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CLINICAL INVESTIGATION **Head and Neck**

RADIATION THERAPY IN THE MANAGEMENT OF HEAD-AND-NECK CANCER OF UNKNOWN PRIMARY ORIGIN: HOW DOES THE ADDITION OF CONCURRENT CHEMOTHERAPY AFFECT THE THERAPEUTIC RATIO?

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Purpose: To determine how the addition of cisplatin-based concurrent chemotherapy to radiation therapy influences outcomes among a cohort of patients treated for head-and-neck cancer of unknown primary origin.
Methods and Materials: The medical records of 60 consecutive patients treated by radiation therapy for squamous cell carcinoma of the head and neck presenting as cervical lymph node metastasis of occult primary origin were reviewed. Thirty-two patients (53%) were treated by concurrent chemoradiation, and 28 patients (47%) were treated by radiation therapy alone. Forty-five patients (75%) received radiation therapy after surgical resection, and 15 patients (25%) received primary radiation therapy. Thirty-five patients (58%) were treated by intensity-modulated radiotherapy.
Results: The 2-year estimates of overall survival, local-regional control, and progression-free survival were 89%, 89%, and 79%, respectively, among patients treated by chemoradiation, compared to 90%, 92%, and 83%, respectively, among patients treated by radiation therapy alone ($p > 0.05$, for all). Exploratory analysis failed to identify any subset of patients who benefited from the addition of concurrent chemotherapy to radiation therapy. The use of concurrent chemotherapy was associated with a significantly increased incidence of Grade 3+ acute and late toxicity ($p < 0.001$, for both).
Conclusions: Concurrent chemoradiation is associated with significant toxicity without a clear advantage to overall survival, local-regional control, and progression-free survival in the treatment of head-and-neck cancer of unknown primary origin. Although selection bias cannot be ignored, prospective data are needed to further address this question.

Radiation therapy, Chemoradiation, Head-and-neck cancer, Unknown primary, Cervical lymph node metastasis.

INTRODUCTION

Squamous cell carcinoma of unknown primary site metastatic to the cervical lymph nodes at presentation represents approximately 1–5% of all head–and-neck malignancies (1–3). Radiation therapy constitutes an integral component in the management of this disease, and comprehensive mucosal (and neck) irradiation, either as primary treatment or in conjunction with surgical resection, is typically used to sterilize all putative sites of cancer. Although Phase III trials have demonstrated the superiority of concurrent chemoradiation vs. radiation therapy alone in both the definitive and the postoperative setting for selected patients with head-and-neck cancer, it must be recognized that patients with head-and-neck cancer of unknown primary origin were specifically excluded from these studies (4–7). As a result, the addition of concurrent chemotherapy is of uncertain value for this subset of patients. This controversy is reflected in the current guidelines issued by National Comprehensive Cancer Network, which considers the use of concurrent chemoradiation for head-and-neck cancer of unknown primary origin as category 3 (''based on any level of evidence, but reflecting major disagreement'') (8). Given the historically high rates of toxicity from irradiation of a significant volume of normal tissue and the relatively high doses required, an analysis of how the therapeutic ratio is altered with the addition of chemotherapy would be particularly instructive. The purpose of this study was thus to compare treatment outcomes after radiation therapy with or without concurrent chemotherapy for patients with head-and-neck cancer of unknown primary origin.

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METHODS AND MATERIALS

Patients

This study was approved by the Institutional Review Board at the University of California, Davis School of Medicine before the retrospective collection of all patient information. Between January 2001 and October 2009, 60 patients with histologically proven squamous cell carcinoma of unknown primary origin involving the cervical lymph nodes were referred for radiation therapy. The median age was 60 years (range, 42–90 years). Thirty-nine men (65%) and 21 women (35%) were included. All patients initially presented with a clinically palpable cervical neck mass, with the median tumor size measuring 4.5 cm (range, 1.0–9 cm). The most common clinical site of nodal involvement for the primary neck mass was level II (43 patients), followed by level III (8 patients), level IV (5 patients), and level I (4 patients).

Pretreatment evaluation included complete history and physical examination and direct flexible fiberoptic endoscopic examination, including direct laryngoscopy, bronchoscopy, and esophagoscopy with blind and directed biopsies. All patients underwent ipsilateral tonsillectomy; 51 of 60 patients underwent bilateral tonsillectomy. Axial imaging with computed tomography (CT) was performed of the head and neck as a component of the initial evaluation, which demonstrated radiologic evidence of multiple lymph node involvement in 24 patients (40%). Metastatic evaluation was performed at the discretion of the treating physicians but generally included chest x-ray and routine blood work. Positron emission tomography (PET) scan was obtained for 19 patients (32%) before treatment. None of the patients had evidence of bilateral neck involvement or distant metastasis.

