



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Review

Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer: A systematic review of literature

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ARTICLE INFO

Article history:

Received 13 January 2017

Received in revised form 7 August 2017

Accepted 21 August 2017

Available online xxx

Keywords:

Radiotherapy

Tube feeding dependence

Prognostic factors

ABSTRACT

Background: Tube feeding dependence is a commonly observed debilitating side-effect of curative (chemo-) radiation in head and neck cancer patients that severely affects quality of life. Prevention of this side-effect can be obtained using advanced radiation techniques, such as IMRT. For radiotherapy treatment plan optimization, it has become increasingly important to develop prediction models that enable clinicians to predict the risk of tube feeding dependence for individual patients. To develop such a tool, information regarding the most relevant prognostic factors for tube feeding dependence is necessary.

Objectives: The primary aim of this systematic review, conducted according to PRISMA guidelines, was to identify prognostic factors that are consistently found to be associated with tube feeding dependence at ≥ 6 months after treatment. The secondary aim was to identify prognostic factors found to be associated with tube feeding placement and use at < 6 months.

Data sources: Articles were identified through a search in MEDLINE, EMBASE and the Cochrane Library. Approximately 2600 articles were screened and selected by inclusion and exclusion criteria.

Results: Fourteen retrospective studies were identified that fulfilled the inclusion criteria and reported on prognostic factors for tube feeding dependence at ≥ 6 months. The studies reported on patient and disease variables, treatment variables and DVH parameters. Two of these studies reported on a model for tube feeding dependence, one including DVH parameters. Additionally, 18 studies were identified that reported on prognostic factors for tube feeding placement and use at < 6 months.

Conclusions: Prognostic factors that were consistently associated with the risk of tube feeding dependence at ≥ 6 months for head and neck cancer patients treated with (chemo-) radiotherapy were DVH parameters, including dose to the larynx, the pharyngeal constrictor muscle inferior and superior, and the dose to the contralateral parotid gland. Furthermore, advanced tumor and nodal stage, pretreatment weight loss, (concomitant) chemotherapy and prophylactic gastrostomy policy were prognostic for tube feeding dependence ≥ 6 months. For tube feeding use at less than 6 months, prognostic DVH parameters included dose and volume to the oral mucosa, dose to the contralateral submandibular gland, and also dose to the larynx and the pharyngeal constrictor muscle inferior and superior. Prognostic patients/disease and treatment factors for tube feeding placement and use at less than 6 months were similar to the prognostic factors for tube feeding dependence at ≥ 6 months, but also included several unique variables such as the use of narcotics prior to treatment and living alone at the time of treatment.

© 2017 Published by Elsevier Ireland Ltd. Radiotherapy and Oncology xxx (2017) xxx–xxx

For patients with head and neck squamous cell carcinoma (HNSCC), estimating the risk for long-term tube feeding dependence after definitive radiotherapy (RT) or chemoradiation (CRT) is challenging.

Xerostomia and painful mucositis with subsequent odynophagia and dysgeusia are well known side effects of RT and CRT. These conditions contribute to acute dysphagia and excessive weight

loss, which consequently may result in the need for tube feeding during treatment. In some cases, radiation-induced changes to healthy tissue such as fibrosis of swallowing structures and/or vascular and neural damage, may result in persistent or even progressive long-term swallowing problems, such as aspiration with repeated pneumonitis and tube feeding dependence [1,2].

In a review of the outcome of CRT and RT for head and neck cancer, tube feeding dependence during treatment was reported in 61% of cases. The long-term feeding tube use ranged between 8 and 18% [3]. At one year after treatment, incidence rates as high as 41% are reported [4].

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Previous studies showed that percutaneous endoscopic gastrostomy (PEG) tube dependence during treatment significantly correlates with poorer long term swallowing function [5–7], worse survival rate [8] and worse quality of life one year after treatment [9]. Another study suggested that tube feeding dependence has more impact on quality of life than the need for a tracheotomy tube or a laryngectomy [10], indicating the importance of preventing long term tube feeding dependence after treatment.

Many investigators focused on prevention of long term dysphagia and tube feeding dependence by strategies such as preventive swallowing exercises [11–25]. However, there is overwhelming evidence that the risk of severe swallowing dysfunction greatly depends on the radiation dose to the relevant swallowing structures [26–46]. Thus, another and likely more effective strategy to prevent tube feeding dependence could be to decrease the dose to anatomic regions involved in radiation-induced swallowing dysfunction. With the clinical introduction of Intensity Modulated Radiotherapy (IMRT), the risk of radiation-induced xerostomia has been significantly decreased [47,48] compared to conventional radiation techniques such as 3D-Conformal Radiotherapy (3D-CRT). Recent studies indicated that the same is true for prevention of swallowing dysfunction, including for tube feeding dependence [49–51]. The increasing use of pencil beam scanning proton therapy will further improve the potential to optimize the dose in head and neck cancer.

