

Management of Cervical Metastases in Advanced Squamous Cell Carcinoma of the Tonsillar Fossa Following Radiotherapy

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Objective: To assess the value of planned neck dissection in patients with a complete response to definitive radiotherapy for squamous cell carcinoma of the tonsillar fossa with advanced nodal disease.

Design: Case series.

Setting: Academic tertiary care medical center.

Patients: A consecutive series of 36 patients with squamous cell carcinoma of the tonsillar fossa with N2 or N3 nodal disease treated with primary radiation therapy with or without concurrent chemotherapy between January 1, 1992, and April 1, 2003, at the University of California, San Francisco, Comprehensive Cancer Center. Patients treated with primary surgery, those treated with palliative intent, or those with preexisting malignancies were excluded.

Main Outcome Measures: Regional control and overall survival.

Results: Of the study group, 15 patients (42%) achieved a complete response, 17 (47%) achieved a partial response, and 1 (3%) was a nonresponder. The response in 3 patients (8%) could not be assessed. Of the 15 patients with a complete response, only 2 (13%) later developed regional recurrences, 1 of which was an isolated recurrence in the neck. Regional control and overall survival at 3 years were 78% and 48%, respectively.

Conclusions: The rate of regional recurrence after a complete response to radiation therapy with or without concurrent chemotherapy for tonsillar squamous cell carcinoma with advanced cervical metastases is low. Our results support close surveillance of the neck in those who have achieved a complete response after radiation therapy with or without chemotherapy.

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SQUAMOUS CELL CARCINOMA (SCC) of the oropharynx can be treated with surgical resection, radiation therapy, chemotherapy, or a combination thereof, depending on the extent of the disease. For advanced disease, the 2 main treatment options are primary surgical resection followed by radiotherapy and primary radiotherapy with or without concurrent chemotherapy, followed by surgical salvage when necessary. Cure and recurrence rates are similar between the 2 approaches. There has been a trend in recent years toward an organ preservation approach to avoid the morbidity of surgical resection of large primary tumors.

Whereas the efficacy of primary radiation therapy for oropharyngeal SCC is generally accepted, the management of cervical metastases after the completion of radiation therapy has been more controversial. For patients with N0 or N1 dis-

ease who demonstrate a complete response to primary radiation therapy or concurrent chemoradiation, there is general agreement that routine surveillance suffices. For patients with N2 or N3 disease who demonstrate a complete response, however, there is considerable debate regarding the optimal management strategy. Some surgeons recommend a planned neck dissection after radiotherapy,¹⁻³ while others opt to observe the patient with close clinical follow-up and imaging studies.⁴⁻⁶ The main advantage of the latter approach is the reduction in the number of unnecessary surgical procedures in patients who would remain disease free even without the planned neck dissection. This is particularly important given the potential morbidity of neck dissection in a previously irradiated field. A disadvantage of this approach is the possibility of failure in clinical examination and radiographic imaging to detect residual or recurrent neck metastases.

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This report describes the outcome of patients with N2 or N3 SCC of the tonsillar fossa treated with primary radiation therapy or concurrent chemoradiation at our institution. Patients who achieved a complete response in the neck were observed. We analyze the treatment outcome and discuss the adequacy of the strategy of close observation vs planned neck dissection for this group of patients.

METHODS

Between January 1, 1992, and April 1, 2003, 36 patients with N2 or N3 SCC of the tonsil and/or tonsillar fossa were treated with primary radiation therapy or concurrent chemoradiation with curative intent at the University of California, San Francisco, Comprehensive Cancer Center. Patients treated with primary surgery or with palliative intent were excluded. One patient with preexisting unresectable hepatocellular carcinoma was excluded, as was a patient with stage III Hodgkin disease. Each patient's condition was staged according to the appropriate classification as outlined by the American Joint Committee on Cancer (1992, 1997, or 2002).

Radiation therapy was delivered using several different protocols. Ten patients were given conventional fractionation to a total dosage between 70 and 74 Gy. Fourteen patients received 72 Gy in 42 fractions over 49 days via the concomitant boost technique. One patient enrolled in RTOG 90-03 was randomized to the 1.6-Gy twice-daily arm with a break, and 2 others were randomized to the 1.2-Gy twice-daily arm. Nine patients since 2000 were treated with intensity-modulated radiotherapy in fractions of 2.12 cGy to the gross tumor volume and 1.8 Gy to the clinical target volume. Of the 36 patients in the total study group, 21 received platinum-based concurrent chemotherapy.

