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Patterns of failure in patients with head and neck carcinoma of unknown primary treated with radiation therapy

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Abstract

Background—To examine patterns of failure and the relationship to radiation doses in patients with head and neck carcinoma of unknown primary (HNCUP).

Methods—We reviewed 85 patients with HNCUP treated with curative-intent RT during 1995–2012.

Results—There have been no failures in the pharyngeal axis. Relapse at initial neck sites of disease developed in 7 patients (8.2%). The median dose to these sites was 70 Gy (range, 63–70). Failure at neck sites without initial disease occurred in four patients (4.7%). The median dose was 54 Gy (range, 50–58.8). There were no contralateral failures in a small cohort of patients receiving unilateral treatment (n=6). Percutaneous endoscopic gastrostomy (PEG) dependence at 12 months was 7.4%, and 2.5% at 3 years. Esophageal stricture developed in 5 patients (5.9%).

Conclusions—RT for HNCUP produces excellent locoregional control rates with acceptably low levels of late toxicity. Doses prescribed to sites of eventual failure did not vary significantly from those sites that were treated and remain in control.

Keywords

Unknown primary; head and neck; radiation therapy

INTRODUCTION

Head and neck carcinoma of unknown primary (HNCUP) is defined by malignancy in the cervical lymph nodes without identification of the primary tumor after extensive workup. HNCUP is a rare condition, representing approximately 5% of all head and neck cancers.¹ The optimal treatment regimen is controversial, and randomized evidence is lacking. Treatment strategies for HNCUP have traditionally consisted of optimizing locoregional

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Conflict of Interest Notification

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control with surgery, radiation therapy, or chemoradiation therapy, and treatment to initially uninvolved sites of the neck and mucosal axis that are at risk of failure. This treatment approach provides for acceptable tumor control but with significant side effects due to the size of the radiation target.

Recent studies in patients with oropharyngeal carcinoma support shrinkage of radiation therapy targets to decrease treatment side effects without adversely affecting cancer outcomes.^{2–4} Several ongoing trials are also investigating treatment de-escalation for selected patients with human papillomavirus (HPV)-associated oropharyngeal carcinoma.⁵ To investigate these insights in the context of patients with head and neck carcinoma of unknown primary, we retrospectively examined the treatment characteristics and patterns of failure in a cohort of HNCUP patients treated at our institution.

MATERIALS AND METHODS

Inclusion criteria

Between 1995 and 2012, a total of 85 patients with head and neck carcinoma of unknown primary and no history of skin malignancies were treated with curative-intent radiation therapy at a single institution. Patients were identified as having HNCUP if, by the time of the initiation of radiation therapy (RT), they had experienced a malignancy in the lymph nodes of the neck, and the primary tumor was not identified upon further workup (which typically consisted of nasopharyngoscopy with laryngoscopy under anesthesia and imaging of the head and neck, chest, abdomen and pelvis). Patient characteristics are listed in Table 1.

Treatment

In general, patients were treated with comprehensive nodal irradiation to the bilateral neck and mucosal axis (nasopharynx, oropharynx, and larynx). Mucosal and neck sites were dose-deescalated or spared at the physician's discretion. Patients were simulated in the supine position utilizing a computed tomography (CT) scan with slice thickness of three mm from the top of the head to the carina. A thermoplastic mask was used for immobilization. Doses typically consisted of 70 Gy prescribed to gross disease, 60–66 Gy prescribed to high-risk or postoperative areas, and 50–54 Gy prescribed to lower-risk subclinical regions.

Port films and treatment plans for each patient were reviewed, and the estimated doses delivered to each nodal level of the neck, the pharyngeal axis, and the oral cavity were collected.

Follow-up

Patients were generally seen at regular intervals every 1–3 months for the first year, every 3–6 months through 3 years, and annually thereafter by a member of a multi-disciplinary disease-management team consisting of a medical oncologist, a head and neck surgeon, and a radiation oncologist. CT scans of the head and neck were obtained at three month intervals, or more frequently if needed. PET CT scans were performed at the discretion of the treating physician. During the follow-up period, patients were referred to a

gastroenterologist in cases of treatment-related malnutrition or esophageal stricture for consideration of percutaneous endoscopic gastrostomy (PEG) tube placement.

Toxicity

Rates of PEG tube dependence and rates of esophageal stricture requiring dilation were also collected. Patients were classified as dilation dependent if, at the time of last follow up, they had undergone dilation without resolution of stricture.

