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Outcomes following chemoradiotherapy for N3 head and neck squamous cell carcinoma without a planned neck dissection

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SUMMARY

Objectives: The optimal management of the N3 neck in head and neck squamous cell carcinoma (HNSCC) remains controversial. We report the outcomes of patients with N3 disease treated with a strategy of concurrent chemo-radiotherapy (CRT) ± induction chemotherapy (ICT) without a planned neck dissection.
Materials and methods: Forty patients with HNSCC N3 disease treated between January 2004 and December 2010 were retrospectively identified. Inclusion criteria for the study were: non-nasopharyngeal HNSCC, N3 nodal disease, intention to treat with CRT ± ICT.
Results: Median age was 60 (range 39–74). Median follow up was 32 months (range 8–88). 34 (85%) of patients received ICT. 35 patients received cisplatin-CRT, 4 carboplatin-CRT and 1 patient was treated with radiotherapy alone due to ICT toxicity. 27 (67.5%) patients had a complete response (CR) to CRT. 5 (12.5%) patients had an incomplete response in both the primary and nodal sites. 8 (20%) patients had a CR in the primary site but incomplete in the nodal regions. The crude rate of regional failure following a CR was 3/27 (11.2%). Isolated regional failure occurred in 1/27 (3.7%) patients who had achieved a CR post-CRT. 3 year overall survival, disease free survival, locoregional control, local control and regional control in the whole cohort were 51.4%, 49.6%, 65.7%, 77.3%, 69.3%, and in patients with a CR were 73.3%, 70.0%, 86.6%, 90.5% and 91.7% respectively.
Conclusion: Isolated regional nodal failure is rare following a complete response to CRT for N3 HNSCC managed without a planned neck dissection.

Introduction

A variety of approaches have been adopted to the management of the node positive neck in the management of stage III/IV head and neck squamous cell carcinoma (HNSCC).[1] These have included surgery followed by post-operative (chemo)radiotherapy (CRT), definitive radiotherapy or chemoradiotherapy with a 'planned' neck dissection independent of nodal response, and a neck dissection reserved for persistent disease post-(chemo)radiotherapy. There has been general agreement that patients with a N1 disease and a complete response to treatment do not require a neck dissection,[1,2] and that a neck dissection is required following an incomplete response.[3] The strategy of a planned neck dissection for the N2/3 neck was developed in the era of radiotherapy treatment without chemotherapy.[4] Concurrent chemo-radiotherapy (CRT) has now been established as the standard of care for unresectable HNSCC[5] and for organ preservation.[6] In addition, induction chemotherapy has been increasingly utilised with survival benefits.[7] With such intensification of non-surgical treatment approaches, improved regional nodal control[1,6,8,9] has opened up the possibility that a neck dissection may not be required in the event of a complete nodal response to treatment for N2/3 disease. The role of a neck dissection in this scenario remains controversial. Isolated neck failure has been found to be low following CRT.[9–13] Post-CRT neck dissection will only benefit patients with isolated disease in the neck, and hence there is concern that a non-selective approach to a post-CRT neck dissection will at best only benefit a small number of patients. Neck dissections are recognised to add to the morbidity of CRT.[11,14] Recent reports have concluded that a planned neck dissection is not required in patients with a complete nodal response.[1,9,10,15]

The vast majority of the published literature relates to N2 disease, due to the scarcity of neck nodes >6 cm (N3). N3 disease is associated with an increased risk of nodal relapse.[10] Reports which combine N2 and N3 lymph nodes contain only a small proportion of N3 patients.[10,12,16] The role of a planned neck dissection following CRT for N3 disease remains an open and controversial

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question.[17] In our centre we have managed patients with a policy of observation following a complete response to CRT, regardless of the initial extent of nodal disease. The purpose of this study is to evaluate the outcomes of this management strategy for N3 patients treated with CRT.

Patients and methods

After institutional review board approval, patients with HNSCC treated with radical chemo-radiotherapy with curative intent between January 2004 and December 2010 at St. James's Institute of Oncology, Leeds, UK were retrospectively identified using electronic chemotherapy and radiotherapy databases, and electronic notes review. 395 patients were identified who received either concurrent CRT, or ICT with the intention of proceeding to concurrent CRT. The electronic notes were retrospectively reviewed and used for the present analysis. Disease staging was performed according to the 2002 classification of the American Joint Committee on Cancer Staging.

Inclusion criteria for the current study were: histologically proven squamous cell carcinoma, neck node metastases >6 cm (N3), treatment with curative intent, documented intention to treat with concurrent CRT. Exclusion criteria were: nasopharyngeal carcinoma, local or regional surgery prior to CRT, presence of distant metastases.

