ORIGINAL ARTICLE

NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT HYPERFRACTIONATED RADIATION THERAPY AND SENSITIZING CHEMOTHERAPY FOR LOCALLY ADVANCED (T3–T4) OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

Veronica Finnegan, BS, James T. Parsons, MD, Bruce D. Greene, MD, Vinay Sharma, MD

The Center for Radiation Oncology, Bethesda Memorial Hospital, Boynton Beach, Florida.
E-mail: jim.parsons@bethesdahealthcare.com

Accepted 9 June 2008
Published online 13 October 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20947

Abstract: Background. Radiation therapy (RT) is commonly used in the management of patients with advanced (T3–T4) oropharyngeal squamous cell carcinomas. In recent years, based upon the meta-analyses of randomized trials, chemotherapy administered concurrently with RT (chemoradiotherapy) has become the standard of care. Twice-a-day hyperfractionated or accelerated-fractionated RT regimens have been shown in a number of randomized trials to significantly improve the rate of local control compared with conventional once-a-day fractionation. Concurrent chemotherapy administered along with hyperfractionated or accelerated RT has been shown to add significant additional benefit over hyperfractionated or accelerated RT alone. Neoadjuvant chemotherapy (usually consisting of cisplatin and fluorouracil) also produces favorable responses in most patients (approximately 75% partial or complete response rates) with advanced head and neck cancer, but its role remains controversial.

Methods. The results of treatment of 23 patients with T3 or T4 oropharyngeal squamous cell carcinomas who received neoadjuvant chemotherapy, followed by hyperfractionated RT (120 cGy twice-a-day to 74.4–76.8 Gy) were retrospectively reviewed. The 14 patients who were most recently treated also received concurrent sensitizing doses of single agent chemotherapy, usually cisplatin. No patient was seen with distant metastasis, and all were treated with curative intent. Ten patients had T3 and 13 patients had T4 primary tumors. Three patients (13%) had stage III disease and 20 patients (87%) had stage IV disease. Ten patients had base of tongue primaries, 12 had tonsillar primaries, and 1 had an oropharyngeal wall primary. Eighteen patients (78%) had clinically involved neck nodes.

Results. Seventy-four percent of patients had partial (>50%) or complete response at the primary site following neoadjuvant chemotherapy. One patient died of cardiorespiratory arrest after the first cycle. Thirteen percent of patients had unplanned interruptions of their RT courses secondary to severe mucositis. Local control at the primary site (minimum 2 years follow-up) was achieved in 17 of 19 (89%) patients. Two- and 5-year absolute survival rates were 71% and 55%, respectively. No patient was gastrostomy dependent beyond 18 months. Four patients developed neck failure after RT alone and none was successfully salvaged.

Conclusion. This study is noteworthy in that it uses both neoadjuvant and concurrent sensitizing chemotherapy along with hyperfractionated RT. There is little information in the literature on this approach. Although the regimen is somewhat toxic, it is less so than many other regimens, which combined full-dose multiagent chemotherapy during the course of RT. The latter regimens also have a significant incidence of permanent dysphagia, gastrostomy dependence, and/or aspiration, complications that were not encountered in this group. The local control rate was high (89%). We continue to recommend this regimen for patients with locally advanced head and neck squamous cell carcinomas. ©2008 Wiley Periodicals, Inc. Head Neck 31: 167–174, 2009

Keywords: head and neck cancer; hyperfractionation; chemoradiotherapy
Advanced oropharyngeal squamous cell carcinomas have, in the past, been treated with primary radiotherapy (RT) reserving surgery for salvage, or alternatively, with surgery and postoperative RT. In recent years, concurrent chemoradiotherapy has largely supplanted RT alone. A few major surgical centers in the United States continue to recommend a primary surgical approach. Although cure rates are roughly equivalent between these 2 approaches,¹ the morbidity of RT is generally considered to be less than the morbidity of a major surgical resection. We and others² therefore generally recommend chemoradiotherapy as the most suitable approach.

