Larynx-Sparing Radiotherapy for Squamous Cell Carcinoma From an Unknown Head and Neck Primary Site

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Abstract: The objective of this study was to evaluate the efficacy of larynx-sparing radiotherapy (RT) alone or in combination with a neck dissection for patients with squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck primary site. Seventeen patients were treated with curative intent between 1997 and 2002; 16 of 17 patients had follow up for at least 2 years. No patient developed a squamous cell carcinoma in a head and neck mucosal site after treatment. One patient (6%) had persistent nodal disease and 1 patient (6%) had recurrent nodal disease 1 year after completing RT. No patients experienced distant metastases. The 5-year cause-specific and overall survival rates were 88% and 82%, respectively. Based on our limited experience, larynx-sparing RT appears to result in a high likelihood of local–regional control and survival and likely reduces both acute and late toxicity.

Key Words: treatment outcome, radiotherapy, larynx, neoplasms, unknown primary

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Squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck mucosal site is relatively uncommon and its management is controversial.[1,2] Treatment decisions are based on nonrandomized case series[3–7] because randomized data from prospective trials comparing treatment options are not available. Treatment alternatives include neck dissection alone, radiotherapy (RT) to the involved neck alone, and RT to both sides of the neck and the potential mucosal primary site.[8–18] We present our experience with the "larynx-sparing" technique. A planned neck dissection may be added after RT if the metastatic adenopathy does not completely resolve.[19] Patients with advanced N2 and N3 disease would probably benefit from concomitant chemotherapy, particularly if the involved lymph nodes are located below the level of the thyroid notch.[20,21] Although RT to both sides of the neck and potential mucosal primary sites reduces the risk of a local–regional recurrence, the 5-year survival rates are approximately 50%, regardless of the treatment strategy.[16] The disadvantage of mucosal RT is the additional morbidity, whereas the disadvantage of RT to the neck alone is the increased likelihood of late complications if RT is subsequently necessary to treat a local recurrence. Thus, it has been our policy since 1964 to irradiate both sides of the neck and the potential primary sites, including the nasopharynx, oropharynx, larynx, and hypopharynx.[16] A subsequent analysis of 130 patients who underwent a diagnostic evaluation at our institution for squamous cell carcinomas metastatic to the cervical lymph nodes from an unknown head and neck primary site revealed that 83% of the primary tumors that were detected were located in either the tonsillar fossa or base of tongue.[22] Thus, in 1997, we modified our treatment technique to irradiate only the oropharynx and both sides of the neck. The RT portals included the nasopharynx with a relatively tight margin because it was necessary to include the retropharyngeal lymph nodes, and a modest expansion of the portals to include the remainder of the nasopharynx was thought to add little additional morbidity.[23] The advantage of this technique, which is not new and has been used sporadically at other institutions, is that the morbidity of RT is diminished by eliminating most of the larynx and hypopharynx from the RT fields.[24] This has been used consistently since 1997 by the senior author (WMM) to treat all patients with unknown primary head and neck squamous cell carcinomas with level 2 and level 3 presentations.

METHODS AND MATERIALS

Seventeen patients were treated with curative intent at the University of Florida between January 1997 and July 2002. All had previously untreated squamous cell carcinomas metastatic to the cervical lymph nodes from an unknown head and neck primary site. Patients received RT alone or combined with a planned neck dissection. Eleven patients were excluded from the study because they were either treated with palliative intent (4 patients) or had the larynx and hypopharynx included in the RT portals (7 patients). Patients had follow up from 0.4 to 7.0 years (median, 4.0 years). One patient was lost to follow up at 0.5 years. Follow up on living patients ranged from 0.5 to 7.0 years (median, 4.0 years). Fourteen patients (82%) were male and 3 patients (18%) were female. Age ranged from 44 to 76 years (median, 57 years). Sixteen patients (94%) were white and 1 patient (6%) was black.

Fifteen patients (88%) presented with metastatic adenopathy confined to 1 side of the neck and 1 patient had

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bilateral metastatic lymph nodes. The distribution of patients according to the level of nodal involvement was level I, none (0%); level II, 16 patients (94%); level III, 7 patients (41%); level IV, 3 patients (18%); and level V, 1 patient (6%). Nine patients (53%) had only level II involvement. The maximum diameter of the largest involved lymph node ranged from 2 to 10 cm (median, 4 cm). All patients were staged according to the 2002 American Joint Committee on Cancer staging system.[25] Distribution of patients according to N stage was N1, 1 patient (6%); N2a, 4 patients (24%); N2b, 7 patients (41%); N2c, 2 patients (12%); and N3, 3 patients (18%).