Statistics

Failure in the primary pharyngeal axis was defined as the development of disease in the nasopharynx, oropharynx, hypopharynx, or larynx. Locoregional failure free survival was defined in terms of recurrence within the primary pharyngeal axis or in the neck. Distant metastases were defined as any clinical or radiographic evidence of disease outside of the head and neck region. Recurrence free survival was defined in terms of recurrence within the primary pharyngeal axis, recurrence at sites of initial disease, recurrence at sites without initial disease, and distant metastases. Overall survival was defined in terms of death from any cause.

The median follow-up among surviving patients is 3.4 years (range, 0.1–12.5). Freedom from failure at the initial site, regional failure free survival, distant metastasis free survival, overall survival, and PEG dependence were estimated using the Kaplan-Meier method.

RESULTS

Initial Treatment

Median doses prescribed to the pharyngeal axis and each level of the neck are summarized in Table 2. Intensity modulated radiation therapy (IMRT), which was initiated within the department in 2000, was used for 63.5% of the cohort.

Unilateral RT was used for 7.1% (n=6). Most commonly, treatment to the contralateral side was omitted for patients who were elderly or had a poor performance status (n=5). In other cases, ipsilateral treatment alone was recommended if the risk of failure on the contralateral side was deemed acceptably low (n=1; isolated level 1 presentation). The decision to treat the ipsilateral neck alone was at the treating physician's discretion.

For the remaining 79 patients that were treated to the bilateral neck, Doses <50 Gy to the nasopharynx, oropharynx, and larynx/hypopharynx were prescribed to 16, six, and 20 patients respectively. These structures were completely spared in five, zero, and one patients, respectively. The range of doses below 50 Gy ranged from 0–49.6 Gy. For the nasopharynx, there were eight patients who received doses >0 Gy – 20 Gy, five patients that received doses >20 Gy – 40 Gy, and three patients that received doses >40 Gy – 45 Gy. For the oropharynx, there were zero patients who received doses >0 Gy – 20 Gy, two patients who received doses >20 Gy – 40 Gy, and two patients who received doses >40 Gy – 45 Gy. For the larynx and hypopharynx, there were eight patients who received doses >0 Gy, – 20 Gy, seven patients who received doses between >20 Gy – 40 Gy, and three patients who received doses >40 Gy

45 Gy. There were a total of four patients that received doses 45 Gy to all three mucosal subsites.

Neck dissections were performed in 65.9% of patients (n=56), with 54 patients undergoing neck dissections prior to RT and two patients after RT. Concurrent chemotherapy was administered with RT for 42 patients (49.4%), two of which (2.4%) also received induction chemotherapy prior to starting chemoradiation therapy.

Locoregional failure

The 5-year locoregional recurrence free survival was 86.4%, shown in Figure 1. The median dose to nasopharynx, oropharynx, and larynx/hypopharynx was 54 Gy. There have been no failures in the sites of the pharyngeal axis that were covered in the target volume. There was one patient with squamous cell carcinoma of a right level II lymph node that was treated with neck dissection and comprehensive RT to the pharyngeal axis and bilateral neck (dose to oral cavity, 22 Gy). He developed a squamous cell carcinoma of the right posterior gingiva 11 months after therapy.

Relapse or progression at the sites of initial gross disease developed in seven patients (8.2%) and included one patient with pretreatment N1 disease, one with N2A disease, three with N2B disease and two with N3 disease. Sites included level II (n=3), level IV-V (n=2), level II-IV (n=1), and a retropharyngeal lymph node (n=1). The median dose to these sites was 70 Gy (range, 63–70). The 5-year freedom from failure at the sites of initial gross disease was 90.8%. There were four recurrences in the contralateral uninvolved neck (4.7%). All four sites were prophylactically treated (median dose 54 Gy, range 50–58.8). There were no contralateral failures in patients that received unilateral treatment. The 5-year locoregional recurrence free survival for patients with N1 or N2a disease was 89.4% vs. 84.3% for patients with N2b disease ($p=0.40$). The 5-year locoregional recurrence free survival for patients treated with chemotherapy was 78.4% vs. 94.1% for patients treated without ($p=0.09$).

Distant Failure

Distant metastases have developed in 11 patients (12.9%), including one patient with pretreatment N1 disease, eight with N2B disease, and two with N3 disease. Eight patients have developed isolated distant metastases (9.4%). Two patients developed simultaneous distant failure and failure in the neck at a site without initial disease, and one patient developed simultaneous distant failure, failure at site of initial disease and failure at a site of no initial disease. The sites of distant failure included the lungs (n=5), liver (n=2), skull base (n=1), axilla (n=1), mediastinum (n=1), and lungs, abdominal lymph nodes, and femur (n=1). Five-year distant metastasis free survival was 85.3%. The 5-year distant metastasis free survival rate was lower for patients with N2b disease (79.3% vs. 95.2%, $p=0.04$). The 5-year distant metastasis free survival was not significantly different for patients treated with chemotherapy vs. without chemotherapy (79.4% vs. 91.0%, $p=0.26$).

