Outcomes in squamous cell carcinoma with advanced neck disease

JAMES A KEIR, OLIVIA JH WHITESIDE, STUART C WINTER, SUSHIR MAITRA, ROGAN C CORBRIDGE, GRAHAM J COX

Oxford Centre for Head and Neck Oncology, Radcliffe Infirmary, Oxford, UK

ABSTRACT

INTRODUCTION Treatment of advanced neck disease (N2c/N3) in head and neck squamous cell carcinoma is contentious. The aim of this study was to review the survival outcome following surgical excision of neck disease and the complications of this surgery.

PATIENTS AND METHODS A retrospective review of the case notes of 39 patients treated at the Oxford Radcliffe Infirmary Head and Neck Unit with squamous cell carcinoma and advanced neck metastases confirmed as either pN2c or pN3 on histological examination was performed. Patients were treated with surgery and, in some cases, with adjunctive postoperative radiotherapy at the centre between August 1996 and November 2004. The study sought to establish the demographics, UICC staging/pathology, method of treatment, complications, recurrence and survival. Kaplan-Meier curves were used for statistical analysis of survival. Comparisons were then made between the cohort and historical control groups.

RESULTS All patients were UICC stage IV disease. The 2- and 5-year overall survival in patients with resectable disease was 63% and 52%, respectively.

DISCUSSION Patients with advanced neck disease have traditionally been thought to have terrible prognosis and, therefore, treatment is controversial. In treating advanced head and neck cancer, there has been a recent trend away from surgery towards chemotherapy and/or radiotherapy.

CONCLUSIONS Comparing this study group to historical controls that include chemotherapy and/or radiotherapy, the outcomes appear favourable. The use of a combination of radiotherapy and surgery is advocated; it is suggested that advanced neck disease can have an acceptable prognosis and morbidity and that local disease control may be achieved.

KEYWORDS

Head and neck and cancer – Squamous cell carcinoma – Neck disease

CORRESPONDENCE TO

James A Keir, Department of ENT, Alder Hey, Royal Liverpool Children's Hospital, Eaton Road, West Derby, Liverpool L12 2AP, UK
E: jameskeir@hotmail.com

Squamous cell carcinoma of the head and neck with advanced cervical metastasis occurs more commonly with certain tumour subsites, in particular the oropharynx, supraglottis and hypopharynx. In addition, with these tumours it is well recognised that, in the contralateral neck, occult metastases are common.¹ We present a cohort of 39 patients with advanced cervical metastasis treated with curative intent.

Patients with advanced cervical metastasis represent a treatment dilemma as their prognosis is generally considered to be poor.^{2,5} Any treatment must offer an improved surgical prognosis with acceptable morbidity and a good quality of life.

Neck dissections have previously been reported to have a high rate of complications, which lead some authors to advocate against performing bilateral synchronous neck

dissection or to perform staged surgery.⁴ We present the demographics and outcomes in a group of patients with head and neck squamous cell carcinoma and advanced cervical metastasis.

Treatment of advanced neck disease (N2c/N3) in head and neck squamous cell carcinoma is contentious. The aim of this study was to review the survival outcome following surgical excision of neck disease and the complications of this surgery.

Patients and Methods

A retrospective review was performed of 39 patients with squamous cell carcinoma and advanced neck metastases,

confirmed as either pN2c or pN3 on histological examination. The departmental policy in treating this group is for surgery combined with postoperative radiotherapy. Prior to commencing treatment, all patients underwent a thorough pre-operative work-up and review in the multidisciplinary clinic as per national guidelines available at the time.⁵ The neck was treated with a comprehensive neck dissection on the affected side, where possible preserving the accessory nerve, *i.e.* modified radical neck dissection (MRND) type one. In the high-risk contralateral neck (primary tumours which involve or cross the midline), a selective neck dissection was performed, usually levels II, III and IV. In the N-positive contralateral neck, a second comprehensive neck dissection sparing the internal jugular vein and the accessory nerve was performed (*i.e.* MRND type two). Patients were treated with surgery by one of the head and neck surgeons and with adjunctive postoperative radiotherapy at the Oxford Radcliffe Infirmary Head and Neck Unit from August 1996 to November 2004. SM and SW reviewed patients' notes for a predetermined data set; the data retrieved were validated by JAK and OJHW. The data set sought to establish the demographics, UICC staging/pathology, method of treatment, complications, recurrence and disease-free/overall survival. Kaplan-Meier curves were used for statistical analysis of survival. The date of neck dissection was chosen as the starting point for the analysis until death or end of follow-up.

