Systematic 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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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.

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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 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 PEG 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 PEG: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:
- Head and neck surgery in (part of) the patients as the primary treatment modality for the primary tumor;
- Studies in children;
- Animal studies;
- Language other than English;
- Treatment for recurrent disease;
- Feeding tube placement for dysphagia in neuromuscular disease or dysphagia after a cerebrovascular accident.

**Results**

The literature search identified 1514 studies within Medline, 1053 studies within EMBASE and 40 studies in the Cochrane library in total.

A large number of studies were excluded 2555 (see Fig. 1) because the authors did not investigate prognostic factors for tube feeding dependence. Other studies were excluded because a multivariable analysis was not performed [34,41,52–64]. Studies that primarily or partly included post-operative patients [65–82] or were performed in patients groups treated with (post-operative) reirradiation [83], were excluded as well. One study was excluded since variables associated with the duration of gastrostomy tube dependence were investigated [15]. Twelve studies were excluded since the authors used endpoints including (long-term) feeding tube placement, use or dependence, in patients treated with primary (chemo-) radiotherapy but did not perform a separate multivariate analysis for prognostic factors for feeding tube placement, use or dependence alone [31,33,84–93]. Eventually, a total of 14 clinical studies with prognostic factors for tube feeding dependence at ≥6 months remained for review (Fig. 1) [46,94–106].

Three studies reporting on prognostic factors for tube feeding dependence at ≥6 months, also reported on prognostic factors for feeding tube placement or feeding tube use at <6 months; these factors are secondary to the main question of the article and are reported in a separate table (Supplement 2).

**Characteristics and endpoints of the studies**

The characteristics of the 14 clinical studies that were reviewed are summarized in Supplement 1. The endpoints (Table 1) used in these studies were diverse, ranging from prolonged dependence (≥6 months) on feeding tubes, length of PEG requirement (>12 months vs. ≤12 months) to tube feeding dependence at 6, ≥6, =12 or ≥12 months. In one study the 10th percentile of the duration of PEG dependence at 7 months was used as an endpoint [103]. In two studies, requirement of permanent enteral nutrition was the endpoint of interest for our review [95,96].

The definition of tube feeding dependence varied between studies. Some studies used the actual time that the tube was used for oral supplementation, while other studies used the time between installation and removal of the PEG tube as a surrogate parameter for dependence.

Twelve studies were retrospective cohort studies [46,94–104] in which patients were identified from either a (institutional) database or by chart review and two studies [105,106] were prospective cohort studies. Five studies included patients with all primary locations of locally advanced HNC [46,97,102,105,106] while some studies only included patients with specific tumor locations, such as oropharyngeal carcinoma [94,103,104], larynx, oropharyngeal or hypopharyngeal cancer (+/- unknown primary) [98–100], or patients with hypopharyngeal cancer [95,96,101].

**Exclusion criteria**

Three studies did not report on the exclusion criteria [95,96,103]. Some studies specifically reported that patients with residual or recurrent disease or an incomplete response at the primary site at follow-up were excluded from the analysis [94,97–9,101,104–106]. Two studies reported that patients who had a tumor recurrence in the first 6 months after the end of treatment were not evaluated for the endpoint of the study [95,96].

**Follow-up**

The duration of follow-up for each study is shown in Supplement 1. Standardization of follow-up was neither performed or not mentioned in most studies [94,97–101,104]. Some studies provided minimal information on some form of standardization of follow-up but were mostly not specific about what was assessed and/or at what time point [46,95,96]. Other studies were more specific about the type of acute and late toxicity that was assessed and/or at which time points [102,103,105,106].

**Surgical treatment**

Studies with (part of) patient groups undergoing surgery of the primary tumor were excluded, but some studies included patients who had undergone a pre- or post-(chemo-) radiotherapy neck dissection [36,46,98–100,104]. In some studies salvage surgery was performed in cases of residual disease after (chemo-) radiotherapy or disease recurrence [46,95,96,100].

**Pretreatment swallowing status and PEG tube placement**

Seven studies did not exclude patients with significant pretreatment dysphagia [46,94–97,102,103]. One study mentioned that patients with pretreatment tube feeding dependence due to dysphagia were excluded [99]. In three other studies, patients with pretreatment tube feeding dependence due to dysphagia were excluded, but patients with mild to moderate dysphagia were not [102,105,106]. Three studies did not provide information on baseline swallowing function [98,100,104].

