

Changing paradigms in the treatment of residual/ recurrent head and neck cancer – implications for dysphagia management

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Abstract

Despite advances in head and neck cancer treatment provision, recurrence rates remain high with the added risk of successfully treated patients developing a second primary. There have been numerous recent developments in treatment options for people with residual/ recurrent/ new primary head and neck cancer in a previously irradiated field. This is due to improved surgical interventions including microvascular reconstruction techniques and transoral robotic surgery. In the era of highly conformal radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), there may be opportunities for re-irradiation. These advancements are now increasingly employed in the context of locoregionally recurrent disease. With results being reported from an increasing number of clinical trials, systemic therapies, including treatment with immunotherapy, offer the potential for increased survival with less treatment-related toxicity. Dysphagia is recognised as a significant toxicity following radical surgical and radiation-based approaches, particularly when multimodal treatment is required. Increasingly, late radiation-associated dysphagia is gaining greater attention in the literature. Many of those presenting with residual and recurrent disease do so against a background of co-morbidities as well as persisting and late treatment-related toxicity. We report on the management of dysphagia in the context of residual/ recurrent or new primary disease in a pre-irradiated field and suggest areas for further research.

KEYWORDS: recurrent head and neck cancer, dysphagia, quality of life.

Introduction

Over 9000 patients are treated for head and neck cancer (HNC) in the UK annually (Paleri et al 2018) and the incidence is increasing (Schache et al 2016). Squamous cell carcinomas (SCC) account for the majority of these tumours, with an increasing number associated with the human papillomavirus (HPV). Despite ongoing advances in the treatment of primary HNC, the recurrence rate remains high at 20-30% for advanced disease (Mandapathil et al 2014). Patients may experience residual disease after radical treatment, identified within a 12-month period, or recurrent disease identified at the same site within 5 years, or indeed develop a new primary in a previously irradiated field (Hardman et al in press). Recurrent/ residual head and neck cancers (R/R HNC) including new primary disease which occurs in a previously irradiated field present some of the greatest challenges in HNC practice. This is further complicated by the poor evidence base to support management decisions. There are significant implications for communication and swallowing function and quality of life (QoL), and the important, but challenging decision-making related to supportive care alone (Mehanna et al, 2016).

Although potentially curative treatment options are available for R/R HNC, including surgery and re-irradiation, patients have traditionally been considered to have a poor prognosis and, as a result, the majority are treated with palliative intent or best supportive care (Mehanna et al, 2016). A careful balance between the desire to secure disease control and maintain functional outcomes is critical and the decision to opt for non-curative treatments may be based on the potential functional morbidity that attempted curative treatment may have.

The literature over the past two decades would suggest that survival outcomes are improving for patients with R/R HNC, with 71% survival at 2 years following salvage surgery for laryngeal cancer (Weber et al 2003) and 50% 5-year survival for selected patients treated with surgery for oropharyngeal cancer (OPC) (Jayaram et al et al 2016). More recently, immunotherapy is being utilised with agents such as Nivolumab and Pembrolizumab augmenting the range of treatment options available in the management of recurrent disease (Cohen et al., 2019; Burtneess et al 2019).

In addition to existing and novel treatment options, palliative and best supportive care are essential elements to address not only physical symptoms, but also spiritual and psychological well-being that considers the needs of patients and their families.

Multidimensional swallowing evaluation to inform patient counselling and treatment decision-making

Dysphagia is one of the most serious issues resulting from HNC and/or its treatment, with swallowing ability being a priority concern for patients up to one year following treatment (Roe et al 2014; Wilson et al 2011). Dysphagia is an independent predictor of survival and is associated with higher risk of pneumonia, poorer oral intake, prolonged gastrostomy use, poor nutritional status, weight loss and fundamental changes to eating patterns, social life, and subsequent QoL (Patterson et al 2016).

People may present with dysphagia as a symptom of the disease. Furthermore, the presence of ongoing swallowing difficulties following radical surgery, as well as persisting or late radiation-associated dysphagia can present significant challenges (Cohen et al 2016). The evaluation and careful selection of patients with R/R HNC for treatment with curative intent is the 'crux' of successful management (Mehanna et al 2016). Inherent in this evaluation is a multidimensional evaluation of swallowing function. Even for patients undergoing treatments with palliative intent, a thorough baseline assessment of function is required to optimise patients and maximise QoL throughout their treatment.

Patients with R/R HNC should undergo appropriate and extensive counselling regarding expected outcomes. A multidisciplinary approach to treatment decision-making should include an evaluation of performance status, psychological status, co-morbidity, previous and persisting toxicities and social support networks (Mehanna et al 2016).