Recurrence Free Survival

Five-year recurrence free survival was 75.2%, shown in Figure 2.

Overall survival

Five-year overall survival was 74.5%, shown in Figure 3. There was a trend toward significance for overall survival among patients with N1 – N2a disease compared with patients with N2b disease (89.1% vs. 67.1%, $p=0.051$). The 5-year overall survival was 76.0% for patient treated with chemotherapy vs. 74.9% for those patients treated without ($p=0.94$).

Toxicity

PEG tubes were used in 43.5% of patients, of which 51.4% had a prophylactic PEG. The rate of PEG dependence for all patients at 12 months was 7.4%, and 2.5% at 3 years. 50% of patients that were treated with unilateral therapy also received a PEG tube, one of which was PEG dependent at time of death 7.7 months after therapy. Among patients treated with bilateral therapy, the rate of PEG dependence at 12 months was 7.5% and 2.5% at 3 years. There were no differences in PEG dependency between patients who received <50 Gy and 50 Gy to the larynx ($p=1.00$). Patients were more often managed with PEGs if they received chemotherapy. Of the 42 patients receiving chemotherapy, 28 received a PEG (66.7%) vs. 9 of the 43 patients who did not receive chemotherapy (20.9%). The time of PEG dependence was statistically significantly higher for patients treated with chemotherapy ($p=0.009$). PEG rates did not vary with use of IMRT ($p=0.11$).

Esophageal stricture requiring dilation developed in 5 patients (5.9%), and 1 patient continued to require dilations at the time of last follow-up.

DISCUSSION

The optimal management of head and neck squamous cell carcinoma of unknown primary is controversial. Strategies range from surgical excision alone to a multimodal approach incorporating neoadjuvant chemotherapy and postoperative radiation or chemoradiation therapy. In the absence of prospective randomized evidence, retrospective reports have demonstrated that patients with N1 or N2a disease without extracapsular extension can be managed with surgery alone,^{6–9} whereas radiotherapy or chemoradiotherapy is indicated for more advanced disease.

Comprehensive irradiation of the bilateral neck and pharyngeal mucosa has traditionally been used to reduce the risk of locoregional recurrence.^{1, 10} Results from M.D. Anderson Cancer Center showed excellent outcomes with this approach, with a 5-year regional control rate of 96% with a single node involved, 86% when multiple nodes were involved, and 8% rate of primary mucosal tumor development. Only 1 patient developed disease recurrence in the contralateral neck.¹¹

Others have advocated for treatment of the involved side of the neck alone to help mitigate toxicity. Studies comparing unilateral to bilateral neck irradiation have shown mixed results. Several single-institution reports have shown no difference in locoregional control rates^{12–15} or overall survival rates¹⁶ between patients with HNCUP treated with unilateral and bilateral neck treatment, whereas Beldi et al. showed improved outcomes with more extensive treatment volumes.¹⁷ Reddy et al demonstrated adequate control of the ipsilateral neck with

unilateral irradiation, but contralateral failures were more common.¹⁸ In clinical practice, unilateral treatment is often recommended for patients with more advanced disease undergoing treatment with palliative intent, and it is unclear from these studies whether the populations undergoing unilateral RT were biased in this way.

Although the treatment-related complications were generally low in the M.D. Anderson study,¹¹ comprehensive mucosal and nodal irradiation can nevertheless cause significant toxicity, limit surgical salvage options, and make re-irradiation difficult or impossible. Consideration of the optimal target volume and dose for these patients continues to remain vital to reduce the incidence of treatment-related side effects and preserve future treatment options. The current study investigated the relationship between patterns of locoregional failure and dose prescribed to subsites of the head and neck in patients treated with RT for head and neck cancer of unknown primary. The goal was to determine if sites of failure were related to underdosing, or conversely if sites with a low risk of failure were overtreated and could be considered for sparing or de-intensification.

In our study, images from CT-based planning were used to review plans of patients that were treated with curative-intent two-dimensional, three-dimensional conformal, and intensity-modulated radiation therapy. This allowed for visualization and estimates of dose delivery to each subsite of the head and neck. The median dose prescribed to the sites of initial gross disease (70 Gy) appears to be adequate, supported by the high control rates in these areas. The median dose to levels of the neck outside of the initial gross disease was 54 Gy, which again appears to be an effective prophylactic dose based on the rarity of failures.