In six studies, prophylactic PEG tube placement was performed, in most studies only in patients treated with CRT [97,98,102,103,105,106]. One study performed prophylactic PEG tube placement as a general policy, also in patients treated without systemic therapy [97]. Two studies only placed a PEG tube prior to treatment in case of pretreatment dysphagia and weight loss [46,99]. One study was not specific about the indications for pretreatment PEG tube placement [102]. Another study recommended PEG tube placement in cases of weight loss, aspiration, subjective dysphagia or involvement of the base of tongue [100].

Several studies used a reactive approach in patients that did not have a feeding tube placed prophylactically [46,99,102,103,105,106]. In one study an exclusively reactive tube placement approach was used [95]. Two studies do not specify what type of approach was used regarding feeding tube placement, but appeared to use a reactive approach [94,96]. In one multi-institution study the approach that was used varied and depended on the treatment center [104]. One study primarily used nasogastric feeding tubes and only used PEG tubes for patients after CRT if they required further tube feeding [101].
Exclusion of patients with recurrent disease

Some studies specifically reported that patients with residual or recurrent disease or an incomplete response at the primary site at follow-up were excluded from the analysis [94,97–99,101,104–106]. Two studies reported that patients who had a tumor recurrence in the first 6 months after the end of treatment were not evaluated for the endpoint of the study [95,96].

In three studies, patients with recurrent and/or residual disease during follow-up were not excluded [46,100,102]. In one study, no specific information was provided on this item [103].

Chemotherapy and radiotherapy

In all studies at least some patients received concurrent CRT and/or induction chemotherapy. The chemotherapy regimens that were used varied considerably among studies.

In 3 out of 14 studies, only IMRT was used [97,103,104], while in 8 studies either IMRT, 3D-CRT or 2D-CRT [46,98,100,102,104–106] or only 2D and 3D-CRT was applied [99]. In three studies, the radiation technique was not mentioned [95,96,101].

Not all studies reported the total radiation dose that was given.

In the studies that did report the total radiation dose, the median dose was 70 Gy with radiation dose ranges varying between 50 Gy [106] and 79 Gy [97], with varying fractionation schedules [46,95–103,105,106].

In four studies, most patients were treated with bilateral irradiation to the neck nodes [97,104–106].

In the remaining studies, information regarding (bilateral) neck irradiation was not provided [46,94–96,98–103].

Delineated and sparing of swallowing organs at risk

In 10 out of 14 studies the swallowing organs at risk were either not delineated, or it remained unclear if these organs at risk were delineated.

The remaining 4 studies reported that swallowing organs at risk were delineated and/or attempts were made to spare these structures [46,97,103,106]. The most frequently mentioned swallowing organs at risk were the pharyngeal constrictor muscles (superior, middle and inferior), but in these studies no attempts to reduce the dose were reported [46,97,103,106]. Some authors reported on the delineation, and sometimes sparing of, specific structures.
such as the oral mucosa [103], larynx [46,97,103,106], parotid glands [46,97,103,105,106], soft palate [46,97], base of tongue [46,97,106], (cervical) esophagus [46,97,106], esophagus inlet muscle [106] or submandibular glands [106]. The delineation guidelines that were used varied widely between the different studies [26,92,97,121–124]. Information regarding delineation guidelines and sparing of swallowing structures are mentioned in Supplement 1.

**Swallowing and speech rehabilitation**

In most studies, referral for swallowing or speech rehabilitation was not standard of care or was not mentioned [46,95–101,104]. Only some authors reported on occasional [94,102,105,106] or frequent [103] management by, or referral to, a speech and/or swallowing pathologist. Only in one study, the exercises that were performed by patients were specified [94].

**Rates of tube feeding dependence**

Tube dependence rates varied significantly between studies. At 6 months, the tube feeding dependence rates varied from 3.4% [95] to 53.0% [98]. At 1 year, the tube feeding dependence rate varied from 6.9% [105] to 29% [99]. At 2 years, the tube feeding dependence rate varied from 3.7% [104] to 10% [98].

**Reported patient and disease variables**

The patient and disease variables that were significantly associated with tube feeding dependence at ≥6 months in the multivariable analysis are listed in Table 2.

**Reported predictive treatment variables**

Table 3 shows the treatment variables that were significantly associated with tube feeding dependence at ≥6 months.

**Reported DVH variables**

We could only identify 4 studies that reported on the associations between DVH parameters and tube feeding dependence at ≥6 months (Table 4) [46,97,103,106]. There were also five studies reporting on DVH parameters that are associated with tube feeding use at <6 months (Supplement 2) [50,103,117,119,120].

