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MAIN ARTICLE

Should elective neck dissection be routinely performed in patients undergoing salvage total laryngectomy?

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Abstract

Background: The prevalence of occult neck metastasis in patients undergoing salvage total laryngectomy remains unclear, and there is controversy regarding whether elective neck dissection should routinely be performed.

Method: A retrospective case note review of 32 consecutive patients undergoing salvage total laryngectomy in a tertiary centre was performed, in order to correlate pre-operative radiological staging with histopathological staging.

Results: The median patient age was 61 years (range, 43–84 years). With regard to lymph node metastasis, 28 patients were pre-operatively clinically staged (following primary radiotherapy or chemoradiotherapy) as node-negative, 1 patient was staged as N1, two patients as N2c and one patient as N3. Fifty-two elective and seven therapeutic neck dissections were performed. Pathological analysis up-staged two patients from clinically node-negative (following primary radiotherapy or chemoradiotherapy) to pathologically node-positive (post-surgery). No clinically node-positive patients were down-staged. More than half of the patients suffered a post-operative fistula.

Conclusion: Pre-operative neck staging had a negative predictive value of 96 per cent. Given the increased complications associated with neck dissection in the salvage setting, consideration should be given to conservative management of the neck in clinically node-negative patients (staged following primary radiotherapy or chemoradiotherapy).

Key words: Laryngectomy; Head And Neck Cancer; Squamous Cell Carcinoma; Salvage Therapy; Neck Dissection

Introduction

Radiotherapy (RT) and chemoradiotherapy have become standard treatments for patients with all but the most advanced squamous cell carcinoma (SCC) of the larynx. Laser excision is an option for early cancer. Primary total laryngectomy is often performed for advanced bulky disease, though some patients with quite advanced cancer are still also suitable for chemo-radiotherapy.[1] High local control has been reported in randomised controlled trials of chemoradiotherapy. Nevertheless, around 10 per cent of patients undergo salvage total laryngectomy because of persistent or recurrent disease.

Elective neck dissection performed at the time of primary total laryngectomy is recommended for supraglottic and glottic grade 4 tumours (National Comprehensive Cancer Network Guidelines®). In this way, occult neck disease, which can be missed in up to 30 per cent of patients on pre-operative staging, is treated.

However, the position is less clear in the salvage setting. Salvage neck surgery is challenging, and affected patients are at a high risk of post-operative complications and prolonged hospital stay.[2,3] If such patients could be reliably pre-operatively staged, those considered free of neck disease could potentially be managed without elective neck dissections. This would reduce post-operative complications such as pharyngocutaneous fistula.

The frequency of occult nodal disease in recurrent laryngeal cancer has been reported to range from 3 to 17 per cent, with a higher trend of up to 28 per cent

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in supraglottic recurrence.[2,4,5] It is unclear why such variation exists in the literature. Furthermore, technological radiological developments continue apace, meaning that historical datasets may not be applicable to current practice.

This study aimed to assess the negative predictive value of contemporary pre-operative investigation in patients undergoing salvage laryngectomy. We also briefly describe our complication rates though these are more thoroughly described in a previous publication from our unit.[6]

Materials and methods

After local ethics committee approval, a retrospective analysis was performed of 32 consecutive patients who underwent salvage total laryngectomy following primary RT or chemoradiotherapy for laryngeal SCC between 2003 and 2010.

All patients underwent pre-operative computed tomography (CT) scanning of the neck and thorax, magnetic resonance imaging (MRI), and fine needle aspiration cytology (FNAC) when indicated. Patients' treatment was planned in our multidisciplinary head and neck tumour board meetings. Only patients with no evidence of distant metastasis and those treated with curative intent were included in this analysis.

In line with our multidisciplinary team's normal approach, salvage laryngectomy patients with evidence of neck disease were managed with bilateral modified radical neck dissections. Patients without evidence of neck disease underwent bilateral selective neck dissection of levels 2–4.