The histologic diagnosis was established as follows: fine-needle aspiration, 11 patients (65%); incisional biopsy, 1 patient (6%); excisional biopsy, 4 patients (24%); and neck dissection, 1 patient (6%). The histologic differentiation was as follows: well to moderately differentiated, 3 patients (18%); poorly differentiated, 8 patients (47%); and not specified, 6 patients (35%).

All patients underwent a physical examination, including multiple comprehensive head and neck examinations, and chest roentgenogram or computed tomography (CT) of the chest. All but 1 patient (who was deemed ineligible for general anesthesia) underwent panendoscopy with directed biopsies of the head and neck mucosal sites. Five patients (29%) who had adequate lymphoid tissue in the tonsillar fossa underwent a tonsillectomy. All patients underwent head and neck CT scans, 3 patients (18%) underwent head and neck magnetic resonance imaging (MRI), and 2 patients (12%) underwent 2-(F-18) fluoro-2-deoxy-D-glucose single photon emission computed tomography (FDG-SPECT). FDG-SPECT is no longer used at our institution, and fluorodeoxyglucose positron emission tomography (FDG-PET) is not routinely used in the diagnostic evaluation of these patients.

Parallel-opposed portals were used to treat oropharynx, nasopharynx, and upper cervical lymph nodes; the inferior border was placed at the thyroid notch (Fig. 1).[26] The fields were treated to 64.8 Gy in 36 fractions with radiation off of the spinal cord at approximately 45 Gy. The neck below the level of the thyroid notch was routinely irradiated with an anterior *en face* portal to 50 Gy in 25 fractions. A tapered midline block extending to the level of the bottom of the cricoid cartilage was used to shield the larynx. Thereafter, the portals were reduced and the involved portions of the low neck were boosted an additional 10 to 20 Gy at 2 Gy per fraction. Treatment was usually administered with 6 MV x-rays. The posterior strips were boosted as necessary with 10 MeV electrons after reduction off of the spinal cord. All patients were treated with continuous-course RT. Sixteen patients (94%) were treated with once-daily fractionation, and 1 patient (6%) was treated with twice-daily fractionation.

In patients treated with once-daily fractionation, RT doses ranged from 55.8 to 66.6 Gy (median, 64.8 Gy). Fifteen of 17 patients received 64.8 Gy at 1.8 Gy per fraction. One patient treated with twice-daily fractionation received an RT dose of 64 Gy at 1.23 Gy per fraction.

Five patients were treated with RT alone, 11 patients underwent a unilateral neck dissection, and 1 patient underwent a bilateral neck dissection.