In addition to primary RT, we have used neoadjuvant cisplatin and fluorouracil chemotherapy during the period of the present report. Most patients (approximately 75%) respond favorably to neoadjuvant chemotherapy in terms of tumor shrinkage, and we regard these responses as contributing importantly to the therapeutic endpoints observed in the present series. In recent years, following an international trend using concurrent chemotherapy and RT, we have additionally recommended sensitizing doses of chemotherapy (usually cisplatin) during RT.

It has further been our impression for the last 2½ decades that twice-a-day hyperfractionated RT is superior to conventional once-a-day treatment.³⁻⁸ Hyperfractionated RT was used in all patients in the current series. We are not aware of other series using neoadjuvant chemotherapy followed by hyperfractionated chemoradiotherapy.

The following are the results of treatment of 23 consecutive patients treated at Bethesda Memorial Hospital, Boynton Beach, Florida, for locally advanced (T3 or T4) oropharyngeal cancer (tonsil, base of tongue, soft palate, or oropharyngeal wall) who received neoadjuvant cisplatin–fluorouracil chemotherapy, followed by twice-a-day RT with or without concurrent low-dose sensitizing chemotherapy.

### PATIENTS AND METHODS

Between June 1986 and March 2006, 23 patients (16 men, 7 women) with T3 or T4 squamous cell carcinoma of the oropharynx received neoadjuvant chemotherapy followed by twice-a-day RT at Bethesda Memorial Hospital with curative intent. Results of the treatment were retrospectively reviewed under Institutional Review Board approval. All patients gave written informed consent before initiating treatment. Twenty-one patients were non-Hispanic White, 1 was Black, and 1 was Hispanic. Ages ranged from 42 to 79 years (mean, 62; median, 59).

Table 1 shows the distribution of patients by T and N classification. Three patients (13%) had stage III disease and 20 (87%) had stage IV disease.⁹ Ten patients had T3 primary disease (5 base of tongue and 5 tonsillar region) and 13 patients had T4 disease (5 base of tongue, 7 tonsil, and 1 pharyngeal wall). Lesions were designated as T4 if there was trismus, bone invasion, direct extension of tumor into the soft tissues of the neck, or tongue fixation. Eighteen patients (78%) had clinically involved lymph nodes. None had distant metastases.

All patients received neoadjuvant chemotherapy. The usual intent was 3 cycles of cisplatin and fluorouracil as described elsewhere.¹⁰ Twenty patients received cisplatin–fluorouracil (11 patients had 3 cycles, 5 patients had 2 cycles, and 4 patients had 1 cycle), and 3 others received docetaxel in addition to 3 cycles of cisplatin and fluorouracil. RT was given to the primary site and upper neck at 120 cGy twice-a-day (6 hours between fractions) to all patients, with total doses of 7440 to 7680 cGy via 6-MV X-rays.³ Reductions off the spinal cord were made after 4320 to 4560 cGy tumor dose. Supplemental RT to the posterior neck area was administered with electrons. All patients received once-a-day RT to the low neck as described elsewhere.¹¹ Although the usual intent was to start RT approximately 3 weeks after cycle 3 of chemotherapy, 7 patients had delays of 4 to 7 weeks for a variety of reasons relating to dental extractions, scheduling, patient delays, or toxicity.

All 23 patients had minimum follow-up of 1 year or until death; no patient was lost to follow-up. Twenty-one (91%) patients were treated greater than 2 years ago. All patients who began treatment with curative intent are included in this report even if they did not complete treatment.

A modified radical neck dissection was performed in 2 patients after RT. No positive lymph nodes were found in either patient. Neck dissec-

### Table 1. Distribution of patients by T and N classification.

<table>
<thead>
<tr>
<th>T classification</th>
<th>N0</th>
<th>N1</th>
<th>N2a</th>
<th>N2b</th>
<th>N2c</th>
<th>N3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>
tion was recommended to 2 additional patients but was declined.

Fourteen patients (61%) received sensitizing chemotherapy concurrent with their RT, usually consisting of 30 mg/m\(^2\) of cisplatin administered once a week.