All gross nodal disease in our patients was specifically targeted, or "boosted," to 70 Gy, whether with traditionally planned radiation or intensity-modulated radiotherapy. It is our institutional policy to treat gross neck disease to 70 Gy, rather than to limit the radiation dose to 60 Gy in anticipation of a planned neck dissection.

Response to radiation or chemoradiation was assessed at 6 to 8 weeks after completion of the treatment. A complete response was defined as the lack of visible residual tumor at the primary site and the complete regression of palpable neck disease. Patients with residual tumor at the primary site or a residual neck mass on clinical examination were considered to be partial responders and were recommended to undergo salvage surgery. Of the patients who underwent a posttreatment computed tomographic (CT) scan, those with a residual neck mass greater than 1 cm or with abnormal morphologic features (central lucency or extracapsular involvement) were also considered partial responders. Regional control and overall survival times were calculated from the completion of radiation therapy to the time of death or last follow-up.

The study design and protocol were reviewed and approved by the University of California, San Francisco, Committee on Human Research.

RESULTS

Thirty-six patients with N2 or N3 SCC of the tonsillar fossa treated with primary radiation therapy or chemoradiation were included in the study. The age at presentation ranged from 34 to 84 years (median, 53 years). All

Table. Tumor and Nodal Staging of Patients*

Tumor Stage	Nodal Stage		Total
	2	3	
1	5	0	5
2	14	2	16
3	5	0	5
4	6	4	10
Total	30	6	36

*Data are given as number of patients.

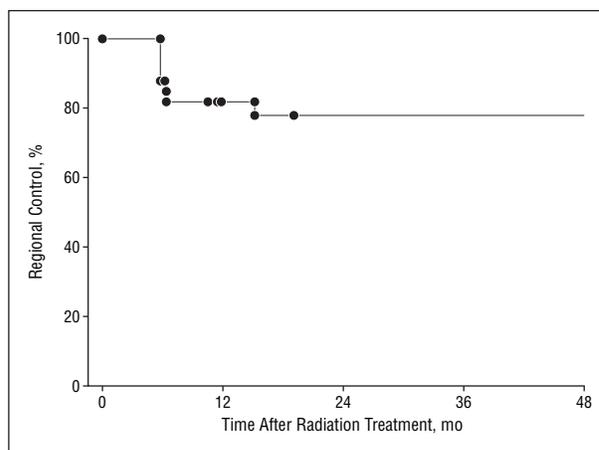


Figure 1. Regional control after radiation treatment.

patients except 2 were men. The tumor and nodal staging of the study group is shown in the **Table**.

None of the 12 patients treated before 1998 received concurrent chemotherapy. Of the 24 patients treated since 1998, all received concurrent chemotherapy except for 3, one of whom was human immunodeficiency virus positive and another with a history of cirrhosis secondary to hepatitis. The median follow-up is 24 months from the completion of radiation therapy (range, 2-120 months).

Of the 36 patients, 15 (42%) achieved a complete response to radiation therapy, 17 (47%) achieved a partial response, and 1 (3%) was a nonresponder. The response in 3 patients (8%) could not be assessed. Regional control at 3 years was 78% by Kaplan-Meier analysis (**Figure 1**).

Of the 15 complete responders, 11 remained disease free at last follow-up (median, 25 months). Nine patients were alive and without evidence of disease, whereas 2 died of other causes but were disease free at the time of death. Of the 4 complete responders who developed recurrence, 1 developed isolated regional recurrence, 1 had regional and local recurrences, 1 experienced treatment failure at the primary site only, and 1 developed distant metastases. All 4 subsequently died of disease. One of the patients with regional recurrence experienced recurrence at 7 months' posttreatment and underwent a salvage neck dissection, but developed local recurrence 11 months later. The other patient with regional recurrence was a patient who delayed the initial

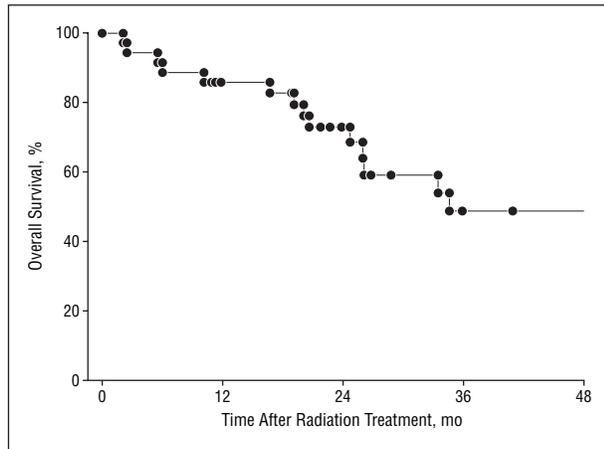


Figure 2. Overall survival after radiation treatment.

primary radiation by 2 years after diagnosis, declined maintenance chemotherapy after the initial treatment, and developed the regional recurrence at 16 months after completion of radiation therapy. He declined further treatment.