Results

Patient age at presentation ranged from 39–83 years (mean, 55 years). There were 33 males and six females. The primary tumour location was 16 in the oropharynx, nine in the hypopharynx, eight in the larynx, three in the mouth, two in the skin and one unknown head and neck primary.

Thirty-five patients presented histologically with pN2c disease and four patients with pN3 disease. All patients were UICC stage IV disease (for a breakdown of T-stage see Fig. 1). In three cases, it was not possible to assess the stage of the primary site as patients had initially undergone radiotherapy to the primary site and then had a recurrence of cervical metastasis requiring surgical intervention or there was no known primary. Twenty-eight patients were found to have extracapsular spread (72%).

The average length of stay in hospital was 19 days. Treatment of the primary site was by radiotherapy in only two cases and by surgery in the remaining. The type of surgery to the primary site is shown in Figure 2. Surgery to the primary site was abandoned in two cases as primary tumour extended into the skull base or was fixed to the carotid artery.

In addition to surgery to the primary site, the 39 patients underwent a total of 74 neck dissections in various

combinations including selective, modified radical and radical neck dissections. In all, 24 selective neck dissections (SND), 28 modified radical neck and 24 radical neck dissections (RND) were performed. Of the MRND, 81% had one internal jugular vein sacrificed and both were preserved in 19%. Of these patients, 61% had the accessory nerve preserved; it is our policy to sacrifice the accessory nerve if disease was surrounding, or adherent, to it. In 37 patients, the neck dissections were bilateral and two patients underwent unilateral neck dissection. Thirty-one patients received postoperative radiotherapy with a mean dose of 57 Gy (range, 17–66 Gy). Five died before radiotherapy could be given, one received palliative radiotherapy for irresectable disease, one patient refused radiotherapy and one patient had postoperative chemoradiotherapy. Three of the five deaths occurring prior to radiotherapy were due to the development of early local disease recurrence or metastatic disease. One death was due to respiratory arrest secondary to an exacerbation of chronic pulmonary airway disease and one was due to cor pulmonale. Four patients received postoperative chemotherapy for recurrence; two cases received this 1 year postoperatively and two cases at 3 years' postoperatively. Major postoperative complications related to neck dissection occurred in 20% of patients, the most frequent being chyle leak. Neck recurrence within 2 years was noted in seven patients (18%), all occurring in patients with pN2c on histology. Eight patients had metastatic distant spread at 2 years (21%). The sites of distant spread were lung in five, bone in two and liver in one. The mean time to distant recurrence was 12.5 months (range, 1–45 months). Overall survival and disease-free survival Kaplan-Meier curves are shown in Figure 3. The 2- and 5-

Figure 2 Type of surgery performed at the primary site in the study group.

year overall survival in patients with resectable disease was 63% and 52%, respectively. The 2-year disease-free survival in patients with resectable disease was 50%. The 5-year disease-free survival in patients with resectable disease was 46%.

Long-term functional outcome in the study group was compromised by shoulder discomfort in three cases and neck stiffness in one case. Patient follow-up ranged from 1–96 months (mean, 30 months).

Figure 3 Overall survival and disease-free survival Kaplan-Meier curves.

Discussion

Patients with advanced neck disease have traditionally been thought to have terrible prognosis and, therefore, treatment is controversial. In treating patients with advanced head and neck cancer, there has been a recent trend away from surgery towards chemotherapy and/or radiotherapy thereby improving tumour response rates and disease control whilst attempting to achieve organ preservation.^{6–12} Ahmed *et al.*⁶ used concomitant chemoradiotherapy and surgical salvage for N3 nodal disease. Intra-arterial cisplatin and radiotherapy was given with surgical salvage for patients with N3 nodal disease. No neck recurrence was reported. The 3-year overall survival rate was 41%. Wolf *et al.*⁸ used induction chemotherapy and radiotherapy for patients with N2 and N3 disease and compared these with conventional treatment of surgery and postoperative radiotherapy. Overall survival of patients with laryngeal cancer and N2 or N3 disease who were randomised to induction chemotherapy and radiotherapy was 43% at 5 years and was similar to that of the N2 and N3 patients who received conventional therapy. Recondo *et al.*⁸ treated N3 disease alone with neo-adjuvant chemotherapy. With a median follow-up of 38 months, the disease-free survival rate was 0%. From these studies, it has been suggested that large volume lymph node metastasis is unlikely to be cured by radiotherapy or by chemoradiotherapy alone.^{8,9} Given these results, it is uncertain how this group of patients should be managed and whether aggressive surgery still has a role.