Following surgery, routine pathological analysis of neck specimens was performed. These results were then compared with the tumour board pre-operative documentation. As a secondary exercise, we collected survival data from follow-up consultations to investigate survival outcomes associated with pathological lymph node metastasis stage using the Kaplan–Meier method.

Results and analysis

Patients

A total of 32 patients underwent surgery between October 2003 and July 2010. Twenty-nine patients were male, three were female. The median patient age at the time of the procedure was 61 years (range, 43–84 years). All patients underwent total laryngectomy, and 9 of the 32 patients (28 per cent) also underwent partial pharyngectomy. Twenty-nine patients (91 per cent) underwent bilateral neck dissections, one (3 per cent) underwent a unilateral neck dissection and two (6 per cent) had no neck dissection.

Oncological outcomes

With a median follow up of 18 months (range, 1–106 months) for the whole cohort, 5-year overall survival was 37 per cent, disease-specific survival was 47.4 per cent, locoregional recurrence free survival was 71.7 per cent and distant recurrence free survival was 95.5 per cent (Figure 1).

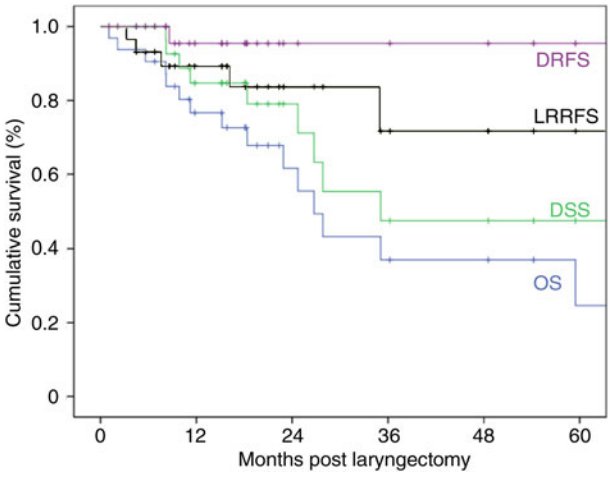

FIG. 1

Kaplan–Meier survival curves following salvage laryngectomy. DRFS = distant recurrence free survival; LRRFS = locoregional recurrence free survival; DSS = disease-specific survival; OS = overall survival

The pathological lymph node metastasis (N) stage is known to be an important predictor of outcome in head and neck cancer. However, possibly because of our small cohort, overall survival of pathologically staged N+ patients was not statistically significantly worse than pathologically staged N_0 patients ($p > 0.05$) (Figure 2).

Negative predictive value

Twenty-eight patients were pre-operatively clinically staged (following primary RT or chemoradiotherapy) as N_0 and four were staged as N+ (one patient was staged as N_1, two were N_{2c} and one was N_3). In the 28 N_0 patients, 52 elective dissections were performed, and in the 4 N+ patients, 7 therapeutic neck dissections were performed, based on pre-operative investigations.

A total of 1277 lymph nodes were retrieved from the 59 neck dissections. Of the 1277 nodes, 17 (1.3 per cent) were positive in 6 patients. Only two patients clinically staged as N_0 (following primary RT or chemoradiotherapy) were proven to have occult metastasis on post-operative pathological examination. This gives an occult metastasis rate (per neck) of only 2 out of 52 (4 per cent).

No patients were down-staged from clinical N+ (following primary RT or chemoradiotherapy) to pathological N_0 (post-surgery).

The sensitivity, specificity, and positive and negative predictive values are outlined in Table I.