The most important DVH parameters found to be prognostic for tube feeding dependence at ≥6 months were the dose to the larynx, the superior and inferior pharyngeal constrictor muscle, the contralateral parotid gland and the mean dose to the cricopharyngeal muscle. Wopken et al. [106] presented a multivariable NTCP-model based on a large prospective cohort study consisting of a number of dose distribution parameters and other factors, which enables estimating the risk of tube-feeding dependence at 6 months after completion of radiotherapy.

**Reported prognostic factors for feeding tube placement and use under 6 months**

Factors that were prognostic for tube feeding placement and use at <6 months are reported in Supplement 2. The reported factors that were significant are listed in Table 2.
Table 3
Treatment variables that are predictive for tube feeding dependence ≥6 months at multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic treatment</td>
<td></td>
</tr>
<tr>
<td>Concomitant chemotherapy</td>
<td>[105,106]</td>
</tr>
<tr>
<td>Concomitant cetuximab</td>
<td>[106]</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>[104]</td>
</tr>
<tr>
<td>&lt;50% response to induction chemotherapy</td>
<td>[96]</td>
</tr>
<tr>
<td>Radiotherapy treatment</td>
<td></td>
</tr>
<tr>
<td>Treatment with 3D-CRT (as opposed to IMRT)</td>
<td>[94]</td>
</tr>
<tr>
<td>Accelerated radiotherapy</td>
<td>[105,106]</td>
</tr>
<tr>
<td>Bilateral neck irradiation</td>
<td>[105]</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
</tr>
<tr>
<td>Postradiotherapy neck dissection</td>
<td>[99]</td>
</tr>
<tr>
<td>Supportive treatment</td>
<td></td>
</tr>
<tr>
<td>Adherence to swallowing exercises</td>
<td>[94]</td>
</tr>
<tr>
<td>Prophylactic gastrostomy</td>
<td>[102]</td>
</tr>
<tr>
<td>Enteral nutrition during therapy</td>
<td>[95]</td>
</tr>
</tbody>
</table>

Abbreviations: 3D-CRT: 3D conformal radiotherapy, IMRT: intensity modulated radiotherapy.

Table 4
DVH parameters that are predictive for tube feeding dependence ≥6 months at multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Threshold value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V50</td>
<td>92%</td>
<td>[103]</td>
</tr>
<tr>
<td>Dmean</td>
<td>50.7 Gy</td>
<td>[97]</td>
</tr>
<tr>
<td>V35</td>
<td>79%</td>
<td>[97]</td>
</tr>
<tr>
<td>V40</td>
<td>65%</td>
<td>[97]</td>
</tr>
<tr>
<td>V45</td>
<td>46%</td>
<td>[97]</td>
</tr>
<tr>
<td>V50</td>
<td>41%</td>
<td>[97]</td>
</tr>
<tr>
<td>V55</td>
<td>37%</td>
<td>[97]</td>
</tr>
<tr>
<td>V60</td>
<td>33%</td>
<td>[97]</td>
</tr>
<tr>
<td>V65</td>
<td>29%</td>
<td>[97]</td>
</tr>
<tr>
<td>V70</td>
<td>10%</td>
<td>[97]</td>
</tr>
<tr>
<td>PCM superior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dmean</td>
<td>67.6 Gy</td>
<td>[103]</td>
</tr>
<tr>
<td>Dmean</td>
<td>–</td>
<td>[106]</td>
</tr>
<tr>
<td>PCM inferior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V40</td>
<td>65%</td>
<td>[97]</td>
</tr>
<tr>
<td>V45</td>
<td>58%</td>
<td>[97]</td>
</tr>
<tr>
<td>V50</td>
<td>48%</td>
<td>[97]</td>
</tr>
<tr>
<td>V55</td>
<td>21%</td>
<td>[97]</td>
</tr>
<tr>
<td>V60</td>
<td>15%</td>
<td>[97]</td>
</tr>
<tr>
<td>V65</td>
<td>6%</td>
<td>[97]</td>
</tr>
<tr>
<td>Dmean</td>
<td>50.7 Gy</td>
<td>[97]</td>
</tr>
<tr>
<td>Dmean</td>
<td>41 Gy</td>
<td>[46]</td>
</tr>
<tr>
<td>Dmean</td>
<td>41%</td>
<td>[46]</td>
</tr>
<tr>
<td>Dmean</td>
<td>–</td>
<td>[106]</td>
</tr>
<tr>
<td>Contralateral parotid gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dmean</td>
<td>–</td>
<td>[106]</td>
</tr>
<tr>
<td>Cricopharyngeal muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dmean</td>
<td>–</td>
<td>[106]</td>
</tr>
</tbody>
</table>

Abbreviations: PCM: pharyngeal constrictor muscle, Gy: Gray, Dmean: mean dose, V (number): volume receiving (number) Gy. Percentages were rounded to whole numbers.

