

N2-N3 NECK NODAL CONTROL WITHOUT PLANNED NECK DISSECTION FOR CLINICAL/RADIOLOGIC COMPLETE RESPONDERS—RESULTS OF TRANS TASMAN RADIATION ONCOLOGY GROUP STUDY 98.02

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Abstract: *Background.* The aim of this study was to determine the incidence of isolated nodal failure in patients with N2/3 disease who achieved a complete clinical and radiological response (CR) at 12 weeks postchemoradiation, when no planned neck dissection was performed.

Methods. We analyzed the nodal response and subsequent neck control of 102 patients with initial N2/3 disease treated on the Trans Tasman Radiation Oncology Group 98.02 study.

Results. With a median 4.3 years follow-up, the patterns of first failure in the CR patients were local 4%, local and nodal 2%, distant 28%, and locoregional plus distant (within 1 month) 6%. There were no patients who had only neck failure.

Conclusion. Patients in this trial with N2/3 disease who obtained a clinical and radiological complete response to chemoradiation had a zero incidence of isolated neck failure without a planned neck dissection. The continued use of planned neck dissections in this patient subset cannot be justified. ©2008 Wiley Periodicals, Inc. *Head Neck* **30**: 737–742, 2008

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Management of the neck after definitive treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) with chemoradiation remains controversial. There are many centers worldwide that practice planned neck dissections. Using this approach, all patients with pretreatment N2 (>3 cm) or N3 disease proceed to a neck dissection regardless of their response to chemoradiation. This practice originated because historically the complete response (CR) rates of large neck nodes to (conventionally fractionated) radiation therapy were low and salvage of patients who had neck failure was poor, so all patients were planned to have a neck dissection.

Concurrent chemoradiation is the current standard of care in the nonsurgical management

of locally advanced HNSCC and yields significantly higher rates of neck nodal CR than radiotherapy alone.^{1,2} However, proponents of planned neck dissections point to the high rates of pathologic positivity in planned neck dissections specimens in patients with N2/3 disease treated with chemoradiation³⁻⁷ and the (purportedly) low morbidity of planned neck dissections to justify the ongoing practice.

Axiomatically, a planned neck dissection can only benefit patients who are destined to have failure in the neck alone. In those who would never fail, the operation is unnecessary, and in those destined to fail in the primary and/or at distant sites, it is futile. The morbidity of a neck dissection following chemoradiation may be debatable,⁸⁻¹⁰ but clearly any unnecessary surgery is unnecessarily morbid. Therefore, it is important to select out those patients who can be safely observed.

The aim of this study was to determine, in the setting of a multicenter prospective clinical trial, the incidence of isolated nodal failures in patients with N2/3 disease, who achieve a complete clinical and radiological response at 12 weeks postchemoradiation, when no planned neck dissection was performed.

PATIENTS AND METHODS

We analyzed the nodal response and subsequent neck control in 84 previously untreated patients with N2/3 nodal disease from SCC of the oral cavity, oropharynx, hypopharynx, or larynx treated on the randomized phase II Trans Tasman Radiation Oncology Group (TROG) 98.02 study. We also included another 18 patients with N2/3 nodal disease treated on the "extension phase" of this study giving 102 patients in all. The extension phase was identical except that there was no randomization and all patients received cisplatin and tirapazamine chemotherapy concurrent with radiation therapy.

Results of the randomized phase of TROG 98.02 study have been published previously.¹¹ One hundred twenty-one eligible patients were accrued from 13 institutions between September 1998 and May 2002. All patients received radical radiotherapy plus concurrent chemotherapy consisting of either cisplatin (75 mg/m²) and tirapazamine (290 mg/m²/day) on day 2 of weeks 1, 4, and 7 and tirapazamine alone (160 mg/m²/day) on days 1, 3, and 5 of weeks 2 and 3 (CIS/TPZ) or cisplatin (50 mg/m²) on day 1 and infusional 5-flu-

orouracil (360 mg/m²/day) on days 1 to 5 of weeks 6 and 7 (chemoboost). For this analysis, we grouped the 2 chemotherapy arms together, as our aim was to study the outcome of patients who achieved a nodal CR, not to compare different chemoradiation regimens.