Complications

The very high rate of complications suffered by this patient cohort has been described previously.[6] In brief, more than half of our patients had post-operative

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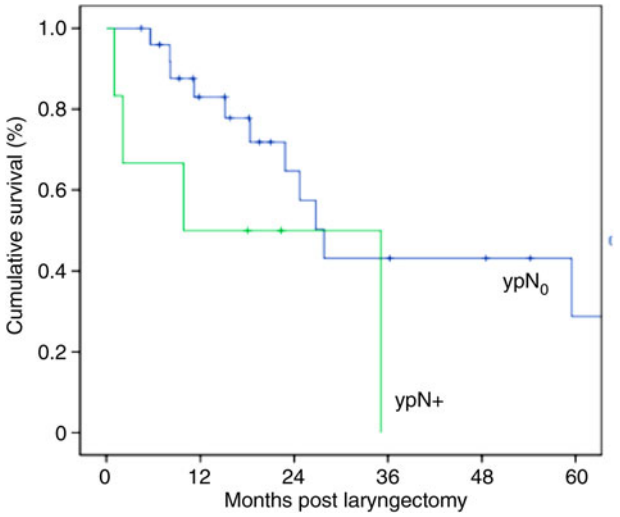

FIG. 2

Kaplan–Meier overall survival curves for patients pathologically staged as node-positive ('ypN + ') versus those staged as node-negative ('ypN$_0$') ($p > 0.05$).

TABLE I

DIAGNOSTIC VALUE OF CT IN DETECTING POST-CHEMORADIOTHERAPY NECK METASTASIS

Parameter	Value (%)
Sensitivity	78
Specificity	100
Positive predictive value	100
Negative predictive value	96

CT = computed tomography

infections despite antibiotic prophylaxis. All patients with wound infections ultimately developed pharyngocutaneous fistulas at an average of 12 days post-operatively.

Univariate analysis revealed three variables with significant correlation to wound infection: alcohol consumption ($p = 0.01$), clinical lymph node metastasis stage ($p < 0.01$) and pre-operative albumin levels of less than 3.2 g/l ($p = 0.012$). Transoesophageal puncture was not associated with a higher risk of complications. The time delay from completion of RT or chemoradiotherapy and salvage surgery was correlated with post-operative complications. The median time interval in patients that developed fistulas was 16.5 months whereas those who did not develop fistulas underwent surgery an average 27 months later.

Tumour stage was not associated with an increased risk of complications. Counterintuitively, N_0 was associated with more complications than N+ disease, despite the fact that the former group underwent selective neck dissection at levels 2–4, compared with modified radical neck dissection in the N+ group.

Discussion

Laryngeal cancer is the only cancer for which survival rates have worsened over the last 20 years.[7,8] The reasons for this have been contested,[8–10] but potentially include worsening co-morbidities and the increasing use of RT or chemoradiotherapy as the primary treatment modality.

Although surgeons' workload for primary laryngectomy has decreased, the need for salvage laryngectomy has increased. Indeed, persistent or recurrent disease following RT or chemoradiotherapy has been reported to be as high as 50 per cent.[11]

In some of these patients, salvage surgery is still feasible and can achieve cure. However, the effects of high-dose RT and chemotherapy on tissue mean that these patients are at a higher risk for post-operative complications.[2,3,12] Salvage surgery is defined as 'clean-contaminated' surgery, and local wound infection rates range from 40 to 61 per cent.[13–16] The reasons for this high complication rate are discussed elsewhere, but it seems to be driven more by the extent of surgery than by nodal stage.[13,17,18] Chemoradiation also seems to be associated with more complications than RT,[15,19,20] though we found no significant difference, which is in agreement with an earlier study.[21]

Given the above, the surgeon must be convinced of the survival benefit of carrying out a neck dissection before recommending it to a patient. This survival benefit is clear in N+ patients, but the question of how much occult disease is missed on pre-operative investigation is a matter of contention. If pre-operative investigation was reliable, we could spare the patient the morbidity of an elective neck dissection[2,4,5,22,23] without impacting on oncological outcome. On the other hand, this might be the last chance for cure that the patient has, and if the occult metastasis rate is too high, then the surgeon should recommend elective neck dissection.[22,24] It must also be emphasised that despite aggressive treatment, the overall prognosis for these patients is dire, with a five-year overall survival rate of less than 50 per cent.

