Research Article

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Comprehensive versus Less-than-Comprehensive Fields in the Radiotherapeutic Management of Unknown Primary Cancer of the Head and Neck

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ABSTRACT

Purpose : To compare clinical outcomes among patients treated with comprehensive and non-comprehensive radiation fields for squamous cell carcinoma of occult primary origin involving the cervical lymph nodes.
Methods and Materials : From January 2014 to April 2018, a total of 33 patients at a single institution were treated by intensity-modulated radiation therapy for squamous cell carcinoma metastatic to the cervical lymph nodes of occult primary origin. Seventeen patients (52%) were treated by primary radiation; 16 (48%) were treated after neck surgery. N-classification was N1 (3 patients); N2a (8 patients); N2b (15 patients); N2c (2 patients); and N3 (5 patients). Human papillomavirus was positive in 19 patients (58%) and negative in 14 patients (42%). Ten patients (30%) were lifelong never-smokers. Concurrent platinum-based chemotherapy was delivered to 26 patients (79%). Patients were categorized as receiving comprehensive (15 patients) or non-comprehensive radiation (18 patients) treatment fields.
Results : Twenty-seven patients were alive at the time of this analysis, yielding an overall survival of 82% with a median follow-up time of 27 months (range, 5-65). Cancer-specific survival at 2 years for patients treated comprehensively versus non-comprehensively was 74% and 100%, respectively (p= 0.13). The rate of primary emergence was 6% with no difference observed between groups (p=0.89). The rate of 2-year regional control was 76% and 94% for patients treated comprehensively and non-comprehensively, respectively (p=0.47). The corresponding incidence of Grade 3 acute toxicity was 67% and 45%, respectively (p= 0.20).
Conclusion : Radiotherapeutic management for occult primary cancer of the head and neck is subject to widely variable treatment fields. This study failed to identify differences in oncologic outcomes between patients treated with comprehensive and non-comprehensive fields.

INTRODUCTION

Squamous cell carcinoma of occult primary site metastatic to the cervical lymph nodes is an uncommon diagnosis of the head and neck, representing 1-5% of malignancies in this location [1-3]. Technological advances have aided physicians in identifying a primary site of disease in more than half of these patients [4,5]. Radiation remains an integral component of therapy for this disease, either as primary treatment or in conjunction with surgical resection. However, the appropriate radiation fields remain an area of controversy given the lack

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of studies evaluating this issue and the relatively rare nature of this disease. Classically, radiation delivered to the bilateral neck and pharyngeal axis has been used to sterilize all putative sites of disease. This comprehensive approach encompasses high volumes of normal tissue and requires high doses that result in significant treatment-related morbidity. As a result, techniques have been proposed selectively excluding the contralateral neck and even portions of the pharyngeal axis, and studies have been conducted treating patients with these more limited fields [6-10]. The purpose of this analysis was to compare clinical and quality-of-life outcomes among a cohort of patients treated with comprehensive and non-comprehensive radiation fields who presented with squamous cell carcinoma of occult primary origin involving the cervical lymph nodes.

MATERIALS AND METHODS

Patients and work-up

From January 2014 to April 2018, a total of 33 patients with histologically-proven squamous cell carcinoma (SCC) of occult primary origin involving the cervical lymph nodes were treated with radiation therapy at a single institution. Approval was obtained from the Institutional Review Board before retrospective patient collection. The initial presentation for all patients was an enlarged cervical lymph node mass. The most common site of nodal involvement was level II (52%). All but two patients presented with unilateral neck disease, and no patient had evidence of distant metastatic disease. Median age was 61 years (range, 48-87 years). Twenty-nine men (88%) and 4 women (12%) were included; all patients were Caucasian. Nodal staging was performed using the American Joint Committee on Cancer (AJCC) 7th edition manual. Clinical N staging was as follows: 3 patients with N1 (9%), 8 with N2a (24%), 15 with N2b (45%), 2 with N2c (6%), and 5 with N3 (15%). Ten patients (30%) were lifelong never smokers. HPV status, determined by p16 immunohistochemistry, was positive in 19 patients (58%) and negative in 14 patients (42%). All HPV-negative patients were former or current smokers with a median 25 pack-year history (range, 8–60 pack-years). In the HPV-positive group, 10 were never smokers with 9 being former or current smokers having a median 40 pack-year history (range, 10–60 pack-years).