Results for neck recurrence in advanced neck disease have been controversial in the literature. Regional control in patients undergoing selective neck dissection with radiotherapy compared to modified neck dissections with radiotherapy has been demonstrated to be comparable in patients with a N0 to N2c nodal stage.¹⁵ Regional recurrence rates are also comparable for radical (17.5%, CI 13.1–21.9) and modified radical neck dissections (14.3%; CI 7.1–21.5) with radiotherapy in patients with advanced neck disease (N2 or greater).¹⁴ The regional recurrence rates reported in this study are, therefore, similar to those reported in the literature. Selective neck dissection may be used for control of the contralateral, clinically negative neck particularly when the primary site is in the midline.¹⁵

Literature review

We carried out a limited literature review to compare our group with previously cited cases. Any such comparison is complex. The series often differ in many respects, including: (i) variations in patient population such as demographics, co-morbidities and primary site; (ii) staging systems utilised; (iii) histological characteristics; and (iv) the type of surgical procedures performed. The review used Medline through PubMed (1950–2005) and Ovid (1958–2005) and searched for papers on patients with advanced neck disease (N2/N3) in head and neck squamous cell carcinoma. Those papers using an old staging system were excluded. All those identified were retrospective, non-randomised studies (Table 1).

Richards and Spiro¹⁵ found the overall survival to be 56% in groups with resectable squamous cell carcinoma of the head and neck and advanced neck disease (N2 or N3) treated by neck dissection and postoperative radiotherapy at 2 years' postoperatively. As we have stated, comparison with the literature is complex in this heterogeneous group and Richards and Spiro make no comment on demographics or

co-morbidities. Selective neck dissections were not used in this paper but a similar postoperative radiotherapy regimen was undertaken. Histological examination in this paper revealed 81% were N2a or N2b and the remainder N2c or N3 which is the comparable group examined in our paper. No comment is made on the primary site stage. Extracapsular spread has been shown to be correlated with a higher incidence of neck recurrence and a poorer prognosis;^{16–18} in this paper extracapsular spread was present in 44%, however, we note that it was not documented in 51%.

Chan *et al.*¹⁹ classified patients into four groups depending on the treatment received: (i) those treated with neck dissection followed by radiotherapy; (ii) those who had a pre-operative radiotherapy followed by planned neck dissection surgery; (iii) those who were treated only with neck dissection surgery due to a refusal to have radiotherapy or who died before radiotherapy; and (iv) those who had pre- or postoperative chemotherapy with or without chemotherapy. All patients had squamous cell carcinoma of the head and neck and advanced neck disease (N3). The primary sites in this study were not as at an advanced stage as in our study (T1 in 11.1%, T2 in 17.8%, T3 in 24.5% and T4 in 11.1%). They found the best overall survival in the group treated with neck dissection and postoperative radiotherapy. At 5 years' postoperatively, this was found to be 38.9%. The best neck recurrence rates were again in the postoperative radiotherapy arm and were 7.7% at 1 year and 53.9% at 5 years. No mean dose for postoperative radiotherapy was given but the range was 45–50 Gy. They make no comment on demographics, co-morbidities or extracapsular spread.

Carvalho *et al.*²⁰ classified patients into three groups depending on the treatment received; (i) those treated by neck dissection with or without adjuvant radiotherapy; (ii) those receiving radiotherapy alone; and (iii) those given supportive care only. A combination of radical neck dissec-

