Oral Oncology 64 (2017) 9–14

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Laryngeal tumours and radiotherapy dose to the cricopharyngeus are predictive of death from aspiration pneumonia

Jolyne O'Hare [a,*], Julia Maclean [b,d], Michal Szczesniak [c,d], Rashmi Gupta [a], Peter Wu [c], Harry Quon [e], Ian Cook [c,d], Peter Graham [a,d]

[a] Department of Radiation Oncology, St George Hospital, Sydney, NSW, Australia
[b] Speech Pathology Department, St George Hospital, Sydney, NSW, Australia
[c] Department of Gastroenterology and Hepatology, St George Hospital, Sydney, NSW, Australia
[d] St George Clinical School, University of New South Wales, Sydney, NSW, Australia
[e] Department of Radiation Oncology & Molecular Radiation Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 27 September 2016
Received in revised form 19 November 2016
Accepted 22 November 2016
Available online 29 November 2016

Keywords:
Head and neck cancer
Aspiration pneumonia
Larynx cancer
Mortality
Cricopharyngeus

ABSTRACT

Objectives: Aspiration pneumonia is an under-reported treatment sequelae following radiotherapy for head and neck cancer (HNC) patients. This study aims to investigate its incidence and risk factors in this population.

Materials and methods: A retrospective review of all HNC patients that had received radiotherapy or chemo radiotherapy with radical intent at a single institution was undertaken (n = 206). Dose delivered to the pharyngeal constrictors, base of tongue and cricopharyngeus was calculated and compared between those patients who had died from aspiration pneumonia and those who are alive or had died from other causes.

Results: In a cohort of 206 patients, the median time of follow up was 3.5 years (IQR 1.8–4.9 years). The cause of death was known in 80 and one of the leading causes of non-cancer related mortality was aspiration pneumonia (n = 12) equating to an annual incidence of 0.016. Patients with a tumour located in the larynx had a higher risk of death compared to other sites (p = 0.005). The mean cricopharyngeal dose was significantly higher in those patients who died of aspiration pneumonia (p = 0.023) compared to those who were still alive or had died from other causes. In a multivariate regression analysis, maximum cricopharyngeal dose is a significant predictor of death from aspiration pneumonia.

Conclusion: Dose to the cricopharyngeus and tumours located within the larynx is associated with an increased mortality due to aspiration pneumonia. Clinical awareness of high risk groups and more studies into causative nature are needed.

Introduction

Concurrent chemoradiation as definitive or adjuvant treatment for head and neck cancers (HNC) carries significant morbidity and mortality with 59% of patients developing long-term dysphagia [1]. Aspiration is a potentially lethal consequence of dysphagia and in this population is commonly silent [2] and therefore difficult to diagnose clinically becoming an under-recognised sequela of radical treatment for head and neck cancer. When aspiration results in pneumonia, it is often managed in the community, leaving the oncologists unaware of true incidence rates following treatment despite carrying a significant impact on quality of life and a detriment survival [3–5]. Numerous longitudinal studies have documented aspiration pneumonia rates between 2% and 65% as early as 3 months following treatment [3,6,7]. Surveillance epidemiology and end results (SEER) database estimates the 5 year incidence of aspiration pneumonia at 23.8% and importantly, a diagnosis of aspiration pneumonia correlates with a negative impact on overall survival [8] specifically in patients with laryngeal cancers where this complication was higher in those treated with chemoradiation [9]. A cohort study within our institution confirmed that aspiration pneumonia accounts for at least 19% of non-cancer related deaths [1] and is likely an underestimation of the true prevalence. Strikingly, a retrospective case series from India identified 60% of in hospital deaths in patients who had undergone head and neck cancer treatment were due to aspiration pneumonia [10].

* Corresponding author at: Northern Ireland Cancer Centre, Belfast City Hospital, Lisburn Road, Belfast, Northern Ireland, BT9 7AB, UK.
E-mail address: Jolyne.ohare@gmail.com (J. O'Hare).

http://dx.doi.org/10.1016/j.oraloncology.2016.11.010
1368-8375/

Aspiration occurs when the protective mechanisms of normal deglutition fail. Swallowing requires coordination of complex voluntary and involuntary muscles with both motor and sensory input collectively leading to a complex motor pattern. The most important components of airway protection include anterosuperior elevation of the hyoid and larynx, inversion of the epiglottis over the superior aspect of the larynx to assist with deflection of the advancing bolus away from the laryngeal vestibule and adduction of the true and false vocal cords. The upper oesophageal sphincter (UOS) also plays a role, with the functional cricopharyngeus being pivotal. Residual bolus commonly leads to aspiration following the swallow in this population. To prevent residual bolus remaining in the hypopharynx following a swallow, the UOS is required to relax and open. Relaxation of the UOS is centrally-mediated and opening of the UOS is a consequence of hyolaryngeal tractional forces and direct physical opening force of a descending bolus [11].