Pre-treatment evaluation included complete history and physical examination. Work-up generally consisted of pan-endoscopy with directed and random biopsies, as well as positron-emission tomography, all of which failed to yield a primary index cancer. Ipsilateral and bilateral tonsillectomy were performed in 7 (21%) and 10 (30%) patients, respectively. Computed tomography (CT) using axial imaging was performed of the head and neck in all patients to confirm radiographic evidence of cervical lymph node involvement and to rule out a primary index lesion. Metastatic evaluation included a CT scan of the chest to rule out distant metastasis and/or second primary cancers. Biopsies of the lymph nodes were obtained using fine-needle aspiration or excisional biopsy.

Treatment

Prior to commencement of definitive treatment all patients were presented at a multi-disciplinary head and neck tumor board for prospective discussion. Seventeen patients were treated by primary radiation and 16 were treated after neck surgery (52% and 48%, respectively). One patient received neck surgery after chemoradiation for a total of 17 patients treated surgically (16 ipsilateral and 1 bilateral modified radical neck dissection). Trans-oral robotic resection of the base of tongue was performed in 5 patients (15%) prior to radiation, none of which yielded disease. All patients treated upfront with surgery were clinical stage N2a and greater; however, the only patient treated surgically after chemoradiation had clinical N1 disease. Eight surgical patients (47%) had pathologic evidence of extra-nodal extension. Concurrent platinum-based chemotherapy was delivered to 26 patients (79%).

All patients were treated by radiation daily with conventional fractionation using intensity-modulated radiotherapy (IMRT). The head, neck, and shoulders were immobilized at simulation in a hyperextended position using a perforated, thermoplastic head mask. A CT simulator was used to obtain axial images with contiguous 3-mm slices without contrast. These images were transferred into a contouring workstation were delineation of target and normal tissue structures were performed at the discretion of the treating physician. The gross tumor volume (GTV) was delineated as the extent of involved lymph node disease. When comprehensive radiation was utilized, the clinical target volume (CTV) generally included the nasopharynx, oropharynx, hypopharynx/larynx, and draining lymph nodes at the treating physician's discretion considering the individual patient scenario. No standardized policy was in place at our institution to guide decision-making.

Radiation Field Design

The treatment plans were retrieved from archive for all patients included in this study and individually evaluated to determine the extent of CTV coverage. Target volumes for the 33 patients were separated by comprehensive (15 patients) and non-comprehensive radiation (18 patients). Comprehensive coverage was defined as encompassing the entire mucosal axis and bilateral necks. Non-comprehensive coverage was defined as treatment fields that omitted mucosal sites (nasopharynx, contralateral or complete oropharynx, or hypopharynx/larynx) or intentionally omitted the contralateral neck. Non-comprehensive target volumes included: entire oropharynx and bilateral necks (5 patients); ipsilateral neck

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only without any mucosal treatment (3 patients); ipsilateral oropharynx and ipsilateral neck (1 patient); ipsilateral oropharynx and bilateral necks (1 patient); nasopharynx and ipsilateral neck (1 patient); entire oropharynx, larynx, and bilateral necks (1 patient); entire oropharynx, nasopharynx, and bilateral necks (4 patients); entire oropharynx, larynx and ipsilateral neck (1 patient); entire oropharynx, nasopharynx and ipsilateral neck (1 patient). The prescribed dose to the pharyngeal mucosal axis varied from 50 Gy to 70 Gy (median, 56 Gy). The median prescribed dose to all treated nodes was 56 Gy with a range between 50 and 70 Gy.