While the median dose to the primary pharyngeal axis was 54 Gy, there were a significant number of patients that received less than 50 Gy, and some that had the nasopharynx (n=7), oropharynx (n=2), and larynx/hypopharynx (n=1) completely spared. Despite these lower doses, there were no failures in the primary pharyngeal axis. These results are consistent with other reports demonstrating a very low rate of primary mucosal failure after comprehensive radiotherapy (median, 9.5%; range, 2–13%)¹⁰ and suggest that some patients may benefit from omission of specific sites of the pharyngeal axis in target delineation.

Although most patients were treated with comprehensive mucosal and nodal irradiation, long-term toxicity as assessed by PEG tube dependency and esophageal dilation was acceptably low and comparable to other series utilizing IMRT that cite long-term PEG dependence rates of 0–4.8%.^{19–25} The use of IMRT in the majority of patients and the adoption of reactive rather than prophylactic supplemental nutrition via PEG tube²⁶ likely contributed to these low rates of toxicity.

Our current practice is to determine the extent of mucosal irradiation on a case-by-case basis, utilizing information from lymph node involvement and virus association to help guide target coverage. When no lymph nodes below level II are involved, the larynx is generally spared,²⁷ while low-lying lymph nodes (levels III and below) dictate larynx and hypopharynx coverage. Patients with Epstein-Barr virus associated tumors should have the nasopharynx covered, and in certain cases treatment to the nasopharynx alone is sufficient. Finally, similar to oropharyngeal cancers, recent data have implicated human-papillomavirus

(HPV) association as a major prognostic factor for disease-free and overall survival in patients with HNCUP.^{28–31} Irradiating the oropharynx alone may be sufficient for a patient with a HPV-associated cancer and no involved lymph nodes below level II. However, any suspicion of nasopharyngeal primary tumors warrants coverage of the nasopharynx, as recent data have associated HPV-positive nasopharyngeal carcinomas with a significantly worse prognosis compared with their HPV-negative counterparts.³²

There are several limitations to this study, including its retrospective design. Although comparable to other series, the number of patients in the current report is relatively low. The use of FDG PET/CT for staging and workup was introduced at our institution in 2003 and almost certainly contributed to differences in detection rates of primary disease, and to stage migration effects between the pre- and post-PET eras, limiting the ability to draw firm conclusions regarding outcomes. Treatment targets were not standardized and volumes were somewhat heterogeneous, limiting the conclusions between dose prescribed to a specific area and subsequent risks of failure. Furthermore, a significant portion of patients were treated with non-IMRT-based radiation therapy, although this did not seem to affect either outcomes or toxicity. Only 21.2% of patients had HPV status (as assessed by p16 immunostaining) available from their pathology report. The lack of HPV status in the majority of patients in the current study is a limitation in interpreting the results. Nevertheless, the high control rates and low toxicity with the current approach are encouraging and offer important insights into efforts to further improve outcomes in this rare and challenging disease.

CONCLUSIONS

Radiation therapy for HNCUP produces excellent locoregional control rates with acceptably low levels of late toxicity. Doses prescribed to sites of eventual failure did not vary significantly from those sites that were treated and remain in control. Our findings suggest that factors other than RT dose prescribed, including HPV status, may ultimately dictate locoregional recurrence risk in patients with head and neck cancer of unknown primary.

Acknowledgments

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Figure 1.
Locoregional progression free survival

Figure 2.
Recurrence Free Survival

Figure 3.
Overall survival

Table 1

Patient characteristics.

Characteristic	No. (%)
Median Age	58 (range 38–90)
Sex	
M	70 (82.4%)
F	15 (17.6%)
Histology	
Squamous cell carcinoma	84 (98.8%)
Lymphoepithelial carcinoma	1 (1.2%)
HPV/p16 status	
Positive	14 (16.5%)
Negative	4 (4.7%)
Unknown	67 (78.8%)
N-Stage	
I	21 (24.7%)
2A	12 (14.1%)
2B	40 (47.0%)
2C	4 (4.7%)
3	8 (8.5%)
Neck dissection	
Pre-RT	53 (62.4%)
Post-RT	2 (2.4%)
None	30 (35.3%)
Chemotherapy	
Concurrent	40 (47.1%)
Induction + concurrent	2 (2.4%)
None	43 (50.6%)
IMRT	54 (63.5%)
Unilateral RT	6 (7.1%)

HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

Table 2

Median doses prescribed.

Nasopharynx	5400 cGy
Oropharynx	5400 cGy
Larynx/hypopharynx	5400 cGy
Oral cavity	1803 cGy
Neck with disease	
Level I	5870 cGy
Level II	6000 cGy
Level III	6000 cGy
Level IV	5040 cGy
Level V	5040 cGy
Neck without disease	
Level I	5000 cGy
Level II	5400 cGy
Level III	5400 cGy
Level IV	5000 cGy
Level V	5000 cGy