The planned radiation therapy was identical in each arm and consisted of 70 Gy in 35 fractions over 7 weeks. The radiation was given via a shrinking field technique. The initial 50 Gy encompassed the gross clinical disease and sites suspected of harboring subclinical disease. The maximal spinal cord dose was 45 Gy. The fields were then reduced in size to treat the areas of gross macroscopic disease to 70 Gy with a buffer zone of 60 Gy around larger nodal masses.

Prior to treatment, all patients underwent a full physical examination, blood tests, CT or MRI of the head and neck, and chest X-ray (or CT of the chest if patient's low neck nodes were involved).

Patients had both a clinical and radiological (CT head and neck) assessment of treatment response at 12 weeks and 26 weeks postcompletion of treatment. A CR was defined as no clinically visible or palpable disease, and no significant abnormality was seen radiologically on CT. For neck nodes, a radiological CR required that any imageable residual at the site of previous adenopathy be <1 cm in maximum diameter and have no other radiologically suspicious features of residual disease.

The protocol specified that patients who achieved a CR at the primary site but had a residual neck mass at 12 weeks were to proceed to a neck dissection. An exception was made for patients with regressing neck masses that were not metabolically active on [¹⁸F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) scan; these patients were monitored closely, and neck dissection took place only if regression ceased or there was a residual mass at the 26-week assessment.

Planned neck dissections were not permitted if a complete clinical and radiological response of the neck nodes was achieved, regardless of the initial nodal size.

Failure was defined as persistent disease in the primary site, progression of disease in the neck in patients not undergoing neck dissection, residual disease left behind following neck dissection (if done), locoregional relapse following CR, or distant metastases.

Statistical Methods. Median and range for follow-up were calculated using the reverse Kaplan-Meier Method.¹² Response rates and rates of iso-

lated neck failure were calculated as simple proportions; 95% 2-sided confidence intervals (95% CI) for these rates were calculated, using exact binomial methods. Locoregional failure-free interval, failure-free survival, and overall survival were measured from the time of randomization (or registration, in the case of patients on the extension phase of the trial) and curves for these were estimated using the Kaplan–Meier method.

RESULTS

The median follow-up time for this study was 4.3 years and ranged from 2.8 to 7.0 years. No patient was lost to follow-up, except 1 who was noncompliant and ceased curative treatment at 32 Gy. He died at 17 months postrandomization, cause unknown.

Patient characteristics are shown in Table 1. There were 12 patients with N2a, 43 with N2b, 27 with N2c, and 20 with N3 neck disease. The nodal CR rates for each nodal stage, as assessed at 12 weeks posttreatment both clinically and radiologically (CR), are shown in Table 2.

The overall nodal CR rate at 12 weeks postchemoradiation was 63% (95% CI 52% to 74%) for N2 disease and 40% (95% CI 19% to 64%) for N3 disease.

There were 81 patients who obtained a clinical and radiological CR in the primary, and 60 who obtained a clinical and radiological CR in the neck. There were 53 patients who achieved a CR in both the primary and the neck. Seven patients had a CR in the neck but not the primary, 28 had a CR in the primary but not the neck, and 14 had a CR in neither the primary nor the neck.

Following are the outcomes of the 28 patients who achieved a CR in the primary but not the neck.

In 11 patients, residual nodal disease resolved completely with ongoing observation. One patient was diagnosed with metastatic disease at the 12 week posttreatment assessment and therefore did not proceed to neck dissection.

Sixteen patients had a neck dissection of which 9 of 16 patients (65%) were pathologically negative. Five of the remaining 7 patients were assessed as having complete clearance of nodal disease at neck dissection. Of these, 3 remain disease free. One patient developed metastatic disease and the other patient was lost to follow-up within 4 months after being assessed as CR; he died at 17 months postrandomization, neck status unknown. Two patients had residual neck disease

	No. of patients
Sex	
Male	84
Female	18
Primary site of disease	
Oral cavity	3
Oropharynx	78
Hypopharynx	15
Larynx	6
T classification	
1	11
2	25
3	31
4	35
N classification	
2a	12
2b	43
2c	27
3	20
ECOG performance status	
0	55
1	43
2	4

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Median (range) age (at registration) was 55 y (38–75 y).

following neck dissection. Both were diagnosed with metastatic disease within 2 weeks of surgery.