Endpoints and Statistical Analysis

Patients were evaluated on follow-up examination 2-4 months after completion of radiation treatment, then every 2-4 months for the first year, 4-6 months for the second year, and then annually thereafter. Endpoints analyzed were overall and cancer-specific survival, primary emergence, local-regional control, and distant metastasis. Control rates were determined by clinical exam, imaging, or pathology. Primary emergence was defined as evidence of tumor at any primary mucosal site of disease as recurrent disease. Regional failure was recorded if there was a mass distinct from the primary site in the cervical or supraclavicular nodal region. Patients with persistent disease were referred for salvage treatment. All endpoints were calculated from the date of diagnosis. Acute and late toxicities were retrospectively graded using the Radiation Therapy Oncology Group and the European Organization for the Treatment of Cancer criteria for assessment of acute and late normal tissue effects [11]. Radiation treatment breaks due only to toxicity were counted. Weight changes were recorded immediately before and after treatment. Three patients were unable to be evaluated for long term toxicity due to death or loss of follow-up. Survival and recurrence endpoints were analyzed using the Kaplan-Meier method, with comparisons among groups performed with two-sided log-rank tests. All categorical data was evaluated using chi-square and Fisher's exact test statistic to identify discrepancies between the groups. All tests were two-tailed, and differences were considered statistically significant at the 0.05 level. Statistical analysis was conducted using SPSS (SPSS Inc., Chicago, IL).

RESULTS

Table 1 outlines the characteristics between patients treated comprehensively versus those treated non-comprehensively. None of the clinical parameters including HPV-status, N-classification, age, or smoking history were significantly different between the two groups ($p>0.05$, for all). With a median follow-up time of 27 months (range, 5-65), twenty-seven patients were alive at the time of this analysis, yielding an overall survival of 82%. The 2-year estimates of cancer-specific survival for patients treated comprehensively versus non-comprehensively were 74% and 100%, respectively ($p= 0.13$), as shown in Figure 1. Among the 6 patients that died during the evaluation period (5 comprehensive, 1 non-comprehensive), 1 died from complications of a primary tumor emergence, 1 as a result of progressive disease at the regional site, 2 from complications related to distant metastatic disease, and 2 died from natural causes. As shown in Figure 2, the actuarial rates of overall survival at 2-years was 57% and 100% among patients treated by comprehensive and non-comprehensive fields ($p=0.11$).

Primary emergence occurred in 2 patients that received definitive chemoradiation (1 comprehensive, 1 non-comprehensive), both involving the laryngeal mucosa. The overall rate of total primary emergence was 6%, with no difference observed between groups ($p=0.89$). One patient presented with isolated laryngeal recurrence 16 months after comprehensive radiation treatment (HPV-positive, current 53 pack-year smoker). The other patient recurred simultaneously in the hypopharynx and larynx, which were intentionally omitted in the radiation fields (HPV-negative, current 25 pack-year smoker). This patient also had concurrent nodal recurrence at the initial site of disease that previously received high-dose radiation (70 Gy). Salvage treatment for these mucosal recurrences consisted of total laryngectomy with or without neck dissection. Both patients recurred soon after at the surgical sites.

Among the entire patient cohort, a total 3 patients (2 comprehensive, 1 non-comprehensive) experienced residual or recurrence of neck disease, yielding a regional control rate of 91% for the population. The rate of 2-year regional control amongst patients treated comprehensively and non-comprehensively, as depicted in Figure 3, was 79% and 94%, respectively ($p=0.47$). One patient had unresectable residual neck disease after receiving induction chemotherapy followed by concurrent chemotherapy and comprehensive radiation (HPV-negative, current smoker, 7 cm initial nodal mass). Sites of regional relapse included: initial nodal region (1 patient), and contralateral neck (1 patient). The contralateral neck failure occurred within a comprehensively irradiated treatment field, presenting simultaneously with thoracic, abdominal, and osseous metastases. The patient that recurred in the initial nodal region received non-comprehensive fields but recurred in an area previously receiving high-dose radiation (70 Gy) 40 months after treatment. All regional recurrences and residual disease occurred in HPV-negative patients with significant smoking histories. The median time for local-regional failure in all patients was 18 months (range, 0-40 months). Distant metastasis developed in 2 patients (6%) at 18 and 46 months. This yielded a 94% 2-year rate of patients free of metastasis. No statistical difference was found for 2-year distant

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metastasis control rates among patients treated comprehensively and non-comprehensively, 93% and 100%, respectively (p=.73). One patient developed esophageal metastases subsequent to mucosal and primary nodal recurrence. The other occurred simultaneous with a regional recurrence, presenting with thoracic, abdominal, and osseous metastases.