Novel pre-operative staging techniques

In the primary laryngectomy setting, despite the variety of possible investigations (endoscopy, MRI, CT, positron emission tomography (PET), or ultrasound with or without FNAC), it is not uncommon for the pre-operative investigation to either over-estimate[25] or under-estimate[26–29] the extent of disease. Overall, occult metastasis rates of roughly 30 per cent are reported for primaries of the oral cavity, oropharynx and larynx.[30]

In order to increase the accuracy of pre-operative staging and reduce the occult metastasis rate, several new techniques have been tested. Three of the more promising techniques are PET-CT, sentinel lymph node biopsy and diffusion-weighted MRI.

The PET-CT technique has been widely studied, and has been reported to have a significant therapeutic impact in changing the management of patients undergoing surveillance.[31] A review of studies on PET-CT for recurrent laryngeal cancer found pooled estimate

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sensitivity of 89 per cent and specificity of 74 per cent.[32] However, few studies have addressed regional disease specifically. A recent publication on the use of PET-CT for detecting regional disease in patients undergoing salvage laryngectomy concluded that the negative predictive value was too low to allow conservative management of the neck.[23]

Sentinel lymph node biopsy is gaining popularity in the management of early oral SCC, with negative predictive values of more than 95 per cent.[33] Though there are reports of sentinel lymph node biopsy used in recurrent carcinoma of the vulva,[34] and in oral or oropharyngeal cancer,[35] to date there are no published studies on recurrent laryngeal cancer. In theory, the post-RT or post-chemoradiotherapy neck may well have aberrant drainage patterns, and it is unclear whether this would make sentinel lymph node biopsy unreliable. The technique would also need some modification to allow 'on-table' injection of the nanocolloid.

Diffusion-weighted MRI has only recently been introduced for head and neck cancers.[36] In the setting of post-RT or post-chemoradiotherapy laryngeal cancer, it has been reported to have better sensitivity and specificity than PET-CT (up to 96 per cent and 100 per cent in some series[37]), although this is not specifically in terms of evaluating the neck. There is little doubt though that diffusion-weighted MRI complements existing techniques and can be easily added to routine follow-up protocols.

Limitations

There remains a concern that micro-metastatic deposits of tumour in the neck will be well under the resolution of even the most advanced imaging technique. Furthermore, these micro-metastases might be currently under-estimated as they may be missed on routine pathological examination.[38] Indeed, roughly 10 per cent of historical pathologically staged N_0 neck specimens show micro-metastasis on careful re-analysis.

- **Various imaging and minimally invasive interventional techniques are available to stage the neck in primary and salvage laryngectomy**
- **Computed tomography has better negative predictive value in ruling out neck metastasis in salvage rather than primary laryngectomy**
- **Salvage neck dissection is associated with a high risk of complications**
- **Conservative management may be considered for the clinically node-negative neck in the salvage laryngectomy setting**

This raises the possibility that our pathologically staged N_0 patients actually did have micro-metastatic disease resected during elective neck dissection. This would presumably have a survival benefit though the exact survival significance of micro-metastatic disease is controversial. For example, Bohannon *et al.*[2] and Temam *et al.*[39] showed no survival benefit associated with elective neck dissection in the pathologically staged N_0 neck. This implies that the impact of any micro-metastatic disease missed on routine pathological examination would be too small to have a significant effect on survival.

Conclusion

Although limited by small numbers and its retrospective nature, our data suggest that the rate of occult neck disease in the salvage laryngectomy patient group is low. With the high rates of post-operative complications associated with salvage neck dissection, a conservative approach to the neck may be considered for patients clinically staged as N_0 (following primary RT or chemoradiotherapy). This would help to limit the significant morbidity of salvage surgery without adversely affecting the oncological outcome. Larger, preferably prospective studies are needed to further evaluate this suggestion.

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