Discussion

For the selection of patients with head and neck cancer for different strategies to prevent severe swallowing dysfunction, it is crucial to know which factors are important to estimate the risk of tube feeding dependence. In particular, modern radiation technologies such as IMRT can only be fully explored to prevent side effects if the dose distribution parameters associated with the risk of this side effect are known.

We performed this review to identify the parameters that are consistently found to be predictive for tube feeding dependence at ≥6 months after the end of treatment. We were particularly interested in DVH parameters since they can be applied to IMRT and IMPT treatment planning optimization and thus may be used for primary prevention of this severe side effect. Sparing of these swallowing structures by advanced radiation techniques has been shown to be feasible in multiple studies, as mentioned earlier. Dysphagia was found to be significantly correlated to several dose–volume parameters, including the superior, middle and inferior pharyngeal constrictor muscle, the esophageal inlet muscle and the glottic and supraglottic larynx. In this review, almost similar dose–volume parameters were found to be prognostic for tube feeding dependence at ≥6 months: the mean dose to the superior pharyngeal constrictor muscle, the V40 (volume receiving 40 Gy) to V65 and mean dose to the inferior pharyngeal constrictor muscle, the V35 to V70 and mean dose to the larynx, and the mean dose to the cricopharyngeal muscle (see Table 4). These DVH parameters can be used for radiotherapy treatment planning optimization. It is, however, important to realize that dose–volume parameters such as the V5 to V70 are often significantly correlated with each other and also with the mean doses; only the mean doses were found to be significant after analysis in several studies [27,106]. In the aforementioned studies that mention multiple dose–volume parameters per swallowing structure [46,97,103], it is not stated if an analysis was performed to check for correlations between the dose parameters themselves. When aiming to reduce the dose to swallowing structures in radiotherapy treatment planning optimization, use of only the mean dose of relevant swallowing structures as an optimization objective appears to be the best strategy. Using all parameters in optimization will probably result in multiple radiotherapy treatment plans with similar dose distributions.

Another DVH parameter found to be predictive for tube feeding dependence at ≥6 months was the mean dose to the contralateral parotid gland [106]. The mean dose to the contralateral submandibular gland [50] was found to be predictive for tube feeding use at <6 months. Swallowing difficulties are most likely caused by a combination of a) damage to the pharyngeal constrictors and b) hyposalivation caused by radiation damage to the salivary glands. The parotid glands are largely responsible for salivary output during meals [125]. The submandibular glands, on the other hand, are responsible for the production of saliva rich in mucins, which acts as a lubricant in swallowing [126].

Chemoradiotherapy often results in xerostomia and in a significant increase in patient-rated swallowing difficulties [127,128]. These effects can be prevented if both parotid glands are spared to a dose of less than 26 Gy [129]. So, next to reducing the dose to the pharyngeal musculature, a further reduction of the dose to the salivary glands may contribute to prevention of dysphagia, including tube feeding dependence [130]. Due to target volume coverage, sparing of the ipsilateral parotid gland or submandibular gland is often not possible, but reducing the dose to the contralat-
eral parotid gland or submandibular gland alone may be sufficient to result in a reduction of tube feeding dependence [50,106].

The prognostic factors for feeding tube placement and use at <6 months are also reported in this review. The factors that were found to be prognostic for tube feeding placement and use at <6 months resemble the prognostic factors for tube feeding dependence at >6 months. As already mentioned, previous studies showed that percutaneous endoscopic gastrostomy (PEG) tube dependence during treatment significantly correlates with poorer long term swallowing function [5–7]. Therefore DVH parameters that were found to be prognostic for tube feeding use at <6 months, which show a high degree of similarity with the dose–volume parameters prognostic for tube feeding dependence >6 months, may also prove to be important to optimize in radiotherapy treatment planning strategies. One of the dose–volume parameters found to be prognostic for tube feeding use at <6 months is the volume of the oral mucosa receiving radiation [103,119]. Dose to the oral mucosa, together with the additive effect of chemotherapy, can result in severe radiation-induced mucositis necessitating use of opioids. Mucositis is considered the most important acute side effect in patients treated with CRT for HNSCC. It has been suggested that high radiation dose levels to the oral mucosa, leading to mucositis, may result in periods of tube feeding use secondary to deconditioning of the swallowing muscles ultimately resulting in tube feeding dependence [1,131,132].