The incidence of Grade 3 acute toxicity was 67% and 45% among patients treated with comprehensive and non-comprehensive radiation, respectively (p= 0.20). The reported Grade 3 dermatitis rates among comprehensive and non-comprehensive groups were 20% and 11%, respectively (p= 0.64). Acute Grade 3 mucositis rates between comprehensive and non-comprehensive were 47% and 28% (p= 0.26). No Grade 4 or 5 toxicities were observed. On review of patients that lost greater than 10% of pre-treatment body weight, 60% of comprehensive and 39% non-comprehensive met this criteria (p= 0.23). Five (33%) comprehensively-treated patients required hospitalization, compared to 3 (17%) non-comprehensive-treated patients (p= 0.42). The reasons for hospitalization included irretractable nausea/vomiting, neutropenic fever, and gastrostomy tube infection. No difference was observed between groups that required a break from treatment (47% comprehensive and 28% non-comprehensive, p= 0.26). The median number of missed, unplanned treatment days was 3 (range, 0-10) in comprehensive patients versus 2 days (range, 0-5) in non-comprehensive patients. The incidence of late Grade 3 toxicity amongst all patients was 20% with no difference between the cohorts (p> 0.99). No Grade 4 or 5 dysphagia toxicity was observed. The most common late toxicity was dysphagia. The percentage of patients who were dependent on the gastrostomy tube at 3 months (36% comprehensive and 25% non-comprehensive, p= 0.69) and 6 months (14% comprehensive and 19% non-comprehensive, p>=0.99) post-treatment was not significantly different. At 1-year after treatment, the corresponding rates of gastrostomy tube dependence were 14% and 13%, respectively, between comprehensively and non-comprehensively treated patients (p>=0.99).

Table 1

	Patient Population	
	N	**%**
Oropharynx and bilateral neck	6	33
Subtotal mucosa and bilateral neck*	5	28
Ipsilateral neck alone	3	17
Subtotal mucosa and ipsilateral neck**	2	11
Oropharynx and ipsilateral neck	1	5
Nasopharynx and ipsilateral neck	1	5

Table 1. CTV coverage of patients treated with non-comprehensive radiation fields. Notably, the term "subtotal mucosa" was used to refer to less-than-comprehensive pharyngeal mucosal irradiation. *Subtotal mucosal coverage included coverage of the oropharynx and larynx in one patient and oropharynx and nasopharynx in four patients. **Subtotal mucosal coverage included coverage of oropharynx and larynx in one patient and oropharynx and nasopharynx in one patient.

Table 2

	Non-Comprehensive RT N= 18 (100%)	**Comprehensive RT N= 15 (100%)**	**P value**
Age, mean	62.3	61.8	0.89
Gender			0.99
Female	2 (11)	2 (13)	
male	16 (89)	13 (87)	
Smoking Status			0.38
Never	7 (39)	3 (20)	
Former	9 (50)	8 (53)	
Current	2 (11)	4 (27)	
Nodal Stage			0.37
N1	3 (17)	0 (0)	

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N2a	4 (22)	4 (27)	
N2b	8 (44)	7 (47)	
N2c	0 (0)	2 (13)	
N3	3 (17)	2 (13)	
HPV status			0.25
Positive	12 (67)	7 (47)	
Negative	6 (33)	8 (53)	
Radiation approach			0.61
Definitive	10 (56)	7 (47)	
Post-operative	8 (44)	8 (53)	
Chemotherapy			0.99
Yes	14 (78)	12 (80)	
No	4 (22)	3 (20)	

Table 2. Patient demographics and clinical characteristic according to radiation treatment volumes.

