than approximately 20 Gy or if both glands are spared to less than approximately 25 Gy (mean dose).<sup>17</sup> For complex, partial-volume radiation therapy patterns (e.g., IMRT), each parotid gland mean dose should be kept as low as possible, which is consistent with the desired CTV coverage.

Indeed, due to the heterogeneity of the published data with respect to study design (i.e., use of stimulated vs unstimulated salivary flow, observer- vs patient-reported symptoms, and variable quality of life and toxicity instruments), the currently available predictive models are imprecise and both linear and sigmoidal functions have been suggested to correlate dose, volume, and complications.<sup>18-20</sup> Furthermore, uncertainties exist with regard to spatial variation in radiation sensitivity within the parotid glands as well as the contribution of the submandibular and minor salivary glands.<sup>21</sup> Additionally, studies have shown that the parotid glands are dynamic structures that undergo shrinkage and displacement during radiation and thus affect dosimetry to this OAR and adjacent areas.<sup>22,23</sup>

The potential of contouring error and variabilities contributing to recurrences must also be acknowledged. While consensus guidelines for the delineation of the neck have been adopted for use, these are only meant for a definitive setting. In the postoperative setting, where fascial planes are often distorted and artificial changes make appreciating anatomy more difficult, significant challenges exist in the delineation of risk levels. There was no difference in the rates of regional recurrence for patients who were treated with definitive versus postoperative IMRT in the present series but the inherently variable approaches with regard to target volume delineation that exist between the two cohorts have the potential to confound our findings and make drawing definitive conclusions difficult. Regardless, the practice of carving out the parotid gland OAR from regions that are known to be at risk for a tumor recurrence in the ipsilateral neck and the resulting underdosage at the parotid-level II interface can lead to unfavorable outcomes. Our study also illustrates how a cursory review of dose-volume

histogram data can overlook spatial deficiencies in target coverage since it is possible to attain the D95 goal to the entire PTV while inadequately dosing selected critical portions at high risk for recurrence.

Others have also demonstrated that inadequate attention to detail with respect to treatment planning has the potential to affect the survival of patients with head and neck cancer. Bolero et al demonstrated the importance of physician experience when IMRT is used to treat patients with head and neck cancer.<sup>24</sup> In their analysis, the risk of all-cause mortality decreased by 21% for every additional 5 patients who were treated per provider per year. Notably, the effect of experience was not observed when non-IMRT techniques were employed, which again suggests that target volume delineation is critical to optimize outcomes for patients who are treated with IMRT for head and neck cancer.

Peters et al similarly reviewed the radiation plans of 820 patients who were treated in a prospective trial of chemoradiation for head and neck cancer and showed that poor compliance to quality guidelines resulted in a 24% and 20% decrease in 2-year local-regional control and overall survival, respectively.<sup>25</sup> Importantly, incorrect target delineation and/or planning were the most commonly observed deficiencies.

## Conclusions

Our findings demonstrate that attempted sparing of the parotid gland in the node-positive neck can result in marginal misses in the region of the ipsilateral parapharyngeal space and level II cervical nodal region. This study also raises questions about how aggressive parotid gland sparing using IMRT should be pursued.

Although limited by the retrospective design of comparing 2 groups of sequentially treated patients with differing follow-up periods, these results have important clinical implications. Nearly all of the observed regional recurrences had clinical and/or pathological evidence of disease in level II but the presence of level III and/or IV involvement should also warrant caution in ipsilateral parotid-gland sparing due to a poorer prognosis that is historically associated with these disease characteristics. The decision to perform parotid gland-sparing IMRT in the node-positive neck should be made with caution and likely be individualized on a case-by-case basis with consideration of the clinical and pathological factors that influence the likelihood of disease recurrence in the ipsilateral cervical neck.

## References

1. Chen AM, Farwell DG, Luu Q, Vazquez EG, Lau DH, Purdy JA. Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2012;84:170-175.

2. Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol*. 2014;110:172-181.
3. Dawson LA, Anzai Y, Marsh L, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2000;1117-1126.
4. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinderman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2008;71:377-385.
5. Chao KSC, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2003;55:312-321.
6. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomized controlled trial. *Lancet Oncol*. 2011;12:127-136.
7. Gregoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and post-operative neck. *Radiother Oncol*. 2006;79:15-20.
8. Mendenhall WM, Mancuso AA. Radiotherapy for head and neck cancer—is the “next level” down? *Int J Radiat Oncol Biol Phys*. 2009;73:645-646.
9. Harari PM. Beware the swing and a miss: Baseball precautions for conformal radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70:657-659.
10. Chen AM, Farwell DG, Luu Q, Chen LM, Vijayakumar S, Purdy JA. Marginal misses after postoperative intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2011;80:1423-1429.
11. Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:660-665.
12. Eisbruch A, Marsh LH, Dawson LA, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: Implications for target delineation in high neck and for parotid gland sparing. *Int J Radiat Oncol Biol Phys*. 2004;59:28-42.
13. Bussels B, Maes A, Hermans R, Nuyts S, Weltens C, Van den Bogaert W. Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer. *Radiother Oncol*. 2004;72:119-127.
14. IMRT Documentation Working Group, Holmes T, Das R, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. *Int J Radiat Oncol Biol Phys*. 2009;74:1311-1318.
15. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys*. 1999;45:577-587.
16. Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: Initial results. *Int J Radiat Oncol Biol Phys*. 2001;49:907-916.
17. Deasy JO, Moiseenko C, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys*. 2010;76:S58-S63.
18. Wang ZH, Yan C, Zhang ZY, et al. Impact of salivary gland dosimetry on post-IMRT recovery of saliva output and xerostomia grade for head-and-neck cancer patients treated with or without contralateral submandibular gland sparing: A longitudinal study. *Int J Radiat Oncol Biol Phys*. 2011;81:1479-1487.
19. Hunter KU, Schipper M, Feng FY, et al. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: Prospective study of patient-reported, observer-rated, and objective outcomes. *Int J Radiat Oncol Biol Phys*. 2013;85:935-940.
20. Chen WC, Lai CH, Lee TF, et al. Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: Correlations with parotid dose and quality of life. *Oral Oncol*. 2013;49:42-48.
21. Beetz I, Schilstra C, Visink A, et al. Role of minor salivary glands in developing patient-rated xerostomia and sticky saliva during day and night. *Radiother Oncol*. 2013;109:311-316.
22. O’Daniel JC, Garden AS, Schwartz DL, et al. Parotid gland dose in intensity-modulated radiotherapy for head and neck cancer: Is what you plan what you get? *Int J Radiat Oncol Biol Phys*. 2007;69:1290-1296.
23. Robar JL, Day A, Clancey J, et al. Spatial and dosimetric variability of organs at risk in head-and-neck intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;68:1121-1130.
24. Boero IJ, Paravati AJ, Xu B, et al. Importance of radiation oncologist experience among patients with head-and-neck cancer treated with intensity-modulated radiation therapy. *J Clin Oncol*. 2016;34:684-690.
25. Peters LJ, O’Sullivan B, Giralt J, et al. Critical impact of radiotherapy compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. *J Clin Oncol*. 2010;28:2996-3001.