Induction chemotherapy

Standard ICT consisted of 2–4 cycles of PF (cisplatin 80 mg/m^2 day 1 and 5-fluorouracil (5FU) 800 mg/m^2 days 2–5, three weekly).[18] From 2006, ICT with TPF (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1 and 5-fluorouracil (5FU) 750 mg/m^2 days 2–5 as a continuous peripheral infusion, three weekly) was available for selective fit patients.[19]

Concurrent chemotherapy

Concurrent chemotherapy consisted of cisplatin 100 mg/m^2 days 1, 22 and 43. Carboplatin AUC 4 was substituted for cisplatin if creatinine clearance was <55 ml/min. Cisplatin was administered as an overnight inpatient stay.

Radiotherapy

The majority of the patients in this study were treated with 3-dimensional conformal radiotherapy as previously described.[19,20] For patients treated with induction chemotherapy, pre-chemotherapy imaging was used to define target volumes in line with recent guidance.[21] The clinical target volume included primary site and bilateral level I, II, III, IV, V lymph nodes. Retropharyngeal lymph nodes were variably included depending upon tumour site and stage. Treatment was routinely planned with a two phase conformal technique of two lateral parallel opposed 6MV photon fields with multiple field-in-fields, with a matched anterior neck field. The posterior border of the lateral photon fields was brought anterior to spinal cord to avoid cord toxicity after 40 Gy in 20 fractions. Matched electron fields were applied to the posterior neck. If dosimetry using this technique was predicted to be unsatisfactory e.g. for gross tumour volume in the low neck, treatment could be planned using a 5–7 field technique. Standard doses were 70 Gy in 35 fractions over 7 weeks with 50 Gy in 25 fractions over 5 weeks to the matched anterior neck, although alternate dose regimens could be used at clinician discretion.

Intensity modulated radiotherapy (IMRT) was used to treat patients from late 2009. Treatment was planned according to previously described principles.[22]

Response assessment and follow-up

Tumour response was routinely assessed 3–4 months after the completion of the treatment. Evaluation of tumour response was by clinical examination, nasoendoscopy and imaging of the primary site and the neck; examination under anaesthetic and biopsies were performed in the event of any clinical or radiological abnormality. A neck dissection was not routinely performed and was considered only if there was an incomplete nodal response. To considered as a complete response on post-treatment imaging, a lymph node needed to be <1 cm, oval shaped with smooth borders, without necrosis, and no evidence of extracapsular spread.[23] Patients with less than a complete response were evaluated for salvage surgery. Subsequently, patients were followed up with physical examination, and flexible endoscopy every 6–8 weeks in the first year after treatment, every 3 months for an additional 2 years, and every six monthly until discharge at 5 years. Any site of treatment failure was classified by location: in the primary site, regional lymph nodes or distant.

Statistical analysis

The following endpoints were used for assessment: overall survival (OS), disease free survival (DFS), overall survival, DFS, locoregional control, local control and regional control were analysed using Kaplan–Meier product limit curves. Time was measured from the day of the last radiotherapy treatment. Patients who relapsed but for whom salvage therapy was successful were considered failure free at the time of event occurrence. In the overall survival estimates, deaths due to all causes are included in the calculations. Chi-squared test and Fisher's exact test were used to compare variables. Statistical significance was declared at $p < 0.05$.

Results

Forty patients with HNSCC N3 disease treated with either concurrent CRT or ICT with an intention to proceed to concurrent CRT were identified. Median follow up was 32 months (range 8–88). Patient demographics and disease characteristics are shown in Table 1. Details of chemotherapy and radiotherapy treatment are shown in Table 2. Overall 34 of 40 patients were treated with ICT. For patients who received ICT ($n = 34$), 0, 1, 2 and 3 cycles of concurrent chemotherapy respectively were delivered to 1, 12, 21 and 0 patients respectively. Of note one patient treated with ICT (PF) received radical radiotherapy without concurrent chemotherapy due to toxicity experienced during ICT. For the patients treated without ICT ($n = 6$), 0, 1, 2 and 3 cycles of concurrent chemotherapy respectively were delivered to 0, 1, 2 and 3 patients respectively.

Response assessment included clinical and radiological assessment. Radiological assessment was by CT for 17 patients, MRI for 15 and 18-flurodeoxyglucose (FDG) PET-CT for 5. Radiological response assessment was not performed in three patients with overt clinical progression. Median time to response assessment imaging following completion of radiotherapy was 4 months (range 2–6). 27 of 40 patients (67.5%) had a complete response (CR) in both the primary and nodal sites of disease. 17 of 24 (70.8%) of patients with an oropharyngeal primary compared with 10 of 16 patients with a non-oropharyngeal primary achieved a CR ($p = 0.58$). 5 (12.5%) patients had an incomplete response in both the primary and nodal sites. 8 patients had a CR in the primary site but incomplete in the nodal regions (20%); two of these patients had