Figure 1

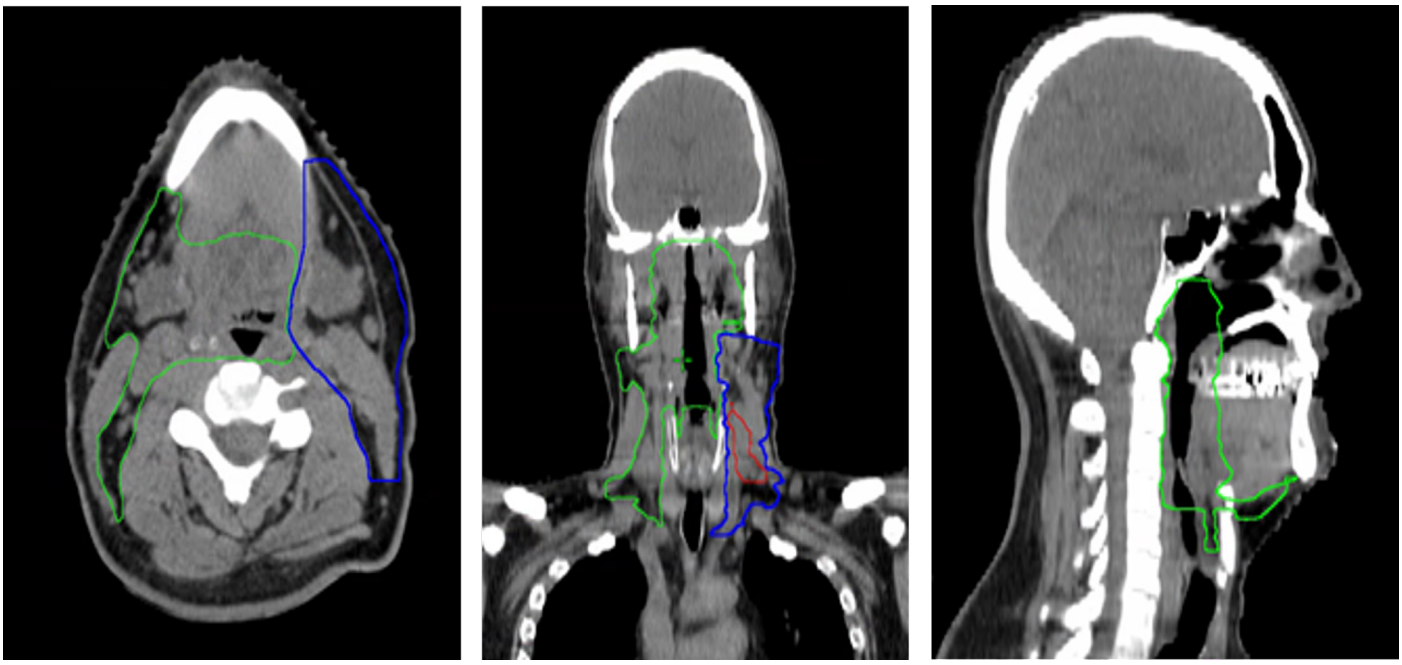

Figure 1. Cancer-specific survival according to radiation treatment coverage.