Table 1 Summary of disease-specific survival rates from the literature

Reference	Therapy employed	Overall survival			
		1 yr (%)	2 yrs (%)	3 yrs (%)	5 yrs (%)
[This paper]	Surgery and postoperative radiotherapy	71	63	52	52
Ahmed <i>et al.</i> ⁵	Chemoradiotherapy and surgical salvage for N3 disease	–	–	41	–
Wolf <i>et al.</i> ⁷	Induction chemotherapy and radiotherapy	–	–	–	43
Richards and Spiro ¹⁴	Surgery and postoperative radiotherapy	–	56	–	–
Chan <i>et al.</i> ¹⁸	Surgery and postoperative radiotherapy	–	–	–	38.9
Carvalho <i>et al.</i> ¹⁹	Surgery and postoperative radiotherapy	69.2	–	26.9	–
Smeele <i>et al.</i> ²⁰	Surgery and postoperative radiotherapy	–	491	–	–

tion, extended radical neck dissection and selective neck dissections. In 88.9% of these patients, adjuvant radiotherapy was performed. This was pre-operative in 14.8% and postoperative in 74.1% of the patients undergoing neck dissection. The median dose of adjuvant radiotherapy was 6000 cGy (range, 1000–8000 cGy). All patients had squamous cell carcinoma of the head and neck and advanced neck disease (N3). The primary site was more advanced than in our study (T1 in 3.6%, T2 in 12.9%, T3 in 30.4%, T4 in 50.4%, occult primary in 0.9% and staging unavailable in 1.8%). They found the best overall survival in the group treated by neck dissection. The best overall survival was in patients receiving surgery and postoperative radiotherapy over 6000 cGy at 1 year and 3 years' postoperatively to be 69.2% and 26.9%, respectively.

Smeele *et al.*²¹ treated patients with neck dissection before planned radiation therapy to the primary tumour and neck. All patients had squamous cell carcinoma of the head and neck and advanced neck disease (N2/N3). The primary sites in this study were not as at an advanced stage as in our study (T1 in 29.7%, T2 in 29.7%, T3 in 32.4% and T4 in 8.1%). They found the disease-specific survival at 2 years' postoperatively to be 49%. Radiotherapy instead of surgery was used to preserve function, treat small primary tumours potentially curable with radiotherapy, co-existent patient morbidity and patient refusal to submit to major surgery. A mixture of resectable and unresectable disease was, therefore, present. Neck recurrence at 2 years was noted in 16 patients (43%). Distant metastases were present in 55% at 2 years. Our control of distant metastasis is, therefore, markedly better than in this group. They make no comment on demographics or co-morbidities. No information on the type of neck dissections were available in this paper and 30 of 37 patients in the study received higher mean dose of postoperative radiotherapy (66.9 Gy). Compliance for radiotherapy was at a comparable level to our study (14%). Histological examination in this paper revealed 78% were N2c or N3 and the remainder N2a or N2b, which represents a smaller group of patients than in our study. The primary site was T1 in 29%, T2 in 29%, T3 in 32% and T4 in 8%. In this paper, extracapsular spread was present in 95%.

Conclusions

Although there are problems with comparisons with the historical controls in the literature as outlined, we have demonstrated excellent results in our centre that may be attributed to aggressive surgical treatment with post-operative radiotherapy. A summary of the survival in the literature is shown in Table 1.

The risk of problems with long-term functional outcome has been stated to be as high as 19% for selective

neck dissections, 42% for modified radical neck dissections and 58% for radical neck dissections.¹⁴ Only 10% of our patients had a significant problem with functional outcome but a meaningful analysis of our group with the literature is difficult due to multiple variations in the types of neck dissection carried out and the differing treatments to the primary site.

We suggest that patients with advanced neck disease can have an acceptable prognosis and morbidity and that control may be achieved. This is particularly relevant given the terrible prognosis in these patients if untreated. NICE gives stage IV disease a 2-year historical survival of 48.6%.²² Our paper has shown that a 63% 2-year survival is achievable in resectable disease. Surgery and adjuvant therapy could achieve the best outcome in this group. However, the authors recognise the limits of this relatively small, retrospective study and the need for a large prospective, multi-centre, randomised, controlled trial, which should include surgery and adjuvant therapy as one of its treatment arms.