Once diagnosed with R/R HNC, referral for evaluation by a speech and language therapist (SLT) should be considered. As well as establishing the patient's current functional status, it contributes to the informed consent process as part of treatment planning. The importance of dietetic evaluation is critical to optimise nutritional state and fitness for treatment.

Surgical management of R/R HNC:

Surgery is the most widely used treatment for R/R HNC and, from the literature, appears to be offer the best chance of cure for those in whom it is possible (Jayaram et al 2016). The aim of open surgical resection is complete macroscopic clearance with widely clear margins, which can result in large defects which require reconstruction. This can have a major functional impact on communication, swallowing and QoL (White et al 2013). The consequential large functional deficits have to be balanced against the potential benefit of longer survival (Mehanna et al, 2016). Open salvage surgery for R/RHNC has been associated with a high complication rate at 48% with poor healing and prolonged hospital stays (Zafereo et al 2009). Successful resection can be difficult due to the complex three-dimensional anatomy and proximity and adherence to the internal carotid artery and other great vessels (Mehanna et al 2016). Access procedures using a mandibulotomy or lingual release are frequently required. In the setting of previous radiotherapy, the risk of osteoradionecrosis is substantially increased, in addition to extensive disruption to the oral cavity and floor of mouth musculature (Hamilton & Paleri, 2017). Recent advances in transoral robotic surgery (TORS) have facilitated access to the oropharynx obviating the need for mandibulotomy or lingual release (Hamilton & Paleri, 2017). The use of TORS is now being extended to the treatment of R/R HNC (Hamilton & Paleri, 2017). A multicentre case control study showed that patients treated with TORS had a significantly lower incidence of tracheostomy, feeding tube use, and shorter hospital stay, with significantly decreased incidence of positive margins and significantly higher survival than matched patients treated with open surgery; 2-year recurrence-free survival rate of 74% vs 43% ($p = .01$) (White et al 2013). A UK-based study reports disease-specific survival rate of 77% at 42.6

months following TORS for recurrent OPC. Clinician-reported functional outcome scores suggest the potential for some swallowing recovery post- surgery (Paleri et al 2018; Brady et al 2019) with low long term gastrostomy (5.0%) and tracheostomy rates (1.9%) (Hardman et al in press).

Re-irradiation

In unresectable disease, the era of highly conformal radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), has meant re-irradiation may be considered as a potentially curative treatment option (Botts et al 2016). However, there have been few studies of this approach and the only randomised trial to compare re-irradiation plus concomitant chemotherapy versus palliative methotrexate chemotherapy demonstrated increased progression- free survival but failed to demonstrate an improvement in overall survival (Tortochaux et al 2011). Post salvage surgery re-irradiation has been investigated in the setting of adverse histopathologic features such as a positive resection margin or nodal involvement with extracapsular spread (Botts et al 2016). Again, there are limited data on this approach and the only randomised study of salvage surgery alone versus salvage surgery plus post-operative chemoradiotherapy (CRT) demonstrated improved disease-free, but not overall, survival for 65 (of 130) patients randomised to adjuvant CRT (Janot et al 2008). This result was achieved at the cost of far greater (39% versus 10%) late grade 3 or 4 toxicity in the patients who received CRT. Severe toxicities of re-irradiation include dysphagia requiring gastrostomy, trismus, soft tissue and skin necrosis, osteoradionecrosis, myelopathy, and carotid artery blowout (Dionisi et al 2019).

Systemic treatments

Patients with non-resectable R/R HNC should be offered the opportunity to participate in clinical trials of new therapeutic agents, including immunotherapies (Mehanna et al 2016). Immunotherapy is based on functional restoration of the host immune system, helping to circumvent various tumour evasion strategies (Szturz & Vermorken, 2017). It has been shown to be both an effective and safe treatment in both first and second line treatments for R/R HNC (Cohen et al 2019; Burtness et al 2019)

In the second line setting, the KEYNOTE-040 randomised, open-label, phase 3 study investigated the safety and efficacy of pembrolizumab versus methotrexate, docetaxel, or cetuximab. The median overall survival was 8.44 months (95% CI 6.4–9.4) with pembrolizumab and 6.9 months (5.9–8.0) with standard of care (hazard ratio 0.80, 0.65–0.98; nominal $p=0.0161$). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 vs 85 [36%] of 234) (Cohen et al 2019). In the first line treatment setting the KEYNOTE-048 randomised, open-label, phase 3 study demonstrated that pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic HNSCC and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive recurrent or metastatic HNSCC (Burtness et al 2019).