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Figure 2

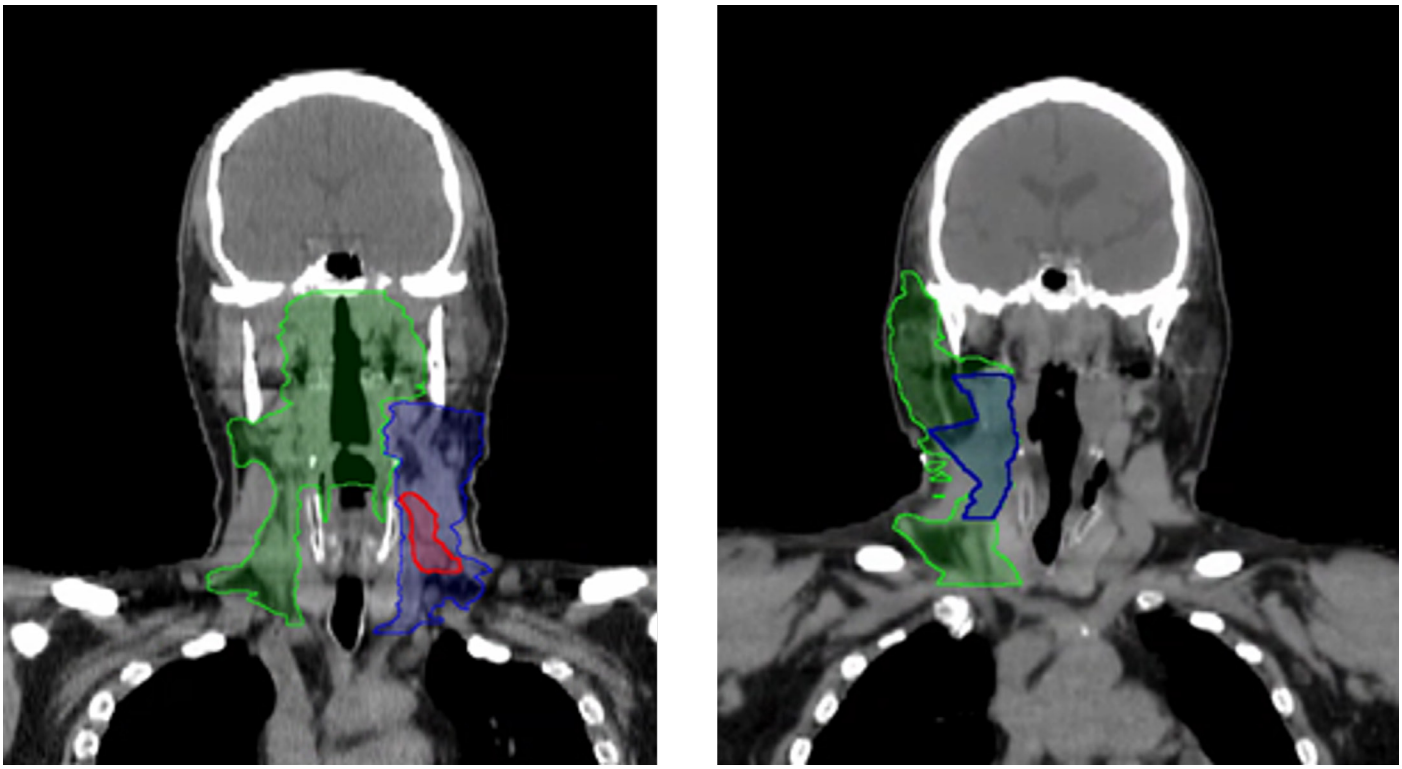

Figure 2. Overall survival according to radiation treatment coverage.