Pre-existing dysphagia was a result of the tumor causing damage to muscles and nerves involved in swallowing. The severity and presentation of pre-existent dysphagia is dependent on location, and is often more severe in patients with advanced locoregional stages (e.g. higher T- and N-stage). These are also the patients that are primarily treated with (chemo-) radiotherapy [133]. It is common to treat these patients with bilateral neck irradiation, another prognostic factor for tube feeding use at <6 months and dependence at >6 months [105,118]. Sparing of the structures involved in swallowing becomes more difficult in this patient category.

Already during, but also shortly after radiotherapy, radiation-induced effects are evident in the skin and mucosa resulting in mucositis and edema, desquamation and erythema [134]. As already briefly mentioned, oral mucositis (causing pain), can result in difficulty in oral eating. This condition often results in (place- ment and) over-reliance on a feeding tube. Early effects, such as acute dysphagia and mucositis, but also xerostomia, were shown to be significantly correlated with dysphagia at 6–12 months post-treatment [135]. Progressive radiation-induced fibrosis of normal tissue, including muscles and nerves, together with atrophy are, however, thought to be largely responsible for post-radiation dysphagia [136].

Patients with pre-existing dysphagia, who often start using a feeding tube before or early in the course of treatment, are very likely to become feeding tube-dependent. Pre-existing dysphagia is, therefore, a relevant factor to consider in predictive modeling for tube feeding dependence. It may be therefore interesting to develop a separate model for patients with and without pre-treatment dysphagia. In the studies by Wopken et al. [105,106] both patients with and without pre-treatment dysphagia form the cohort in which these models were developed.

Use of narcotics prior to treatment was also a prognostic factor for tube feeding use at <6 months. A possible explanation the authors give for this finding is that patients requiring narcotics prior to treatment have more comorbid disease, or a worse baseline functional status, and therefore potentially need enteral supplementation for a longer period [110]. On the other hand, a possible explanation for the finding is that pain medication resulting in the analgesia of pain, leads to a consequent increase in oral intake and less feeding tube use. In a recent study of HNC patients treated with (post-operative) (chemo-) radiotherapy, gabapentin use, medication used for neuropathic pain, was found to result in a reduction of tube feeding use [74]. Patients that are treated with radiotherapy for head and neck cancer are reported to experience both neuropathic and nociceptive pain [137]. The use of prophylactic gabapentin was not only shown to result in reduced PEG use, but also in reduced need for high-dose opioids [138–140]. In these studies, patients were treated with both primary and post-operative (chemo-) radiotherapy. It may be interesting to further investigate the effect of prophylactic gabapentin use as a possible strategy in the reduction of post-treatment feeding tube dependence in a cohort of patients treated with primary (chemo-) radiotherapy. For now, use of narcotics before/during treatment appears to be a relevant prognostic factor for the development of an NTCP model for tube feeding dependence. The use of pain medication alters the tolerance of the patient to radiation-induced toxicity, due to analgesia of pain. Therefore it may also be important to investigate the difference between models based on patient groups that either did or did not use pain medication before/during treatment.

Most studies that were included in this review were composed of a mixed population of patients who were treated with either radiotherapy with or without chemotherapy. Chemotherapy was already mentioned to have an additive effect on radiation-induced toxicity and was found to be prognostic for tube feeding placement, use (<6 months) and dependence (>6 months) [94,105,106,115,117,118]. Assessing the influence of chemotherapy on the reported dose–volume parameters for swallowing structures relevant for the development of tube feeding dependence is difficult. This effect was not specifically investigated in any of the studies of this review. In the study by Sanguineti et al. [103], an analysis was performed to assess which factors, including dose–volume parameters, are predictive for tube feeding dependence longer than 3.3 months. The study compared patients treated with concomitant chemoradiotherapy and prophylactic PEG placement versus patients treated with radiotherapy alone and reactive PEG placement. The models based on these two groups of patients differ slightly: in the model for patients treated with chemoradiotherapy and prophylactic PEG, the dose to the oral mucosa, pharyngeal constrictor muscle superior and larynx was found to be predictive, while in the radiotherapy-alone treated group, the dose to the larynx was not. So, based on this one study, it could be stated that chemotherapy does appear to influence the DVH parameters found to be prognostic for tube feeding use. This effect was not found in the same study for the endpoint tube feeding dependence at 7 months. The exact effect of chemotherapy on (DVH parameters for) swallowing structures remains to be investigated.

