



Systematic review and meta-analysis of the impact of dosimetry to dysphagia and aspiration related structures (DARS)

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INTRODUCTION

Dysphagia is a prevalent complaint that usually occurs with a diagnosis of head and neck cancer and its treatment. Factors known to influence swallowing function include age, gender, comorbidities, tumour stage and location, type of treatment and the involvement of a Multidisciplinary Team (MDT) (Shune et al 2012, Terrel et al 2013, Denaro et al 2013, Christopher et al 2017, Friedland et al 2011.)

Advancements in radiotherapy technology has achieved better quality of life for patients, by achieving a heterogenous radiation field and minimizing radiation dose to normal tissue (Rathod et al 2013).

The existing systematic reviews were outdated given new literature on this topic. Incorporating a quality rating and meta-analysis was also considered important.

The aim of this systematic review and meta-analysis is to determine if the radiation dose to dysphagia and aspiration related structures impacts the swallowing outcomes of patients undergoing head and neck cancer treatment.

METHOD

The PRISMA checklist was followed for all aspects of this systematic review and meta-analysis.

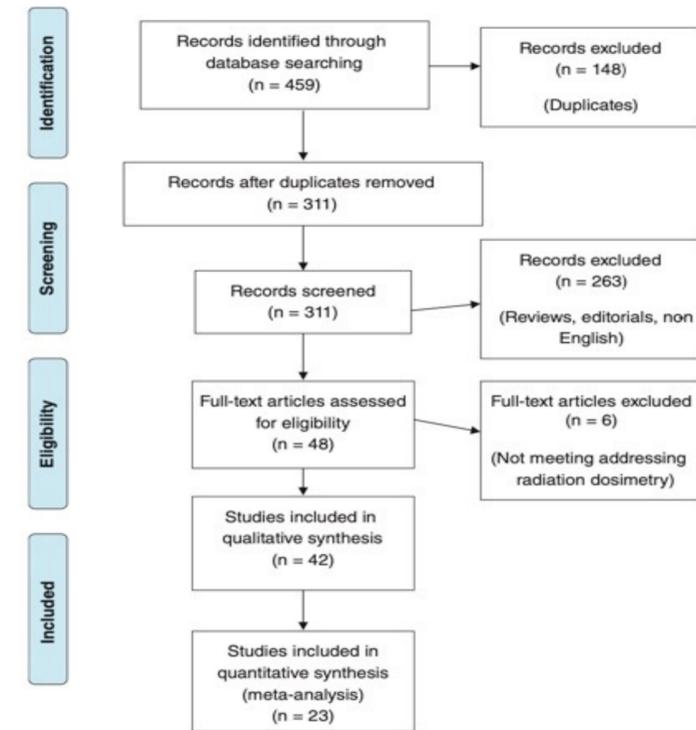
Search Strategy: An electronic database search of PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Medline, dissertation abstracts on The University of Sydney database, CINAHL, SCOPUS and Google Scholar was carried out for peer-reviewed journals from January 2000 until December 2017.

Inclusion and Exclusion Criteria: Studies were included in the review if they (a) reported on adult participants diagnosed with head and neck cancer, who had received radiotherapy with or without chemotherapy for treatment and (b) presented data on how the dosimetric volume effects the swallowing organs or how different regimes of radiotherapy compared.

Data Extraction: Studies were independently checked for adherence to the inclusion criteria by two of the four authors (EC and HB), with discrepancies discussed between all authors until agreement was reached. Each article received two independent assessments to evaluate inter-rater reliability. The quality of all included articles were measured using the Downs and Black checklist.

Meta-analysis – statistical analysis: The common outcomes of interest were the proportion of patients with aspiration and feeding tube dependence following radiation. A fixed-effects meta-analysis was used to calculate the estimated pooled effect across studies. Studies were weighted using the inverse-variance approach²⁴, The I² statistic was calculated in each case to investigate the extent of heterogeneity across studies.

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 flow diagram



RESULTS

Figure 2 & 3 summarise the fixed-effect meta-analysis, for aspiration and presence of a feeding tube at baseline, < 12 months and > 24 months. There is significant heterogeneity for each time point meaning use of pooled results, while potentially useful to predict incidence of aspiration and PEG dependence, should therefore be on a provisional basis.