Local control was calculated by the direct method.\(^\text{12}\) Two patients who were treated less than 2 years ago were excluded from the local control analysis. Two patients who died of intercurrent disease, metastases, or treatment complications within 2 years of treatment, who were continuously free of disease at the primary site, were also excluded from the local control analysis. Survival was calculated by the absolute method (eg, number of patients alive at 5 years/number of patients treated >5 years ago).

**RESULTS**

**Acute Toxicity of Neoadjuvant Chemotherapy.** One patient (who was treated less than 2 years ago) died of cardiorespiratory arrest following his first cycle of chemotherapy. Two patients required hospitalization for pulmonary emboli. Three patients refused further chemotherapy after the first cycle due to intolerance. An additional patient developed a transitory electrolyte imbalance and another developed transient renal insufficiency.

**Acute Toxicity of Radiation Therapy.** Severe mucositis was noted in all patients. Sixteen patients (70%) required percutaneous gastrostomy (14 patients) or Dobhoff feeding tubes (3 patients; 1 patient had both). Six of these patients had their gastrostomies before RT. Gastrostomy was recommended but refused in 1 other patient. In 3 patients, the gastrostomy feeding tubes were still being used 6 months after treatment was completed.

Three patients (13%) had unplanned treatment interruptions (greater than 1 week) of their RT due to severe mucositis. The interruptions lasted 10 days (2 patients) to 4 weeks (1 patient).

**Response to Neoadjuvant Chemotherapy.** Seventeen patients (74%) had a major response (greater than 50% shrinkage) at the primary tumor site following neoadjuvant chemotherapy. Fifteen of the 17 had 75% or greater shrinkage. A less than 50% response of the primary tumor was seen in 5 patients, and 1 patient had 30% growth of his primary tumor during neoadjuvant chemotherapy.

**Table 2.** Local control with minimum 2-year follow-up (21 patients) according to T classification and primary site (number of patients with local control/number of patients treated).

<table>
<thead>
<tr>
<th>T classification</th>
<th>Excluded*</th>
<th>T3</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base of tongue</td>
<td>0</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
</tr>
<tr>
<td>Tonsil</td>
<td>2</td>
<td>4/5</td>
<td>3/3</td>
<td>7/8</td>
</tr>
<tr>
<td>Pharyngeal wall</td>
<td>0</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9/10</td>
<td>8/9</td>
<td>17/19 (89%)</td>
</tr>
</tbody>
</table>

*Excluded patients who died of intercurrent illness (0 patients), complications of treatment (0 patients), regional metastasis (1 patient), or distant metastasis (1 patient) before 2 years with primary site continuously controlled.

**Local Control.** Twenty-one of the 23 patients completed treatment greater than 2 years ago and are eligible for local control analysis (Table 2). Of these 21 patients, 2 died of regional or distant metastatic disease within 2 years continuously free of disease at the primary site and were excluded from local control analysis. Of the remaining 19 patients, 2 experienced local failure (11%). One patient with a T3 tonsil cancer recurred at the primary site 3 years after treatment. Surgical salvage was refused and palliative chemotherapy was administered. Another patient with a T4 cancer of the oropharyngeal wall had persistent disease at the primary site and died of local recurrence within 1 year. The overall local control rate with minimum of 2 years follow-up was thus 17 of 19 (89%).

One additional patient (treated less than 2 years ago and not included in Table 2) responded poorly to neoadjuvant chemotherapy and died with local persistence shortly after completing RT. If the 2 patients with less than 2 years’ follow-up (1 who died of cardiorespiratory arrest after cycle 1 of chemotherapy and the other with local persistence) are both scored as having had local persistent disease, then the crude local control rate for the entire series would be 19 of 23 patients (83%).

**Regional Control.** Four patients (N1, N2b, N2c, and N3, respectively), all of whom received RT without neck dissection, had tumor recurrence in the neck. None was successfully salvaged. Only 1 patient underwent attempted surgical salvage. One of the 4 patients had simultaneous distant metastasis, which precluded surgery, whereas the other 2 patients had unresectable disease.