Patients receiving best supportive care have an average overall survival of four months. Studies of palliative chemotherapy generally show longer survival rates,

depending on the regimen (Mehanna et al 2016). No large, well-designed randomised trial has been undertaken to definitively show an overall survival benefit of palliative chemotherapy over best supportive care in these patients (Mehanna et al 2016) and it is difficult to imagine how such a study could be performed within the modern framework of medical ethics. Until recently, triple therapy with platinum, cetuximab and 5-fluorouracil (the so-called EXTREME regimen) provided the best first-line treatment outcomes for the management of patients with recurrence who had a good performance status and who were fit to receive systemic therapy (Mehanna et al 2016). Patients who were not fit for EXTREME regimen were treated with combinations of platinum and cetuximab or platinum and 5-FU. In a large multi-site retrospective review of outcomes including 733 patients across 71 sites, for patients treated with platinum based combinations, overall survival was 8.0 months (95% CI: 7.0–8.0), with one-year survival reaching only 30.9% (95% CI: 27.5–34.3). (Gruenwald et al 2020). More recently, however, the results of the KEYNOTE-048 study have shown that patients with tumours that express the marker programmed death ligand-1 (PD-L1) at a combined pathological score (CPS) of 1 or greater experience better outcomes with single-agent pembrolizumab or combined pembrolizumab-chemotherapy when compared to EXTREME regimen (Burtness et al 2019).

Regardless of palliative systemic treatments being administered, our clinical experience has shown that patients with R/R HNC are at high risk of oropharyngeal dysphagia from their previous radical treatment(s) and tumour burden. Aspiration-related complications, including pneumonia, poor nutritional status, and general performance status, may preclude a patient's ability to tolerate standard of care first-

line palliative chemotherapy, first- or second-line immunotherapy and/or clinical trial entry. Thorough baseline evaluation of swallowing and nutritional status is imperative to optimise the patient, minimise symptom burden, including late toxicity, and maximise QoL.

Implications for swallowing management

Assessment requirements:

In our clinical practice, evaluation includes a thorough clinical bedside examination of swallowing function including case history and oromotor function. The 100ml Water Swallow Test is undertaken (Patterson et al 2007) along with a series of clinician- and patient-reported measures. Clinician-reported measures include all domains of the Performance Status Scale for Head and Neck Cancer (PSS-HN) (List et al 1990), and maximum interincisor opening (MIO). Patient-reported outcomes are collected using the MD Anderson Dysphagia Inventory (MDADI) (Chen et al 2001). An instrumental swallowing evaluation using Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and/or videofluoroscopy is also undertaken to evaluate swallowing safety and efficiency using standardised rating scales also constitutes our standard of care. FEES includes secretion rating scales (Murray et al 1990; Miles and Hunting, 2019), an oedema rating scale (Patterson et al, 2007), the Penetration Aspiration Scale (Rosenbek et al, 1996), and the Yale Residue Scale (Neubauer et al 2015). Videofluoroscopy outcomes are graded using the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) (Hutcheson et al 2017).

National guidance highlights the need to evaluate the social support structures available for patients in order to determine their ability to cope with the demanding

treatments that may be required in the management of their disease (Mehanna et al 2016). This is important given a potentially protracted course of rehabilitation following treatment. At our centre, we use an holistic needs assessment (HNA) (Macmillan, 2017) to identify patient priorities, physical, emotional, spiritual, mental and social concerns and needs. The HNA is designed for use across tumour groups. However, tumour-specific tools are available, in particular the Patient Concerns Inventory for Head and Neck Cancer (PCI-HN) (Ghazali et al 2013) and Screen IT (Wall et al, 2016).

There can be high complication rates in patients treated surgically for R/R HNC (Zafereo et al 2009). To screen those at increased risk of dysphagia and other complications, a Geriatric 8 is undertaken in patients aged 65 and over. Early findings suggest that this can highlight HNC patients at risk of increased length of hospital stay and gastrostomy dependence following surgery (Starmer et al, 2019).

Findings from the SLT baseline assessment must be fed back to the multidisciplinary team and patients to assist in the decision-making process regarding management. In primary disease management, baseline swallowing function is the most important predictor of post-treatment swallowing (Owen et al 2016) and is the foundation of any pre-treatment counseling regarding the potential impact of treatments.

Therapeutic requirements:

Depending on the treatment pathway, the therapeutic pathway for dysphagia prehabilitation and rehabilitation varies. For curative treatment options including

surgery (either open or TORS) or re-irradiation, pre-treatment evaluation will identify targeted prehabilitation goals including swallowing exercises. The same methods used in the primary disease setting can be used in an effort to try and optimise swallowing function.

Tracheostomy:

Tracheostomy is often required in the case of open salvage surgery (up to 79%) and salvage TORS (14-24%) (White et al 2013; Paleri et al 2018). The three main indications for an elective tracheostomy include (1) bleeding risk (2) reduced upper airway patency and (3) secretion management.