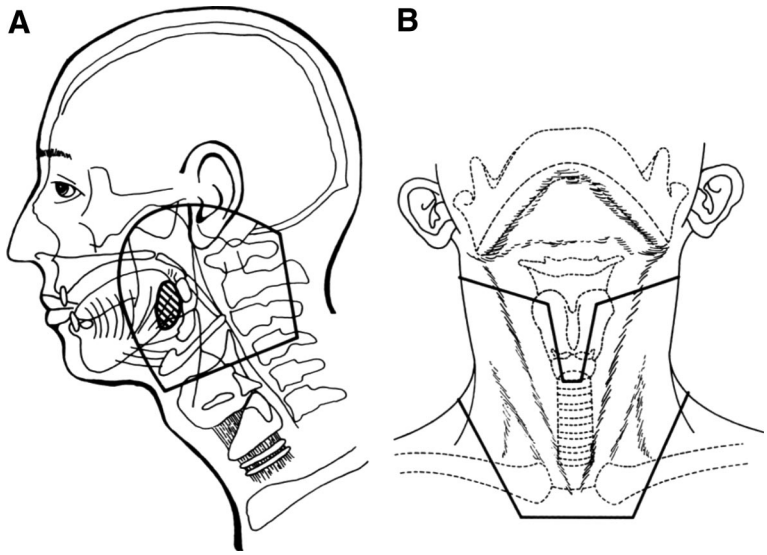

FIGURE 1. (A, B) Radiation portals sparing the larynx. A, Parallel-opposed fields include the primary lesion with a 2- to 3-cm inferior margin. The lower border of the field is placed at the thyroid notch and slants superiorly as the junction line proceeds posteriorly. This substantially reduces the amount of mucosa, larynx, and spinal cord included in the primary treatment portals. B, *En face* low-neck portal with tapered midline larynx block. It is not necessary to treat the supraclavicular fossa unless clinically positive nodes are found in that particular hemineck. A 5-mm midline tracheal block may be placed in the low-neck portal (dashed line). Reprinted with permission from Mendenhall WM, Parsons JT, Million RR. Unnecessary irradiation of the normal larynx. *Int J Radiat Oncol Biol Phys*. 1990;18:1531–1533 (Fig. 2A–B, p. 1533).

One patient received 2 cycles of concomitant chemotherapy with fluorouracil and cisplatin.

All statistical estimates were generated using SAS software.[27] The rates of head and neck mucosal sites control, neck control, freedom from distant metastases, absolute survival, and cause-specific survival were calculated using the product-limit method.[28] Complications were coded as severe if they necessitated hospitalization, surgical intervention, or resulted in death.[29]

RESULTS

No patient experienced a head and neck mucosal site failure after RT. One patient (6%) experienced recurrent cervical lymphadenopathy 1 year after treatment and 1 patient had persistent nodal disease and died 4 months after treatment. No patient developed distant metastases. The 5-year cause-specific and overall survival rates were 88% and 82%, respectively (Fig. 2). No patient experienced a severe complication.

DISCUSSION

Management of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck mucosal site remains controversial. Although the number of patients in our study is limited, our data support our current policy, which is to limit mucosal-site RT to the oropharynx. Although the likelihood of an occult nasopharyngeal primary tumor is low, the nasopharynx is included in the RT portals because it is necessary to irradiate the retropharyngeal lymph nodes and because modest enlargement of the portals to include the nasopharynx (excluding the pituitary gland) probably does not significantly increase toxicity. Patients who present with N1 disease are treated with a neck dissection, and unless there are indications to irradiate the neck (extracapsular extension, multiple positive nodes, and/or violated neck before neck dissection), RT is withheld and the patients are closely observed. In practice, few patients are suitable for neck dissection alone.

Our current practice is to treat the oropharynx, nasopharynx, and upper neck to 64.8 Gy in 36 once-daily fractions with parallel-opposed equally weighted fields with a reduction off of the spinal cord at 45 Gy in 25 fractions. The low neck is treated with an anterior field to 50 Gy in 25 once-daily fractions. The junction between the parallel-opposed fields and low-neck portal is at the thyroid notch. Clinically positive lymph nodes in the low neck and/or posterior strip are boosted to 65 to 70 Gy. Six-megavolt photons are usually used for the parallel-opposed portals and low neck; 10 MeV electrons are usually used to treat the posterior strip after reducing off of the spinal cord at 45 Gy. Patients with advanced N2 and N3 disease receive concomitant weekly 30 mg/m^2 cisplatin during the course of RT. Patients undergo a CT scan 1 month after completing RT, and a planned neck dissection is performed if the likelihood of residual regional disease is thought to exceed 5%.

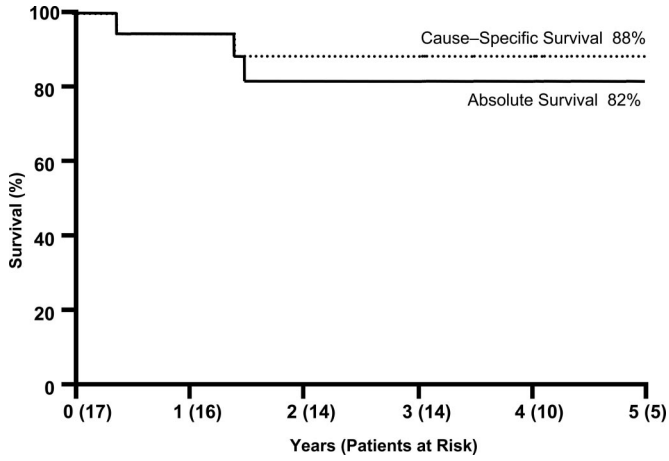

FIGURE 2. Cause-specific survival and absolute survival rates. The number of patients at risk for various time intervals is indicated (in parentheses) on the horizontal axis.

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