References

- Hicks WL, Kollmorgen DR, Kuriakose MA, Orner J, Bakamijan VY, Winston J *et al.* Patterns of nodal metastasis and surgical management of the neck in supraglottic laryngeal carcinoma. *Otolaryngol Head Neck Surg* 1999; **121**: 57–61.
- Shah JP, Shara AR, Medina JE. Cervical lymph node metastasis. *Curr Prob Surg* 1993; **20**: 275–335.
- Feind CR, Cole RM. Contralateral spread of head and neck cancer. *Am J Surg* 1969; **118**: 660–5.
- McGuirt F, McCabe BF. Bilateral radical neck dissections. *Arch Otolaryngol* 1980; **106**: 427–9.
- British Association of Otolaryngologists and Head and Neck Surgeons. *Effective Head and Neck Cancer Management – Consensus Documents 1998 and 2002*.
- Ahmed KA, Robbins KT, Wong F, Salazar JE. Efficacy of concomitant chemoradiation and surgical salvage for N3 nodal disease associated with upper aerodigestive tract carcinoma. *Laryngoscope* 2000; **110**: 1789–93.
- Sanguineti G, Corvo R, Benasso M, Margarino G, Sormani M, Roncallo F *et al.* Management of the neck after alternating chemoradiotherapy for advanced head and neck cancer. *Head Neck* 1999; **21**: 223–8.
- Wolf G, Fisher S. Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. *Laryngoscope* 1992; **102**: 934–9.
- Recondo G, Cvitkovic E, Azli N, Tellez Bernal E, de Vathaire F, Wibault P *et al.* Neoadjuvant chemotherapy consisting of cisplatin and continuous infusion of bleomycin and 5-FU for advanced head and neck cancer: the need for a new stratification for stage IV (M0) disease. *Cancer*. 1991; **68**: 2109–19.
- Janinis J, Papadakou M, Panagos G, Panousaki A, Georgoulas V, Hatzidaki D *et al.* Sequential chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. *Am J Clin Oncol* 2001; **24**: 227–31.
- Mantovani G, Maccio A, Massa E, Mulas C, Mudu MC, Massidda *et al.* Phase II study of induction chemotherapy followed by concomitant chemoradiotherapy in advanced head and neck cancer: clinical outcome, toxicity, and organ function/preservation. *Int J Oncol* 2000; **16**: 1227–33.
- Krengli M, Masini L, Gambaro G, Turri L, Loi G, Aluffi P *et al.* Concurrent

- chemotherapy and 5-fluorouracil and radiotherapy in advanced squamous cell head and neck carcinoma: a retrospective single institution's study. *Tumori* 2001; **87**: 312–6.
13. Chepeha DB, Hoff PT, Taylor RJ, Bradford CR, Tecknos TN, Esclamado RM. Selective neck dissection for the treatment of neck metastases from squamous cell carcinoma of the head and neck. *Laryngoscope* 2002; **112**: 434–8.
 14. Buckley JG, Feber T. Surgical treatment of cervical node metastases from squamous carcinoma of the upper aerodigestive tract: evaluation of the evidence for modifications of neck dissection. *Head Neck* 2001; **23**: 907–15.
 15. Richards BL, Spiro JD. Controlling advanced neck disease: efficacy of neck dissection and radiotherapy. *Laryngoscope* 2000; **110**: 1124–27
 16. Johnson JT, Barnes EL, Myers EN, Schramm VL, Borochovit D, Sigler BA. The extracapsular spread of tumours in cervical node metastases. *Arch Otolaryngol* 1981; **107**: 725–9.
 17. Johnson JT, Myers EN, Bedetti CD, Barnes EL, Schramm VL, Thearle PB. Cervical lymph node metastasis: incidence and implications of extracapsular carcinoma. *Arch Otolaryngol* 1985; **111**: 534–7.
 18. Alvi A, Johnson JT. Extracapsular spread in the clinically negative neck (N0): implications and outcome. *Otolaryngol Head Neck Surg* 1996; **114**: 65–70.
 19. Chan SW, Mukesh BN, Sizeland A. Treatment outcome of N3 nodal head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2003; **129**: 55–60.
 20. Carvalho AL, Kowalski LP, Agra IMG, Pontes E, Campos OD, Pellizon AC. Treatment results on advanced neck metastasis (N3) from head and neck squamous carcinoma. *Otolaryngol Head Neck Surg* 2005; **132**: 862–8.
 21. Smeele LE, Leemans CR, Reid C, Tiwari R, Snow G. Neck dissection for advanced lymph node metastasis before definitive radiotherapy for primary carcinoma of the head and neck. *Laryngoscope* 2000; **110**: 1210–4.
 22. National Institute for Health and Clinical Excellence. *Improving outcomes in head and neck cancers – the manual*. London: NICE
<<http://www.nice.org.uk/page.aspx?o=csghnguidance>> [Accessed 10 September 2006].

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