Seventeen patients achieved a partial response. Thirteen patients underwent salvage neck dissections, 10 of whom had no viable tumor cells on the final pathologic report. Of these 10 patients, 8 remained disease free at last follow-up. Two developed distant metastases and have subsequently died. Of the 3 patients with a positive pathologic result, 1 had a necrotic matted lymph node containing metastatic squamous cells that had questionable viability; this patient remained disease free at last follow-up. The other 2 patients had numerous positive lymph nodes and have since died, with recurrent disease in the neck.

Four patients had a partial response but did not undergo neck dissection. One patient underwent a fine-needle aspiration of the residual lymph node, which showed only necrotic tumor cells. The lymph node has since diminished, and the patient remained free of disease at the 7-month follow-up. The second patient elected not to undergo surgery. The residual neck disease had subsequently diminished clinically and radiographically. A follow-up fine-needle aspiration showed only necrotic debris, and the patient remained free of disease at 23 months. The third patient had distant metastases and, therefore, did not undergo neck dissection. The fourth patient did not undergo neck dissection for unclear reasons and died of unknown causes within 3 months of completion of radiation therapy.

The only nonresponder to radiation therapy achieved a complete response at the primary tumor site but had cervical metastases that progressed through treatment, resulting in carotid encasement. He died of disease 17 months after completing radiation therapy.

Of the 36 patients, 21 (58%) were alive at last follow-up, with 20 free of disease. The minimum length of follow-up for survivors is 6 months. Of the 15 patients who had died, 10 died of disease, 2 died of other causes and were free of disease at the time of death, and 3 died of unknown causes and with disease. The overall survival at 3 years was 48% by Kaplan-Meier analysis (Figure 2).

There is continued debate regarding the role of planned neck dissection after primary radiation or concurrent chemoradiation for advanced cervical metastases of head and neck SCC. Some surgeons routinely perform neck dissection 6 to 8 weeks after completion of radiation therapy regardless of the response to treatment. Other surgeons elect to observe complete responders, citing the morbidity associated with operating in an irradiated field and the low rate of regional recurrence from this approach. Without randomized, prospective, clinical trials to compare the outcomes of the 2 options, patients and physicians must rely on data from series in which one or the other strategy was adopted.

The present study demonstrates a low rate of regional recurrence in a group of patients with SCC of the tonsil treated with primary radiation therapy with or without concurrent chemotherapy with N2 or greater disease. Only 2 (13%) of the 15 patients who had a complete response developed regional recurrence. Because 1 of the 2 later developed a local recurrence, the rate of isolated regional recurrence is only 7% (1/15). This is comparable to the rate of regional recurrence we and others have observed in a group of patients treated with primary radiation therapy with or without chemotherapy for base of tongue SCC. Pletcher et al⁶ showed that 3 of 25 complete responders developed recurrent neck disease, and 2 of the 3 had concurrent local recurrence, leaving a 4% rate of isolated regional recurrence. Similarly, Peters et al⁴ and Clayman et al³ found a 5% and 0% rate of isolated neck recurrence, respectively, in patients with oropharyngeal SCC after a complete response to radiotherapy. These low rates of isolated regional recurrence support the practice of close observation for complete responders.

Several groups have cited the relatively high rates of residual disease in neck dissection specimens from complete responders to advocate planned neck dissections. In a study of 68 patients with base of tongue SCC, Lee et al¹ showed that 33% of the complete responders had persistent tumor cells on pathologic examination of planned neck dissection specimens. Similar findings were reported by Wang et al² and Roy et al.³ These groups performed planned neck dissections for all patients with N2 or greater cervical disease regardless of response to primary radiotherapy, and the findings were used to support this practice.

The high rates of residual neck disease found in planned neck dissection specimens of complete responders stand in sharp contrast to the relatively low rates of regional recurrence in complete responders who were observed. This discrepancy raises several questions. Although histopathologic analysis of neck dissection specimens is considered the gold standard of assessing residual disease after treatment, there is still an element of uncertainty regarding what is considered a positive pathologic specimen. In the present study and in other reports in the literature, there are cases in which the lymph nodes are found to contain largely necrotic debris containing few residual tumor cells of "questionable viabil-

ity.” These are counted as positive pathologic specimens by the study authors, but this may overestimate the true viability of the residual tumor cells. This consideration is supported by the finding of Strasser et al,⁷ who performed Ki67 immunohistochemical staining on post-radiation neck dissection specimens and found that only 27% (3/11) of the pathologically positive specimens contained proliferating tumor cells. Applying this percentage to the 33% of complete responders with positive neck dissection specimens, a rough calculation shows that approximately 9% of complete responders could still harbor proliferating tumor cells, which is comparable to the rates of regional recurrence in patients who are observed.

