

Response of Neck Metastases to Chemoradiation[§]

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Abstract: *Objectives:* To analyze the response of neck disease to treatment with primary chemoradiation.

Methods: Retrospective review of patients with head and neck cancer treated with chemoradiation with curative intent at a Veterans hospital.

Results: Thirty-four patients were identified who received concomitant chemotherapy and radiation: 7 patients with N1, 22 with N2, and 7 with N3 disease. 78% of patients had complete clinical and radiographic response of their neck disease following treatment. Eleven patients underwent neck dissection post treatment. 33% of the neck specimens had pathologically positive nodes. 81% of patients were alive without evidence of recurrent disease in the primary site or neck at last follow-up.

Conclusions: The majority of HNSCC patients treated with chemoradiation have complete response in the neck. Patients with clinical and radiographic evidence of complete response in the neck may not require neck dissection, even with N2 or greater disease.

INTRODUCTION

Multiple treatment modalities have been used for the treatment of head and neck squamous cell carcinoma (HNSCC). Over the last fifteen years there has been a trend toward organ preservation protocols for HNSCC. Since the original studies on laryngeal preservation were published in 1991 [1], there has been a shift toward use of primary chemoradiation, with curative intent, for oropharyngeal and hypopharyngeal squamous cell carcinomas as well. Chemoradiation has been shown to give excellent locoregional control rates for HNSCC and is a reasonable alternative to surgery with postoperative radiation for selected tumors [2]. However, there continues to be ongoing discussion regarding the best management of advanced neck disease with this modality and the role of a planned neck dissection in this setting. Some authors advocate planned neck dissection following CRT for all patients with N2 or N3 disease pre-treatment, while others believe patients without clinical or radiographic evidence of neck disease do not necessarily need a neck dissection [3-8]. This study has two objectives: (1) to analyze the response of neck disease to treatment of HNSCC patients with primary chemoradiation (CRT); and (2) to determine whether a planned neck dissection should be done following chemoradiation in patients who had positive neck disease pre-treatment.

METHODS

Institutional Review Board approval for this project was obtained. Medical records for 280 HNSCC patients were reviewed between March 2000 and January 2006 at the West Los Angeles VA Medical Center. Inclusion criteria included patients with advanced stage (stage III and IV) HNSCC who also had positive nodal disease (N1, N2, or N3) and were treated with primary chemoradiation. To be included these patients also must have completed a full course of conventional external beam radiation (over 5 to 7 weeks) and at least one concurrent dose of chemotherapy (Table 2). Exclusion criteria included squamous cell carcinoma of other areas of the head and neck including salivary glands, distant metastases at diagnosis, absence of cervical nodal disease, and any patients that did not complete radiation therapy or did not receive at least one dose of chemotherapy. A total of 36 subjects were identified and included in this study.

RESULTS

There were 36 HNSCC patients identified during this time period who were treated with primary CRT and had positive cervical adenopathy pre-treatment. Primary sites included the oral cavity, oropharynx, hypopharynx, and unknown primary. There were 35 males and 1 female. The age range was from 47 to 82 (median 62.5). There were 7 patients with N1 disease, 22 with N2 (3 with N2a, 13 with N2b, and 6 with N2c), and 7 with N3 nodal disease. Follow-up ranged from 2 to 66 months (median 22.5) (Table 1).

Nearly all patients received a platinum-based chemotherapy regimen concomitant with their radiation (Table 2). Patients received one to three cycles of chemotherapy, with

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Table 1. Patient Characteristics

Characteristics	Value
Age, range (median), y	47-82, 62.5
Sex	
Female	1
Male	35
Primary site	
Oral cavity	1
Oropharynx	30
Hypopharynx	4
Unknown Primary	1
Primary Stage	
Tx	1
T1	3
T2	8
T3	11
T4	13
Nodal Stage	
N1	7
N2	22
N3	7
Number of neck dissections	12
Positive neck dissections	4
Follow-up, mean (median), mo	24.6 (22.5)

most patients receiving one or two cycles. Conventional external beam radiation doses of 7000—7200 cGy were delivered to both necks in all cases. In addition to physical exam, all patients underwent CT or MRI imaging following completion of CRT and 10 underwent PET scanning.

Table 2. Chemotherapy Regimen

	# Pts.	1 Cycle	2 Cycles	3 Cycles
Cis	4	1	3	
Cis/5fu	29	10	16	3
Cis/Taxol	2	2		
Cis/Etoposide	1			1
Carb/5fu	1	1		
Carb/Taxol	1	1		
Other	1			

Abbreviations: Cis = Cisplatin; 5fu--5-Flourouracil; Carb = Carboplatin.