**Survival.** The 2- and 5-year absolute survival rates were 71% (15 of 21) and 55% (6 of 11),
Complications of Radiation Therapy. One patient developed a soft tissue necrosis and bone exposure and underwent hyperbaric oxygen therapy 7 months after RT. Another developed significant mandibular osteoradionecrosis that required hemimandibulectomy. A third patient developed a 1-cm bone exposure that healed spontaneously within 2 months. One patient developed mild chronic mastoiditis approximately 2 years after treatment. No patient developed an esophageal or hypopharyngeal stricture. No spinal cord injuries were noted. In 3 patients, gastrostomy tubes were still being used 6 months after the treatment was completed. No patient remained gastrostomy dependent beyond 18 months.

DISCUSSION

The present series, despite being small in patient numbers and spanning a 20-year period, is useful, because it provides long-term follow-up and excellent rates of local control on a very homogeneously treated group of patients. The potential benefits of neoadjuvant chemotherapy followed by hyperfractionated chemoradiotherapy are largely unknown and have not been the subject of study in published randomized trials. Our results provide a strong rationale for studies investigating this issue. The current series is therefore noteworthy in several aspects: (1) it is a nonsurgical series; (2) it used only twice-a-day hyperfractionated RT; (3) neoadjuvant chemotherapy was used in all patients; (4) concurrent sensitizing chemotherapy was used in all recently treated patients. We are aware of few other data in the literature on this approach.13 Zahalsky et al,13 when comparing the results of 2 consecutive larynx preservation protocols, noted significantly improved 5-year rates of local control, disease-specific survival, and overall survival when using 3 cycles of cisplatin and fluorouracil followed by concomitant boost RT and concurrent cisplatin compared with neoadjuvant chemotherapy followed by conventional once-a-day RT alone.

Each of the above 4 points is briefly addressed below.

Radiation Therapy versus Surgery. No large randomized trial exists regarding the efficacy of surgery versus RT for patients with oropharyngeal cancer. Although chemoradiotherapy has become the standard of care in many U.S. institutions, there are still a number of major and important U.S. cancer centers that use primary surgery followed by either postoperative RT or postoperative chemoradiotherapy. In a large retrospective review of North America reports on the treatment of oropharyngeal carcinoma, it was noted that the cure rates following primary RT versus primary surgery (± postoperative RT) were equivalent.1 No similar large body of comparative data exists on the relative benefits of chemoradiotherapy versus primary surgery and postoperative RT. Treatment via primary surgery plus postoperative RT was associated with higher morbidity and mortality than primary RT. For this reason, we generally favor primary chemoradiotherapy in patients with locally advanced oropharyngeal cancer.1,2

Hyperfractionation. Hyperfractionated or accelerated twice-a-day RT has been shown to be significantly superior to conventional once-a-day RT in a number of randomized trials, retrospective reviews, and meta-analyses.3–8 In agreement with Brizel,2 we consider such altered fractionation RT regimens as the basis for the best radiotherapy outcomes in treating moderately advanced or advanced squamous cell carcinoma of the head and neck. These techniques allow delivery of higher total doses in shorter overall treatment times without significantly increasing late toxicity. We continue to use the University of Florida hyperfractionated dose schedule of 120 cGy twice-a-day, which has been in continuous use at their institution since March 1978.3

In a recent meta-analysis of 15 randomized trials, which included 6515 patients, Bourhis et al8 noted that hyperfractionated or accelerated RT programs resulted in a 23% relative reduction in the rate of local failure (8.5% absolute) at 5 years compared with conventional once daily fractionation. Although a survival benefit was seen for both the accelerated and hyperfractionated arms, the magnitude of benefit was significantly higher in the hyperfractionated group (8% absolute, 29% relative survival benefit) than the accelerated group (2% absolute, 5.6% relative benefit) at 5 years. Interestingly, the 8% absolute survival benefit is exactly the same as the survival benefit conveyed by concurrent chemotherapy as noted in the discussion which follows. There was a significant benefit in the rate of local-regional control for both altered fractionation regimens when compared with the conventional once-daily RT (p < .0001).
Neoadjuvant Chemotherapy. The use of neoadjuvant chemotherapy remains controversial, but it remains common clinical practice in many centers. In the frequently cited meta-analysis of chemotherapy on head and neck cancer (MACH-NC) collaborative group report, which included 63 trials spanning almost 30 years, no overall survival benefit of induction chemotherapy was reported (2% absolute survival benefit at 2 and 5 years). As would be expected, there was considerable heterogeneity in the chemotherapy regimens used over the 3 decades from multiple institutions and the results differed according to the chemotherapy regimen used. A significant overall survival benefit with platin (cisplatin or carboplatin) plus fluorouracil (hazard ratio of death 0.88) was noted, and this effect was significantly different (p = .05) from that of the other induction regimens (hazard ratio 1.01).