At our centre we encourage early cuff deflation to assess upper airway patency, to facilitate verbal communication with the use of a speaking valve if suitable, and to enhance sensation/ cough reflex to promote independent secretion management.

Given the acknowledged risk of bleeding following TORS, at our centre a covering tracheostomy is placed and patients are typically decannulated at days 10-12 post surgery (Hay et al, 2018; Brady et al 2019). Swallowing rehabilitation in the form of clinical evaluation of swallowing (with or without oral trials) and swallowing exercises commence on day one following surgery to maximise functional outcomes regardless of tracheostomy tube status/ indication. A detailed assessment for airway patency/ suitability for speaking valve placement and swallowing ability will be required including instrumental evaluation.

Maintenance of eating and drinking and swallowing exercises:

In the management of primary HNC, patients are usually encouraged to continue to eat and drink throughout radiotherapy. Early re-introduction of eating/drinking following surgery is also advised to avoid periods of nil-by-mouth (Patterson et al, 2016). Periods of nil-by-mouth are associated with worse swallowing outcomes, thought to be because of subsequent deconditioning of the musculature (Shune et al 2012).

There is an emerging evidence base for the use of pre-treatment dysphagia exercise protocols in the primary HNC disease setting (Patterson et al 2016) and the results of an ongoing multicentre randomised controlled trial are eagerly awaited (NCT03455608). It has been our clinical experience that targeted pre-treatment exercise protocols can also be useful in the R/R HNC setting and are standard of care for patients undergoing salvage surgery (open or TORS) and re-irradiation.

Even in those patients with known swallowing safety issues and also those with a tracheostomy, maintenance of some form of oral intake may be achieved with careful use of repeated instrumental swallowing evaluation to introduce compensatory strategies and swallowing manoeuvres. A free water protocol (Panther 2005) which allow sips of water with good oral hygiene can not only provide comfort to our patients with persisting xerostomia, it can also be a method of potentially reducing disuse atrophy (Patterson et al 2016).

Favourable functional outcomes have been reported for TORS versus open salvage surgery (Paleri et al 2018, White et al 2013). Within our own cohort of patients

undergoing TORS for the treatment of R/R HNC, we have seen that there is the potential for swallowing rehabilitation following surgery (Brady et al 2019). In our experience, TORS may be minimally invasive but requires high-level rehabilitation and a highly motivated patient. Likewise in the open salvage surgery or re-irradiation setting, rehabilitation often takes place over a protracted period using a range of intervention techniques which is based on the literature on rehabilitation of late-radiation induced dysphagia . This includes targeted swallowing exercises, repeated instrumental evaluation and outcome measures. Rehabilitation requires close MDT working. Surgical optimisation techniques are often required including oesophageal dilatation and/or vocal cord medialisation. Emerging interventions such as Expiratory Muscle Strength Training (EMST) which has shown favourable outcomes in the HNC population with regards to cough strength can be employed (Hutcheson et al 2018) and often an intensive block of bolus-driven bootcamp swallowing therapy is required (Malandraki et al 2018). The hallmark of the bolus driven bootcamp is a period of clinician-directed, intensive functional therapy that continually challenges the swallowing musculature. The programme involves a short, intense series of daily therapy sessions over a 2- to 3-week period. The therapy sessions center on mass practice (typically 100+ swallows per session) of the functional task (i.e., swallows) under progressive conditions (i.e. different swallowing textures) (Malandraki et al, 2018).

The use of enteral feeding:

There has been much debate regarding the method and timing of enteral feeding in the primary HNC setting (Paleri et al 2018). This is also relevant in the R/R HNC setting. In our clinical experience, a case-by-case decision should be made

regarding the requirement for gastrostomy and this should be based on shared decision-making with the patient and a thorough evaluation of baseline swallowing function and nutritional status. On a background of persisting swallowing toxicity from previous treatments, eating and drinking may no longer be an enjoyable experience and the option of a gastrostomy may actually enhance QoL. Likewise, and particularly in the non-curative setting, a 'safe route' for the efficient and effective administration of essential medications, including analgesia, in addition to the administration of nutrition and hydration may be the preferred option for the individual patient.

In the setting of curative treatment, in particular salvage surgery, a case-by-case decision should be made for each patient. This should be based on the baseline evaluation of swallowing function, but underpinned by the individual goals of the patient and motivation to engage in swallowing rehabilitation.

Conclusions

Patients with R/R HNC should be counselled on the likely survival and functional outcome of the various treatment modalities available. Early SLT referral is essential for multidimensional baseline evaluation of function, activity limitation and participation restrictions, including social and emotional factors (Nund et al 2019). This ensures patient-centred decision-making regarding treatment, optimised functional status pre-treatment, and maximum rehabilitative outcomes through optimised QoL and reduced symptom burden.

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