Treatment

Forty-five patients (75%) underwent surgery as the initial treatment consisting of ipsilateral modified radical neck dissection (34 patients), selective neck dissection (8 patients), and excisional biopsy (3 patients). The median number of lymph nodes removed was 11 (range, 1–31). Among the patients who underwent surgery, pathologic N stages were as follow: N1, 7%; N2a, 40%; N2b, 36%; N2c, 0%; and N3, 18%. Twenty-one patients (35%) had extracapsular nodal extension. Three patients (5%) had microscopically positive margins documented on pathologic examination. All patients received continuous-course external-beam radiation therapy delivered daily using conventional fractionation. Twenty-five patients (42%) were treated using conventional radiation techniques, and 35 patients (58%) were irradiated using intensity-modulated radiation therapy (IMRT). Concurrent cisplatin-based chemotherapy was administered to 32 patients (53%). A prophylactic gastrostomy tube was placed before the initiation of radiation therapy for 40 patients (67%).

Simulation and target volume delineation

At simulation, the head, neck, and shoulders were immobilized in a hyperextended position using a perforated thermoplastic head mask with the neck supported on a Timo cushion (S-type, Med-Tec, Orange City, IA) mounted on carbon fiber board (S-type, Med-Tec, Orange City, IA). Axial images with contiguous 3-mm slice thickness without contrast were obtained on a CT simulator (Picker PQ2000, Philips Medical Systems, Andover, MA) and transferred into a contouring workstation, where delineation of target and normal tissue structures was performed.

Radiation therapy was delivered using megavoltage equipment with 6-MV photons. The target volumes included the bilateral nodal regions and mucosal axis, including the nasopharynx, oropharynx, larynx, and hypopharynx. For patients treated by conventional radiation therapy, a shrinking field technique was used with initial opposed lateral fields to treat the primary tumor bed and upper neck lymph nodes. In general, the anterior border included the posterior third of the nasal cavities and the anterior tonsillar pillars; the posterior border was placed behind the spinous process, the superior border was placed at the midsphenoid sinus or bottom of the pituitary fossa to encompass the nasopharynx and base of skull, and the inferior border was placed just above the shoulders. Any surgical scar was wired to ensure 2 cm of coverage in all directions. The lower neck nodes were treated with a matched low anterior neck field using an isocentric technique to eliminate divergence into treatment fields. The spinal cord was limited to 45–50 Gy. Electrons were used to boost areas overlying or posterior to the spinal cord after field reductions.

The IMRT was delivered using a simultaneous-integrated boost technique. For patients treated by primary IMRT, the gross tumor volume (GTV) was specified as the gross extent of tumor as demonstrated by imaging and physical examination. The high-risk clinical target volume (CTV1) was the GTV plus a margin of 1–2 cm to account for microscopic disease spread. For patients treated with IMRT postoperatively, the CTV1 was defined as the surgical nodal bed including all areas of extracapsular extension. In most cases, most of the ipsilateral neck was also included in the CTV1. The CTV2 included the prophylactically treated contralateral neck. The pharyngeal axis was generally included in the CTV2, although in a few cases was included in the CTV1. In some additional patients, a CTV3 was created to designate an area at lowest risk within the prophylactically treated neck. The low neck was encompassed within the IMRT plan. The planning target volume (PTV) contained an automated 0.3- to 0.5-cm expansion of the CTV to account for patient setup error to create PTV1, PTV2, and PTV3, if necessary.

Dose specification

Radiation doses to undissected gross disease in the neck ranged from 70 to 74 Gy (median, 70 Gy). For patients treated by conventional radiation therapy, the total doses to the involved tumor bed ranged from 60 to 66 Gy (median, 60 Gy), doses to the pharyngeal axis ranged from 54 to 60 Gy (median, 56 Gy), and doses to prophylactically treated nodal areas ranged from 54 to 63 Gy (median, 54 Gy). For patients treated by primary IMRT, radiation plans were designed to deliver a dose of 70 Gy in 33–35 fractions to at least 95% of the PTV1. For postoperatively treated IMRT patients, radiation plans were designed to deliver a dose of 60–66 Gy (median, 63 Gy) to the PTV1. The prescribed dose to the PTV2 ranged from 54 to 60 Gy (median, 56 Gy); for PTV3, the prescribed dose ranged from 54 to 56 Gy (median, 54 Gy).

Chemotherapy details

Concurrent chemotherapy consisted of cisplatin, which was typically administered for three cycles (100 mg/m^2 of body surface area intravenously on Days 1, 22, and 43). In selected patients, concurrent weekly cisplatin with a dose of 50 mg/m^2 for a median of four cycles (range, 3–6 cycles) was delivered. No additional or maintenance chemotherapy was administered after patients completed radiation therapy.

Endpoints and statistical analysis

Patients were asked to return for follow-up visits 2–3 weeks after the completion of radiation therapy and then every 2–3 months for the first year, every 4–6 months for the second year, and then