Domenge et al17 reported the results of a randomized trial conducted by the Groupe d’Etude des Tumeurs de la Tete Et du Cou (GETTEC) in which 318 patients with oropharyngeal squamous cell carcinoma were randomly assigned (1986–1992) to receive cisplatin–fluorouracil for 3 cycles followed by RT alone or surgery and postoperative RT versus the same treatment without induction chemotherapy. Overall survival was significantly (p = .03) higher in the induction chemotherapy arm (absolute survival benefit at 5 years approximately 12%; median survival 5.1 years versus 3.3 years).

Zorat et al18 reported results of a multicenter Italian randomized trial (1986–1990) in which 237 patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or paranasal sinus were randomly assigned to receive 4 cycles of cisplatin–fluorouracil followed by local-regional treatment alone. All patients had stage III or IV disease. Approximately three fourths of the study group was considered inoperable, and in those patients, local-regional therapy consisted of RT with or without neck dissection. The remaining patients received surgery and postoperative RT. For all patients, there was an absolute 5-year survival difference of 7% in favor of the neoadjuvant patients, but the difference did not reach statistical significance (p = .13). However, among the inoperable patients (who made up the majority of patients in the study), there was a 13% absolute improvement in 5-year survival among patients who received neoadjuvant chemotherapy (p = .04).

Retrospective data specific to patients with advanced oropharyngeal carcinoma come from the University of Florida.10 In their retrospective review of 123 patients with T4 oropharyngeal carcinoma, Nathu et al10 reported 5-year actuarial rates of local control of 63% vs 38% (p = .03) for patients who received neoadjuvant chemotherapy versus those treated with RT alone, respectively. In their series, 29% of patients who received neoadjuvant chemotherapy had a complete response and 52% had a partial response (greater than 50% regression), percentages consistent with those generally reported in other series and in the present communication. Five-year cause-specific survival rates were 58% vs 27% (p = .002), and 5-year absolute survival rates were 42% vs 17% (p = .001) for patients who did or did not receive neoadjuvant chemotherapy, respectively. In multivariate analyses, cause-specific survival and overall survival were both significantly improved in patients receiving induction chemotherapy.

Two additional highly relevant studies regarding the efficacy of induction chemotherapy have recently been published.19,20 These studies add further strength to a growing body of evidence supporting a therapeutic benefit of cisplatin-based induction therapy. Vermorken et al19 reported results of the EORTC 24971/TAX 323 study in which 358 patients with stage III or stage IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were randomized (April 1999–March 2002) to receive either induction docetaxel, cisplatin, and fluorouracil or cisplatin and fluorouracil followed in both arms by RT. RT was administered mostly by conventional fractionation, and no concurrent chemotherapy was used. There were 37 participating institutions in 15 countries. Progression-free survival was significantly higher in the 3-drug arm (p = .007), with a 28% relative reduction in the risk of disease progression or death. Overall survival was also significantly improved, with a 27% reduction in risk of death (10.9% absolute increase in 3-year survival). The 3-drug regimen was also associated with reduced toxicity, fewer treatment delays, and fewer deaths from toxic effects (2.3% vs 5.5% in the 2-drug arm). The authors concluded that the 3-drug regimen results in improved survival and is better tolerated than the classic cisplatin–fluorouracil regimen.