Of the 11 patients who were observed, all had small volume residual nodal disease (10–15 mm). Five of these patients had negative FDG-PET scans at 12 weeks posttreatment, and all went on to have a CR on CT scan at 26 weeks posttreatment. The remaining 6 were managed by close clinical observation, with all patients obtaining a radiological CR on CT scan at 26 weeks posttreatment.

Patterns of failure are shown in Table 3. Importantly, there were no cases of isolated neck failure. For the 53 patients with N2/3 neck disease who had primary and neck CR at 12 weeks, the upper limit of the 95% CI for the true isolated neck failure rate, based on the observed rate of zero, is 6.7%.

For all patients, the 3-year failure-free rate was 53%, locoregional failure-free rate 82%, and overall survival 58%.

DISCUSSION

In this study, using contemporary chemoradiation protocols, the nodal CR rate, as measured clinically and radiologically at 12 weeks postcompletion of treatment was 63% for N2 and 40% for N3 disease. No patient who achieved a neck CR sustained a subsequent isolated neck failure de-

Table 2. Response at 12 weeks by nodal classification.

Response type	No. of patients by N classification		
	N2/3	N2	N3
Response in the neck at 12 wk			
CR	60	52	8
Not CR	42	30	12
Total no. of patients	102	82	20
Clinical and radiological CR (%)	59	63	40
95% confidence interval	49% to 68%	52% to 74%	19% to 64%

Abbreviation: CR, complete response.

spite the fact that planned neck dissection was not allowed.

There are currently no randomized trials directly addressing the issue of a planned neck dissection, and to our knowledge, this is the only report based on data from a prospective multicenter clinical trial. Hitherto, we have been dependent on retrospective single institutional data that should be assessed critically.

The often quoted rates of pathologic positivity (30% to 40%) in neck dissections performed post-chemoradiation^{3,4} are not a valid argument for routine planned neck dissection. These numbers are falsely high because patients in these studies proceeded to a planned neck dissection without prior assessment of treatment response. Consequently, patients with only a partial response (who are much more likely to be pathologically positive) are included. More importantly, the presence of residual disease in a neck dissection specimen does not necessarily mean that the patient has benefited from the procedure, if, for example, synchronous distant metastatic disease is present. Only outcome studies that record the incidence of isolated neck failures are able to truly evaluate the worth of planned neck dissection.

Other studies have shown high pathologic positivity (22% to 32%) following only a clinical assessment to chemoradiation prior to planned neck dissection.⁵⁻⁷ However, a large proportion of patients (34% Lavertu, 49% McHam, 60% Stenson) in these studies did not, for unstated reasons, receive the planned neck dissection. Such unaccountability introduces the potential for major bias in results.

Clinical assessment alone is suboptimal for assessing nodal response and cannot reliably be used to guide patient management. Nonetheless, outcome studies have shown a surprisingly low proportion of patients with just a clinical CR who experience relapse with an isolated neck recurrence.¹³⁻¹⁷

There are very few studies clearly documenting response using both clinical and radiological (CT) assessment prior to planned neck dissection. Sanguinetti et al¹⁸ reviewed 43 node-positive patients, 36 (84%) with N2/3 disease, treated with alternating chemoradiation. Although they used clinical and CT evaluation at 6 to 8 weeks post-treatment, the study was flawed by defining CR as “75% reduction in nodal size.”

It is also important to note that “pathologic positivity” does not equate with subsequent neck failure, particularly when the neck dissection is performed early (2-6 weeks) after completion of chemoradiation where the tumor cell viability in pathologic specimens is uncertain.

Brizel et al¹⁹ reported on node-positive patients treated with chemoradiation who had clinical/radiological response assessment prior to planned neck dissection, the latter performed 6 to 8 weeks following chemoradiation. In this study there were 52 N2/3 patients who were planned for a neck dissection, 27 with a nodal CR and 25 with less than nodal CR. In the 27 CR patients, there was a 26% (7 of 27 patients) pathologic positivity rate, and the neck failure rate was 1 of 27 patients (4%). However, as discussed earlier, one cannot assume that all those who had pathologic residual would have had recur-

Table 3. Patterns of failure in N2/3 patients.