To support decision-making regarding the most appropriate preventive measures on a more personalized basis, it becomes increasingly important to develop tools that enable clinicians to predict the risk of tube feeding dependence for individual patients. To our knowledge, no review exists on prognostic factors for tube feeding dependence. Most predictive models for swallowing dysfunction published to date do not systematically consider clinical and treatment-related risk factors next to dose and volume parameters. This is relevant, as some of these clinical and treatment-related risk factors may confound the relationship between radiation dose distribution parameters and swallowing dysfunction. It is also relevant because the absolute excess risk of a side effect depends both on the dose to organs-at-risk and on the baseline risk determined by other factors.

Therefore, the aim of this systematic review, conducted according to PRISMA guidelines, was to identify prognostic factors that are consistently found to be associated with post-treatment tube feeding dependence at ≥ 6 months. Aside from this primary aim, we also identified prognostic factors found to be associated with tube feeding placement and use at < 6 months, since placement and use of a feeding tube during and directly after treatment add to the risk of long-term feeding tube dependence. Knowledge of these prognostic factors is crucial for the development and the design of retrospective and prospective multivariable NTCP-model studies.

Methods and materials

Search strategy

In order to identify prognostic factors for tube feeding dependence, a literature search was performed in the Medline, EMBASE and the Cochrane libraries in March 2017.

The following keywords were used for the search within Medline:

- #1 “Head and Neck Neoplasms”[Mesh] OR head and neck cancer[TIAB] OR HNSCC[TIAB] OR head and neck squamous cell carcinoma[TIAB]

- #2 “Radiotherapy”[Mesh] OR radiotherapy[TIAB] OR chemoradiotherapy[TIAB] OR radiation treatment[TIAB] OR chemoradiation[TIAB] OR cetuximab[TIAB]
- #3 tube feeding[TIAB] OR dysphagia [TIAB] OR nasogastric tube [TIAB] OR percutaneous endoscopic gastrostomy[TIAB] OR PEG [TIAB] OR percutaneous radiological gastrostomy[TIAB] OR PRG [TIAB] OR percutaneous fluoroscopic gastrostomy[TIAB] or PFG [TIAB] OR radiologically inserted gastrostomy[TIAB] OR RIG [TIAB]
- #1 AND #2 AND #3

For the search in the Cochrane library the following keywords were used:

(head and neck cancer OR HNSCC OR head and neck squamous cell carcinoma) AND (radiotherapy OR chemoradiotherapy OR chemoradiation OR radiation treatment OR cetuximab) AND (tube feeding OR dysphagia OR nasogastric tube OR nasogastric feeding tube OR percutaneous endoscopic gastrostomy OR PEG OR percutaneous radiological gastrostomy OR PRG OR percutaneous fluoroscopic gastrostomy OR PFG OR radiologically inserted gastrostomy OR RIG)

And finally, for the search in EMBASE the following keywords were used:

- #1.1 ‘head and neck tumor’/exp OR ‘head and neck cancer’:ab,ti OR HNSCC:ab,ti OR ‘head and neck squamous cell carcinoma’:ab,ti
- #1.2 ‘radiotherapy’/exp OR radiotherapy:ab,ti OR chemoradiotherapy:ab,ti OR ‘radiation treatment’:ab,ti OR chemoradiation:ab,ti OR cetuximab:ab,ti
- #1.3 ‘tube feeding’:ab,ti OR dysphagia:ab,ti OR ‘nasogastric tube’:ab,ti OR ‘percutaneous endoscopic gastrostomy’:ab,ti OR PEG:ab,ti OR ‘percutaneous radiological gastrostomy’:ab,ti OR PRG:ab,ti OR ‘percutaneous fluoroscopic gastrostomy’:ab,ti OR PFG:ab,ti OR ‘radiologically inserted gastrostomy’:ab,ti OR RIG:ab,ti
- #1.1 AND #1.2 AND #1.3 with a limitation to articles, articles in press and reviews.

The titles and abstracts were screened by the first author (KW). Publications without abstracts were screened based on their titles and full text. Relevant publications were selected for full text review if the article dealt with tube feeding placement, use or dependence in patients with HNSCC treated with RT, with or without induction chemotherapy, or RT with concurrent chemotherapy or cetuximab. References of papers identified were screened to retrieve additional relevant papers.

Papers that met the criteria for full text review were further selected with the following eligibility criteria:

- Prospective and retrospective cohort studies, case-control studies or RCTs;
- Adult study objects with malignancies of the head and neck treated with primary CRT, RT with cetuximab, or RT alone, with or without induction chemotherapy or a pre- or post-operative neck dissection;
- Multivariable analysis for prognostic factors for tube feeding placement, use at < 6 months and dependence at equal to/more than 6 months; with a main focus for this review on tube feeding dependence at equal to/more than 6 months;
- Follow-up period of at least 6 months in studies assessing prognostic factors for tube feeding dependence at equal to/more than 6 months.

Studies were excluded for full text review in case of:

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