78% of all patients had complete clinical and radiographic response of their neck disease following treatment: 86% of N1, 82% of N2, and 57% of N3 (Table 3). One addi-

tional patient had radiographic evidence of neck disease post treatment that continued to diminish in size on subsequent CT scans over the following year. Because of incomplete clinical or radiographic response, eleven patients underwent neck dissection post treatment (2 patients with N1, 6 patients with N2, and 3 patients with N3 disease). One N2 patient underwent bilateral neck dissections because of incomplete clinical response. 33% of the neck specimens had pathologically positive nodes. One of the N1, 2 of the N2, and 1 of the N3 neck dissections had positive nodes (Table 4).

Table 3. Response to Chemoradiation by Nodal Stage

	CR	PR
N1	86% (6)	14% (1)
N2	82% (17)	18% (4)
N3	57% (3)	43% (3)

Abbreviations: CR = complete response; PR = partial response.

Table 4. Nodal Involvement on Neck Dissection

	# of ND	% Positive
N1	2	50% (1)
N2	6	33% (2)
N3	3	33% (1)

Abbreviations: ND = neck dissection.

Two patients who had complete clinical and radiographic response in the neck (without neck dissection) went on to recur at their primary site and die of their disease. Two patients that underwent neck dissection after incomplete response to CRT died of disease (one recurred in the neck and one developed metastatic disease). Three patients (two without neck dissection and one with) died of unrelated causes and had no evidence of locoregional or distant disease at time of death. 84% of patients without neck dissection and 72% of patients with neck dissection were alive without evidence of locoregional or distant disease at last follow-up.

DISCUSSION

Primary CRT with curative intent is increasingly being utilized for advanced stage HNSCC. While control rates at the primary site are high, the management of the neck following CRT remains controversial. Review of the literature demonstrates conflicting opinions. Some authors advocate planned neck dissection following CRT for all patients with N2 or N3 disease [3-5], while others recommend watchful waiting in the absence of clinical or radiographic evidence of disease [6-8]. Optimal imaging techniques are debated as well, and neither CT, MRI, nor PET/CT scanning is a reliable method for detecting persistent nodal disease in the neck following CRT. One recent study showed a negative predictive value of 100% only when physical exam, radiographic studies, and PET all demonstrated complete response [9]. Another recent paper likewise questions the necessity of planned neck dissection following chemoradiotherapy for advanced head and neck cancer, suggesting that molecular

markers in combination with PET/CT may be beneficial in identifying patients who require post-treatment neck dissection [10].

Those who argue in favor of planned neck dissection point to the significant incidence of pathologically positive nodes even in necks without clinical evidence of disease [3]. However, the biological significance and behavior of cancer cells in the nodes following CRT is unclear. These cells may not be viable, and remain in an inactive state indefinitely or ultimately regress with time. This was likely the case in our patient who had a persistent node on CT scan that continued to decrease in size over the following year.

Another argument in favor of a planned neck dissection is the fear that when a patient recurs in the neck following CRT, the recurrence is difficult to detect until it is large and possibly unresectable, due to the fibrosis and scarring that occurs. For this reason, post-CRT patients obviously need close clinical follow-up following treatment, and there should be a low threshold for obtaining imaging studies to aid in decision-making. In addition, if patient compliance is poor, a planned neck dissection several weeks following CRT may be prudent.

In our series, we found an excellent response of cervical nodal disease to primary CRT, even for N2 and N3 disease. Although we had three N2a, thirteen N2b, and six N2c patients (Table 1), due to the relatively small numbers in each category, disease control rates were not sub-divided, as recent literature as not shown significant differences when sub classifying N2 disease [4]. Just over three-quarters of the patients had complete clinical and radiographic response in the neck. However, interestingly there were 2 of 7 patients with N1 disease who did not have a complete response in the neck and required neck dissection, and one of the N1 necks had a pathologically positive node in the specimen. In addition, 3 of the 7 N3 patients had complete clinical and radiographic response in the neck. These observations demonstrate that it may not be possible to predict response of neck disease to CRT based on N stage alone.

The limitations of our study include the small sample size and relatively short median follow-up. In addition, not every patient received the same treatment regimen of chemotherapy and radiation. However, our data point to the need for further studies on the role of planned neck dissection for HNSCC patients treated with primary chemoradiation. Future studies will require collaboration with other institutions

to obtain adequate numbers of patients for conclusive statistical significance.

CONCLUSION

Nodal disease in HNSCC patients responds well to treatment with primary CRT. Our small series demonstrates that patients who have complete clinical and radiographic response in the neck may not need a planned neck dissection post-CRT, even if they had N2 or N3 disease pre-treatment. Careful follow-up is needed for patients who have a complete response in the neck, with regular imaging and physical examination.

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