Figure 3

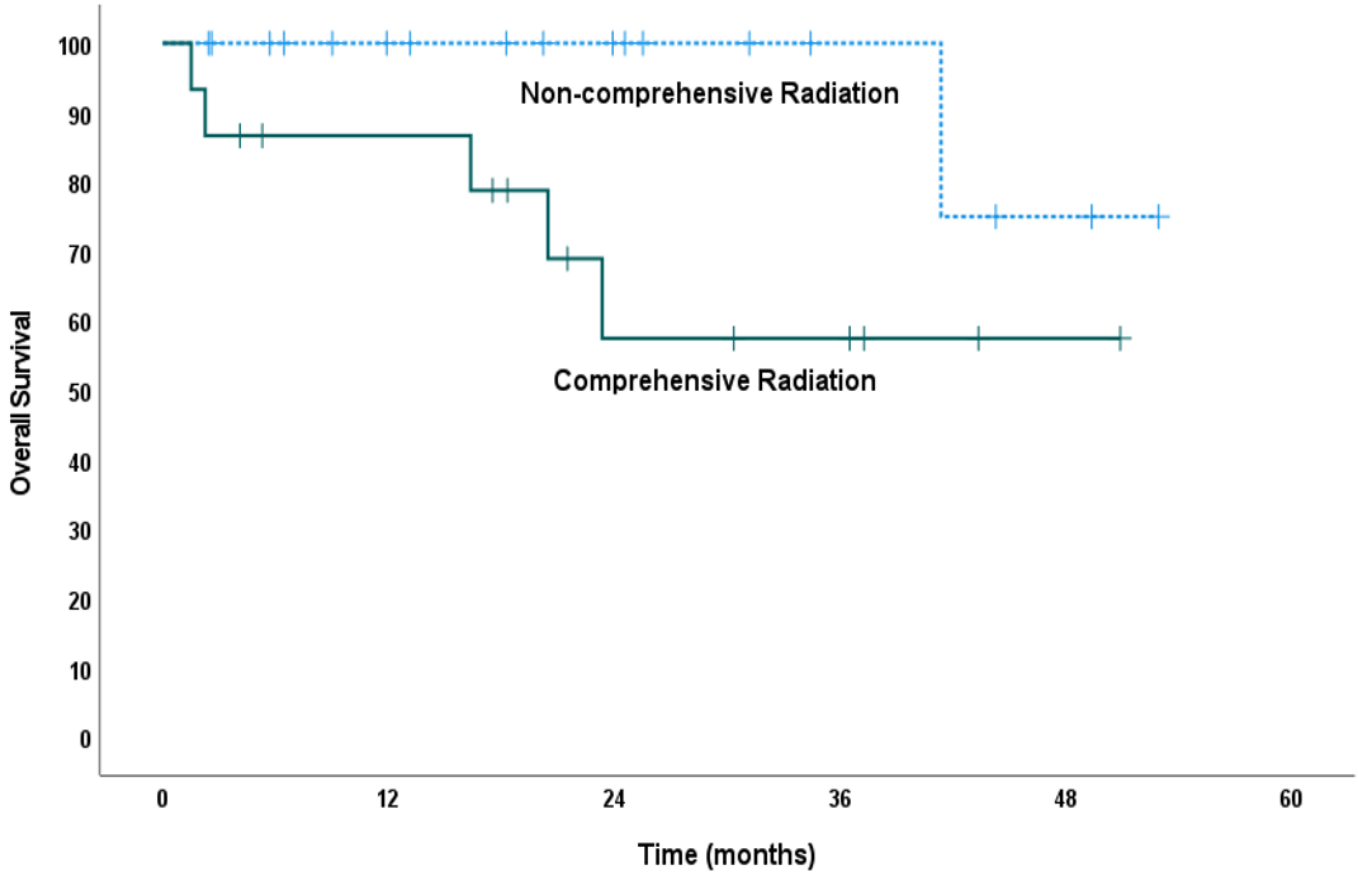

Figure 3. Regional control according to radiation treatment coverage.

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DISCUSSION

Although comprehensive fields traditionally have represented the radiotherapeutic treatment strategy for occult primary cancer of the head and neck, our data supports a trend towards utilization of more selective fields. More specifically, we failed to identify significant differences in outcomes among patients treated with comprehensive and non-comprehensive fields. In addition, trends demonstrating an improvement in acute and late toxicity between varying levels of comprehensive fields was observed. These data suggest that limited treatment strategies using selective, non-comprehensive radiation fields may be preferred in the management of this disease by reducing toxicity without compromising cancer control or survival.

Institutional experiences have led many to limit their mucosal treatment to areas of the highest detection rate among patients initially worked up for an occult malignancy of the head and neck to the cervical lymph nodes. In the present study, no such institutional standard existed; rather, decisions were individualized based on physician bias considering such factors as HPV status, smoking history, and performance status. In recent years, given the increase in incidence in HPV-related head and neck cancer, the most common site of identified primary cancers has been in the oropharynx with values reaching as high as 89% [12]. With this evidence, many researchers believe the chance for primary emergence in other mucosal sites is rare. Baker et al reported on their outcomes after shifting institutional practices to larynx-sparing radiation in this setting. Their 5-year cancer-specific survival rate of 88% suggested larynx-sparing radiation results in high local-regional control, reporting no primary mucosal emergence [10]. Some institutions have explored the option of treating patients only to the oropharynx. Mourad et al found a 96% loco-regional control rate for patients treated selectively to the oropharynx and bilateral necks, with a median follow-up of nearly 4 years [7]. On further follow-up, the authors reported 5-year rates of regional control, primary emergence, and overall survival to be 90%, 10%, and 79%, respectively. The 5-year rate of primary emergence in a non-oropharynx site was 3% [13]. Although limited by sample size, the present study suggests omitting low-risk mucosal areas may provide adequate control for primary emergence.