Whether residual tumor cells identified by histopathologic analysis at 6 weeks' postradiation could give rise to recurrent disease if left in the patient is also unclear. These cells may not be viable, and even viable cells after radiation are not necessarily clonogens. Two partial responders in this study who declined neck dissections continued to show regression of their residual neck disease more than 6 weeks' posttreatment. The residual neck masses subsequently resolved as determined by physical examination and CT scan, and the patients remain free of disease at last follow-up. The rate of partial response as determined by pathologic analysis from neck dissections, therefore, should be considered an upper limit of the true rate of partial response.

The inadequacy of clinical examination and CT in assessing the response of cervical metastases to primary radiation therapy is often cited as an argument in favor of planned neck dissections. Velazquez et al⁸ investigated the sensitivity and specificity of CT in predicting residual neck disease in patients undergoing planned neck dissections after primary radiotherapy and chemoradiotherapy. They found the negative predictive value of CT to be 73% and the positive predictive value to be only 40%. The latter statistic suggests that many of the neck dissections performed for patients with a partial response based on posttreatment CT are expected to result in negative pathologic findings. Our finding that 10 (77%) of 13 neck dissections for partial responders yielded no tumor cells is consistent with this result. Similarly, Roy et al³ found that 13 of 26 partial responders had negative neck dissection results. The current methods of radiologic assessment clearly tend to misclassify true complete responders as partial responders. The inadequate sensitivity and specificity of CT in predicting residual neck disease point to a need for more advanced techniques in noninvasive assessment of the posttreatment neck.

Positron emission tomography with fluorodeoxyglucose (FDG-PET) has shown some promise as an additional diagnostic tool for the assessment of the posttreatment neck. Positron emission tomography with FDG has been shown to be sensitive and specific in detecting recurrent disease.^{9,10} Lapela et al¹¹ showed a positive predictive value of 100% in the identification of recurrent disease by FDG-PET. These reports suggest that a positive FDG-PET result after a negative posttreatment CT result should lower the rate of false negatives from the conventional combination of physical examination and

CT for evaluation of the posttreatment neck. This could potentially reduce the already low rate of regional recurrence in complete responders. However, FDG-PET has also been shown to have a negative predictive value of only 14% to 17% when done 1 to 2 months after the completion of radiation therapy, presumably because of the limited spatial resolution of FDG-PET.¹²⁻¹⁴ Schoder et al¹⁵ recently reported the application of fused PET/CT to head and neck cancer patients and showed a higher accuracy of tumor characterization over conventional PET. The use of this new imaging modality in the assessment of the posttreatment neck may overcome some of the limitations of current techniques.

The close observation strategy for complete responders of radiation therapy may only apply to certain types of head and neck SCC. Data to support the omission of planned neck dissections have mostly come from studies of oropharyngeal SCC patients. It would be unwise to assume that the favorable results seen in oropharyngeal SCC are applicable to other sites without similar supporting data. It is well established that tumors arising from different primary sites in the head and neck may show different biological behavior in terms of aggressiveness and radiosensitivity. In addition, there is potentially a geometric component to the treatment response of nodal disease depending on the location of the primary tumor. It is our institutional policy to specifically target gross neck disease to 70 Gy. We are aware that some institutions prefer to limit the radiation dose to the neck disease to 60 Gy when a neck dissection is planned to limit the potential morbidity in a radiated field. In this case, the only nodes that receive a full tumoricidal dose of 70 Gy are those in close proximity to the primary tumor and are treated incidentally. These are the only nodes that may be observed. We would not consider observation for any initially pathologic lymph node that had received less than 70 Gy.

In conclusion, the strategy of close observation for patients with tonsillar SCC and N2 or greater cervical metastases with a complete response to radiation or chemoradiation therapy is supported by a low rate of isolated regional recurrence. Our results support close surveillance of the neck in those who have achieved a complete response after radiation with or without concurrent chemotherapy. Prospective randomized trials to compare the long-term recurrence and survival rates of patients managed with the 2 different approaches will be required to provide more clarity on this issue.

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