In the same issue of the same journal, Posner et al20 reported results of the TAX 324 trial in which 501 patients were randomly assigned (May 1999–December 2003) to receive 3 cycles of induction docetaxel, cisplatin, and fluorouracil versus...
cisplatin and fluorouracil. Patients were treated in the United States, Canada, Argentina, or Europe in 55 centers. An important difference in this study compared to the Vermorken report is that all patients then received chemoradiotherapy rather than RT alone. Doses were 70 to 74 Gy at 2 Gy per fraction, once-a-day along with weekly cisplatin. There were significantly more patients with T4 tumors in the 3-drug arm. Primary sites were the same as in the Vermorken report. All patients had stage III or stage IV disease. As in the EORTC trial, the 3-drug regimen produced a significant reduction in the risk of disease progression or death ($p = .004$) and significantly improved overall survival ($p = .006$) and a 14% absolute survival benefit at 3 years.

Proof of a survival advantage of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy over chemoradiotherapy alone is lacking and awaits study in randomized trials.

Induction chemotherapy is associated with considerable morbidity in some patients. Fatal toxicity due to induction cisplatin and fluorouracil chemotherapy occurs in approximately 3% to 4% of patients, and was noted in 1 patient (4%) in our series. Neoadjuvant chemotherapy is also associated with other potential toxicities, including renal complications, infection, nausea, vomiting, leukopenia, thrombocytopenia, and mucositis.

**Concurrent Chemoradiotherapy.** Based largely upon the MACH-NC Collaborative Group report, concurrent chemoradiotherapy has become the standard of care in the United States and abroad. In that report, a significant benefit of concomitant chemotherapy (absolute survival benefit of 8% at 2 and 5 years) was noted. Many practitioners currently use single-agent cisplatin in sensitizing doses (rather than full dose multiagent chemotherapy) during RT. The rationale for using concurrent low-dose sensitizing chemotherapy is the higher rate of both acute and late toxicity associated with high-dose aggressive multiagent chemotherapy administered concurrently with hyperfractionated or accelerated RT, including frequent hypopharyngeal or cervical esophageal strictures, chronic aspiration, and long-term gastrostomy dependence. Additionally, toxic death rates of 7% to 8% have been reported when aggressive chemotherapy is combined with hyperfractionated or concomitant boost RT. In some series, more than half of the patients who survived greater than 2 years have remained gastrostomy dependent. In the present series, the cervical esophagus itself was never within the twice-a-day RT volume, as the match line between the low neck portal (which was treated once a day) and the primary portals was always near the top of the thyroid cartilage. Additionally, no patients in the present series received cisplatin and fluorouracil concurrent with RT. Nevertheless, some patients have experienced posttreatment dysphagia presumably secondary to radiation mucosal changes as well as fibrosis and dysfunction of the pharyngeal constrictor muscles.

In an attempt to reduce the risks of severe hypopharyngeal and esophageal toxicity, we favor sensitizing doses of cisplatin (30–40 mg/m$^2$ once weekly) during the course of RT rather than using more aggressive chemotherapy programs concurrent with RT. Although acute reactions are slightly more pronounced than those observed with twice-a-day RT alone, the side effects are generally manageable and none of the patients in the present series have become permanently gastrostomy dependent. Late complications were not observed to be increased by the addition of cisplatin given at 6 mg/m$^2$ daily in a randomized trial.

Jeremic has additionally shown, in a review of 2 successive randomized trials, significantly higher rates of local-regional control and survival in favor of concurrent chemotherapy-hyperfractionated RT versus conventionally fractionated RT alone, hyperfractionated RT alone, or conventionally fractionated RT plus concurrent chemotherapy. Others have shown similar findings with regard to the added benefit derived from using concurrent chemotherapy with hyperfractionated or accelerated RT programs.

Although the approach in this work has significant acute and late toxicities and was associated with a 4% rate of treatment-related mortality, we believe that the approach is generally tolerable and has produced a high rate of local tumor control.

Of note, 4 patients in the present series developed neck failure following RT. In recent years, the trend has been to omit planned neck dissection following RT in patients whose neck disease has responded favorably to chemoradiotherapy. None of the 4 patients in the present series who developed neck recurrence after chemo-RT was successfully salvaged. Few patients have been reported in the literature who have remained continuously free of disease after salvage neck dissection following failed RT of the N-positive neck. In our own series, greater emphasis will again be placed on the routine performance of post-RT
REFERENCES