Type of first failure or death	No. of patients	
	All N2/3	Primary and nodal CR
All patients	102	53
None	51	28
Local failure only	9	2
Nodal failure only	0	0
Local and nodal failure	2	1
Distant failure only	23	15
Locoregional and distant failure (within 1 mo)	6	3
Death without preceding failure	11	4

rence in the neck without planned neck dissection. In the 16 N2/3 patients with a CR who were observed, because of physician and/or patient preference, the isolated neck failure rate was 2 of 16 patients (12.5%). As the treatment policy for all N+ patients was a planned neck dissection, the fact that these patients did not receive the planned treatment places them in a negatively selected group, despite which only 2 failed in the neck alone.

We previously reported a retrospective analysis of 25 patients with nodal disease (84% N2/3) treated with chemoradiation, who were assessed both clinically and radiologically posttreatment. None of the patient who achieved a complete clinical and radiological response proceeded to a planned neck dissection, and there were no isolated neck failures.²⁰

Argiris et al²¹ reviewed 131 patients with N2/3 disease treated with chemoradiation. In this study, 115 of 131 patients (88%) also had a post-treatment CT scan. The neck management policies varied between prior neck dissections (24%), posttreatment neck dissections (47%), and no neck dissections (30%). The median time to neck dissection was 17 weeks. In the subgroup with a clinical CR (not stated what proportion also had a radiological CR), they found an overall high rate of neck control (92% to 98%), and no difference between patients who had a neck dissection (62 patients) or not (30 patients).

Most recently, Forest et al²² retrospectively reviewed 184 locally advanced HNSCC patients, 87% with N2/3 disease, treated with chemoradiation. All patients had a clinical and radiological (CT) assessment of response at 6 to 8 weeks posttreatment. Patients who achieved a clinical and radiological CR in the neck were observed, whereas patients with a partial response in the neck proceeded to a neck dissection. The isolated neck failure rate was similar for both groups (6 of 123 patients (5%) with no neck dissection and 3 of 45 patients (7%) with neck dissection).

Both of these recent large reports are consistent with our current data. Separate from the regional control issue, there is a theoretical possibility that in patients with residual neck disease, delaying a neck dissection until assessment of treatment response at 12 weeks postchemoradiation could potentially increase the risk of developing distant metastatic disease. On first principles, this is unlikely, as the additional observation time relative to the typical 6 weeks posttreatment timing of a planned neck dissection is a very small window in the overall duration of the nodal dis-

ease from initial seeding. Furthermore, the presence of lymph nodal metastases is as likely to be a marker of distant metastatic spread as a source of it. Finally, the empirical data do not support the contention. In our total patient cohort, 29 of all 102 patients (28%) developed metastatic disease, compared with 5 of 28 patients (18%) in the patients who had a delayed neck dissection. Moreover, the overall rate of distant metastatic disease in our series was similar to that reported in planned neck dissection series.^{21,23}

There is now a large body of evidence based on long-term clinical outcomes, not extrapolations from PND pathology, supporting the fact that patients who achieve a complete clinical and radiological (CT) response to chemoradiation have a low (<5%) risk of an isolated neck recurrence. Those who recommend planned neck dissection must justify the morbidity inflicted on over 95% of patients for no benefit. To argue that the morbidity of a planned neck dissection is low is not only hard to substantiate²⁴ but irrelevant to the principle that unnecessary or futile treatment should always be avoided. The challenge, as we see it, is to expand the group in whom planned neck dissection can safely be avoided by identifying patients who have residual anatomic abnormalities that do not harbor viable tumor cells.

We, and others, have found the use of FDG-PET, and particularly CT-PET, very useful in this regard and have demonstrated that patients who have a complete metabolic response at 12 weeks even in the presence of a residual regressing mass, have a very low risk of subsequent failure.²⁵⁻²⁸ In those patients, our policy is to clinically assess patients every 4 to 6 weeks, with repeat of the CT or PET/CT in 12 weeks (26 weeks from treatment). Observation is continued as long as the PET/CT is negative and there is ongoing clinical regression of disease. If regression ceases and/or the PET/CT becomes positive, a neck dissection is performed.

In conclusion, patients in this trial with N2/3 disease who obtained a clinical and radiological CR to chemoradiation had a zero incidence of isolated neck failure without a planned neck dissection. The continued use of planned neck dissection in this patient subset cannot be justified.

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