Figure 2: Forest plot of the pooled proportion of aspiration

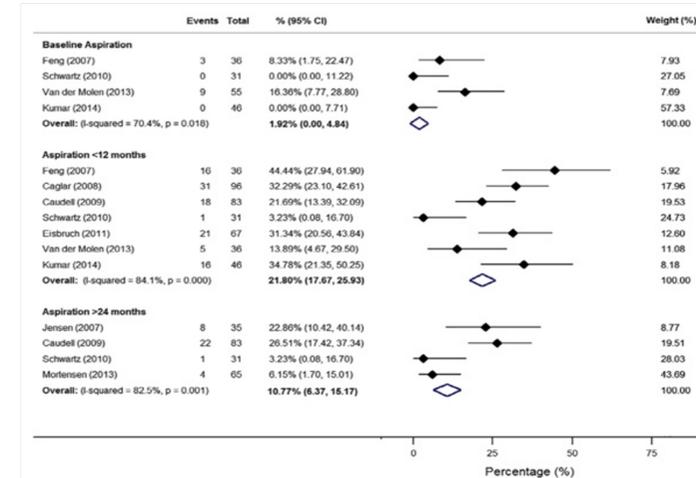
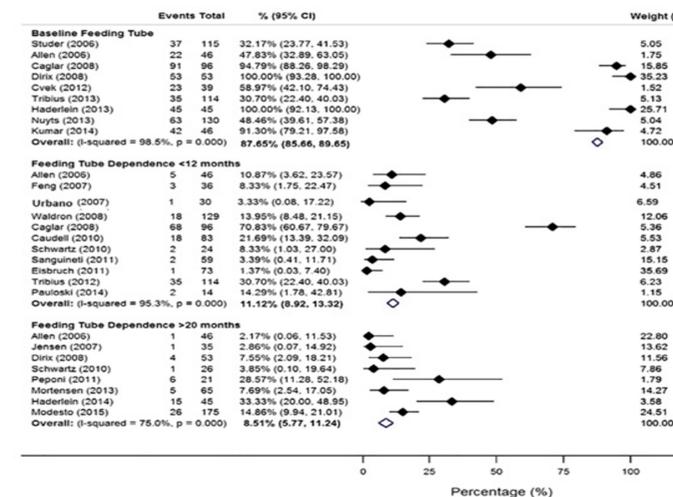


Figure 3: Forest plot of the pooled proportions of feeding tube dependency



42 studies met inclusion criteria, comprising of a total of 3660 participants, with a range of 12 to 200 per study (median 56). The average age of participants was 60 (range 15 to 90 years).

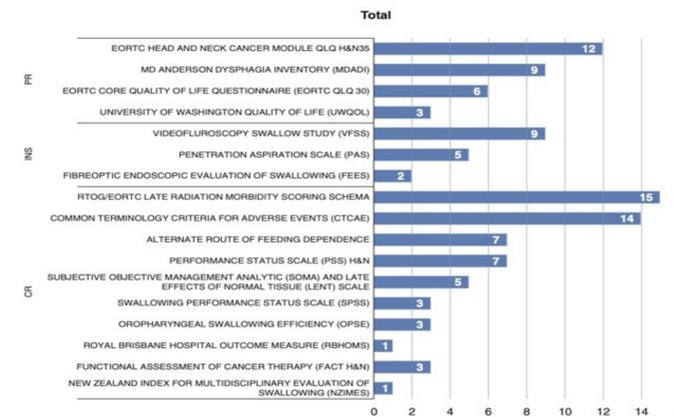
The mean dose received by patients to their primary tumour for definitive radiotherapy was 69.18Gy (range 50-78Gy). Thirty-nine studies found a correlation between the dosimetry to dysphagia and aspiration related structures (DARS) and incidence of dysphagia and aspiration.

The average Downs and Black score was 18/28 (range 12-22). The following studies scored above 20/28; their results indicated reducing dose to DARS;

- Glottis (Schwartz et al 2010): reduced aspiration on modified barium swallow study
- Middle and superior pharyngeal constrictor (Mazzola et al 2014): reduced dysphagia symptoms on the RTOG/EORTC
- Larynx, superior and middle pharyngeal constrictor (Modesto et al 2015): reduced dysphagia symptoms on the CTCAE
- Superior, middle and inferior pharyngeal constrictors (Eisbruch et al 2011): reduced incidence of aspiration on videofluoroscopy swallow study.

All but one study reported a change in dysphagia outcomes after radiation treatment. This sole study had a Downs and Black quality analysis of 15/28 (mean for the study was 17.7, SD = 2.6).

Figure 4 Frequency of dysphagia outcome measures



The heterogeneity of the selected sample studies was high for all measures; use of pooled results, while potentially useful to predict incidence of aspiration and PEG dependence, should therefore be on a provisional basis.

11 studies used instrumental swallowing evaluations. Symptom indexes were the most commonly used measure for dysphagia evaluation. The frequency of dysphagia outcome measures used across the 42 studies are depicted in Figure 4.

DISCUSSION

The average radiation dose to the pharyngeal constrictor muscles and glottic larynx were the most frequent structures associated with dysphagia and aspiration. Lower rates of dysphagia and aspiration were associated with lower radiation dose to the pharyngeal constrictors and oesophageal inlet.

Only 11/42 studies utilized instrumental swallowing assessments, which is required for a physiological or structural diagnosis of dysphagia and/or aspiration. It was most common to use validated patient symptom indexes such as the RTOG or EORTC. 12 (29%) studies included data before or early in their treatment making it challenging to attribute changes in function post-treatment to the treatment regime. Additionally, many studies (31/42, 74%) only concentrated on the acute post radiotherapy changes (i.e. during radiotherapy and within the first-year post treatment) which neglects to investigate the common chronic changes due to radiation fibrosis. The average of 18/28 on the Downs and Black quality analysis prompts consideration of prospective, randomized, blinded studies with adequate statistical power and control of bias in the future.

Heterogeneity between patient groups and assessment methodology (tumour location, outcome measure and assessment timing) was high, making comparisons and broader conclusions challenging.

CONCLUSION

This systematic review with meta-analysis which was the first to bring a quality rating to its methodology on this subject, demonstrated that while there was a wide distribution in study quality and a significant degree of heterogeneity for the articles included, those with higher scores support the hypothesis that there is a relationship between higher doses to structures critical for swallowing, and dysphagia. The structures that appear to be most sensitive to dysphagia and aspiration are the pharyngeal constrictors (superior, middle and inferior) and the glottic larynx.

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