Many have also explored the use of ipsilateral radiation treatment to enhance the therapeutic ratio compared to treatment that covers bilateral necks. Ligey et al found no difference in loco-regional control and survival when comparing unilateral and bilateral neck irradiation, with a nodal relapse rate of 34% and 25%, respectively [9]. Similar rates of survival and recurrence have also been found by Fakhrian et al when treating patients to the ipsilateral neck [14]. Perkins et al showed 1 of 21 patients treated with ipsilateral irradiation to have a contralateral recurrence, and after salvage neck dissection the patient remained disease free for the entirety of the study follow-up, 4 years after surgery [15]. Chen et al reported on 25 patients who selectively received oropharynx-directed ipsilateral irradiation [6] and reported 2-year actuarial rates of locoregional control and overall survival to be 91% and 92%, respectively, with only 1 reported contralateral neck recurrence. Of particular importance, all of these patients were HPV-positive with minimal or no smoking history, highlighting the potential role for treating patients based on favorable clinical parameters and biomarkers.

The volume historically treated with comprehensive fields contains large amounts of normal tissue and has the potential for significant impact on quality of life. To enhance patient outcomes, exclusion of theoretical low-risk areas seems to be of clinical benefit. Indeed decreasing radiation exposure to structures associated with swallowing, eating, and speaking, among others, has been increasingly shown to translate to decreased side effects in the IMRT era [16]. This has caused some to believe that IMRT results in a universal reduction in toxicity compared to 3D-CRT; however, radiation dose spillage is a proven phenomenon in head and neck IMRT and may result in additional toxicities not previously seen [17]. Lazarev et al, for instance, showed that sparing the primary oropharyngeal site after trans-robotic surgery for squamous cell carcinoma offers minimal dosimetric and clinical advantage largely because incidental exposure from the targeting of nearby regions continued to be significant [18]. Multiple beam arrangements in IMRT are advantageous for conforming to tumor topography but radiate a moderate volume of out-of-field tissue in the process. This may limit the benefit of sub-comprehensive fields in the treatment of occult primary tumors as demonstrated by this study.

Many areas of treatment for occult primary malignancy of the head and neck remain controversial. Despite the promising outcomes shown in many studies of selective-field radiation, some conflicting evidence exists favoring the use of comprehensive treatment. Reddy et al compared comprehensive mucosal and bilateral neck radiation to ipsilateral neck radiation alone and found a higher rate of contralateral nodal failure (44% versus 14%) in the latter. They also discovered a primary emergence rate of 44% in the ipsilateral group compared to 8% for the bilateral radiation group [8]. Furthermore, a recent meta-analysis demonstrated the benefit of bilateral neck versus ipsilateral neck irradiation with improved rates of primary emergency, neck recurrence, and 5-year disease free survival. This same study also showed that mucosal plus neck radiation was superior compared to radiation treatment to the neck alone. Although authors did find that comprehensive radiation has higher rates of acute toxicity, they concluded that these toxicities were clinically manageable [19]. Additionally, the benefit from concurrent

use of chemotherapy has come into question by many given the high rate of control with radiation alone [20, 21].

The retrospective nature of this review creates limitations to our study. The potential role of selection bias must be acknowledged, especially since HPV positive patients with unknown primary tumors have been shown to have a better prognosis and were more likely to have received non-comprehensive fields [22]. Similarly, the specific reasons why a patient was treated ipsilaterally versus bilaterally to the neck, or why omission of certain mucosa was performed, was not always clearly defined in the electronic medical records. Because certain patient characteristics or physician-patient discussions may have led to a particular treatment strategy, these could have also influenced outcomes. Similarly, since all patients in this study were Caucasian, our findings might not be translatable to more diverse populations where certain diseases such as nasopharyngeal carcinoma might be more common. Since acute and long-term toxicity was also not always reported accurately on follow-up examination, this may have led to an underestimation of toxicity. Although the present study shows no significant difference in survival and recurrence outcomes between treatment strategies, longer follow-up is needed to confirm the sustainability of these outcomes.

The absence of high-level, prospectively-acquire evidence for this disease leaves occult primary cancers of the head and neck subject to widely variable radiation treatment. Nonetheless, our results showing no difference between patients treated with comprehensive coverage versus those treated with non-comprehensive fields is consistent with results reported by others. While we were not able to identify specific characteristics that predicted for the use of lesser radiation fields, the significant variability in treatment design was still striking. We conclude that selectively omitting certain fields is a reasonable strategy which has the potential to preserve quality of life for patients treated by radiation for cervical lymph node metastasis of unknown primary origin. Further research in this disease entity is needed to develop a standard radiation approach.

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