Some risk factors for death by aspiration pneumonia have been identified, such as male gender, locally advanced tumours and tumours of the hypopharynx [8,10]. Radiotherapy dose and its relationship to dysphagia have been extensively investigated with the pharyngeal constrictor dose predicting for symptomatic dysphagia [12] and the floor of mouth musculature and the risk of clinical aspiration [13]. In terms of aspiration pneumonia, dose to the larynx and inferior constrictor muscles are reported as significant in one small retrospective study, suggesting that early clinically significant aspiration pneumonia does not occur when the mean dose to the larynx is kept under 48 Gy and early upper oesophageal strictures are not identified when the lower constrictor muscles are less than 54 Gy with conventional fractionation [14].

As yet, causative evidence highlighting the significant role aspiration pneumonia may play in the risk of late mortality in the irradiated HNC patient remains to be defined. Identifying risk factors especially dosimetric risk factors will help strengthen a potential causative relationship and provide insights into strategies that may be evaluated to prevent this late complication.

Methods

Study protocol was approved by St Vincent's Hospital Human Research Ethics Committee (HREC/10/SVH/125). The records of patients attending a single institution head and neck clinic from 2004 to 2012 were reviewed. Inclusion criteria included patients who had radical (chemo) radiotherapy or adjuvant (chemo) radiotherapy. Aspiration pneumonia was recorded as a cause of death providing it was both documented on the death certificate and aspiration had been previously confirmed on video fluoroscopy or fiberoptic endoscopic evaluation of swallowing (FEES). Patients treated with palliative intent, those who were aspirating prior to therapy, those who had a laryngectomy and those with whom the cause of death was unknown were excluded from the analysis. Each available radiotherapy plan was restored from archive and the treatment plan was unaltered. For those with missing organs at risk (OAR) contours, retrospective contouring of additional normal structures, the base of tongue, pharyngeal constrictors and cricopharyngeus was carried out on the Pinnacle planning software (Philips Healthcare, Andover, MA) by two independent blinded investigators. To standardise contouring, the UZ Leuven guidelines were used [15]. The radiotherapy plan was recomputed and the mean and maximum dose to each additional structure was recorded.

Initially in a univariate analysis, clinical factors age, gender, tumour stage, tumour location and adjuvant chemotherapy were compared for patients who had died from aspiration pneumonia to those that were still alive or had died from other causes. A multivariate logistic regression was then performed to ascertain the effects of variables significant in the univariate analysis at the 0.25 level at predicting aspiration death. A second multivariate logistic regression analysis was performed to ascertain the effects of dose distribution to the cricopharyngeus, constrictor muscles and base of tongue in two separate models for mean and max dose. Potential confounders identified in univariate analysis above were included in the model with the exception of tumour location which is a key driver of dose shaping and consequently suffered from significant collinearity with dose distribution.

Results

351 patients were treated from 2004–2012 through the multidisciplinary head and neck clinic at our institution. 145 were excluded from analysis for the following reasons: patient had undergone upfront laryngectomy, initial treatment was with palliative intent, the cause of death was unknown or treatment was delivered elsewhere, leaving 206 eligible for analysis. In 11 patients, the radiotherapy plans were not retrievable and therefore subsequently excluded.

The median prescribed radiation dose was 66 Gy (IQR 56-70) and the most common fractionation schedule was 2 Gy per day, 5 days per week. Systemic therapy when administered concurrently included cisplatin, carboplatin or cetuximab. The mean follow up time was 3.5 years (IQR 1.8 – 4.9 years).

Cause of mortality

In 84 patients who died during the follow-up period, the cause of death could not be determined in 4 (5%). Cancer was the major cause of mortality for 47 (59%) and 12 (15%) patients died directly due to aspiration pneumonia and 11/12 (92%) were cancer free at the time of their death. When considering only non-cancer related mortality, aspiration pneumonia was the cause of death in 32% (Fig. 1). Median time to death from aspiration pneumonia since conclusion of treatment was 2.1 years IQR [1.23 2.85].

Risk factors for aspiration pneumonia death

To determine risk factors for aspiration-related mortality, patients were stratified into those who died of aspiration pneumonia (n = 12) and those who were alive at last follow-up or died of known causes other than aspiration pneumonia (n = 206). Patient demographics and univariate analysis results of risk factors are listed in Table 1.

The majority (70%) of head and neck cancers presented with locally advanced disease with 146 patients presenting with stage III or stage IV disease. Mortality due to aspiration pneumonia occurred in all stages of disease without increased risk according to disease stage ($p = 0.782$) (Fig. 2). When the incidence of death by aspiration pneumonia was stratified by tumour location, the risk of aspiration pneumonia tended to be higher in patients whose tumours were located in the laryngeal structures, however this did not reach statistical significance ($p = 0.08$) (Fig. 2).

Patients who died of aspiration pneumonia tended to be older (75 [65.3 77.8] vs 64.8 [62.9 66.8, $p = 0.097$]). Neither gender ratio nor frequency of adjuvant chemotherapy differed between those patients who died of aspiration pneumonia than those who were alive or died of other causes.

A logistic regression was performed to ascertain the effects of variables significant in the univariate analysis at the 0.25 level, specifically age and location. The multivariate logistic regression