Patients treated with definitive chemoradiation who were subjected to prophylactic PEG tube placement, were more likely to retain their feeding tube at 6 and 12 months after treatment than those who were not subjected to prophylactic PEG tube placement. In one study, 41% (6 months) and 21% (12 months) remained feeding tube dependent, compared to 8% and 0%, respectively, without prophylactic PEG tube placement [7]. Prophylactic PEG tube installation is common practice for HNC patients. It is often used for either patients treated with concomitant chemotherapy or those with dysphagia or significant weight loss at baseline. Not surprisingly, all these factors were also found to be prognostic factors.
for tube feeding dependence in several studies that were included in this review, which makes it difficult to exclude selection bias. Previously, a prophylactic PEG policy was advocated [141,142]. Between then and now, there has been a lot of discussion regarding the prophylactic PEG policy [7,143]. The positive effects of a prophylactic PEG tube include fewer treatment breaks and lower medical costs [53,112,144]. The negative effects include complications [145] and unused PEG tubes [143]. These effects have been important considerations in this discussion. Reports have also been made about the possible negative effect of prophylactic PEG tube placement on long-term swallowing function [6,60,84,146]. A recent systematic review [147] investigated the impact of the prophylactic PEG policy on long-term swallowing function, which included several studies that are part of this review. The conclusion was that there is a lack of consensus in literature regarding the use of a prophylactic PEG policy. Therefore, the discussion remains unsettled.

As was already briefly mentioned in the introduction, many attempts to prevent severe long-term dysphagia, including tube feeding dependence, have been made by applying preventative swallowing exercises. In one of the studies included in our review [94], non-adherence to swallowing exercises was found to be a prognostic factor for the duration of tube feeding dependence in patients with oropharyngeal cancer. Unfortunately, there are only a few other studies included in this review that mentioned (non-routine or routine) referral for swallowing rehabilitation, but none of these studies actually included this factor in their multivariable analyses for prognostic factors for tube feeding dependence.

The use of preventative swallowing exercises to prevent severe long-term dysphagia in head and neck cancer patients treated with (chemo-) radiation has been evaluated in several randomized trials [13,14,18–21]. In a recent review by Perry et al. [148] a comparison was made based on these trials. It compared therapeutic exercises and treatment as usual in advanced stage head and neck cancer patients who were treated with surgery and/or (chemo-) radiotherapy. The patients in the included studies presented with dysphagia or were at risk of dysphagia. Aspiration and oropharyngeal swallowing efficiency were the main dysphagia outcome measures. The conclusion of this review was that there is currently no evidence to support the advice, to suggest or implement swallowing exercises before, during or immediately after head and neck cancer treatment to reduce the possibility of dysphagia as a treatment side effect. A lot more research regarding this preventative measure is needed to prove that there is a benefit in swallowing rehabilitation for head and neck cancer patients.

There are several limitations to the studies included in this review

First, three studies included only or predominantly patients with oropharyngeal cancer [94,103,104] and three other studies exclusively included patients with hypopharyngeal cancer [95,96,101]. The prognostic factors found in these studies may not apply to patients with other primary tumor sites.

Secondly, in several studies, patients with recurrent or residual disease were not excluded. Recurrent or residual disease can be the cause of (tumor-related) dysphagia and consequent tube feeding dependence. In addition, salvage treatments, such as surgery, can by itself result in tube feeding dependence for this patient group.

Finally, patients included in these studies have been treated with a wide range of treatment regimens, including different chemotherapy agents and schedules and/or the use of elective or therapeutic pre- or post-radiotherapy treatment neck dissections [46,97–100,104].

We only identified two studies that reported on the development of prediction models to predict the risk of tube feeding dependence for individual patients [105,106]. Some of the potential prognostic factors identified in this review for both tube feeding dependence at >6 months and feeding tube placement and use at <6 months have not been taken into account in these models. The addition of these potential prognostic factors may further increase the predictive power of these models.

Conclusion

Prognostic factors that were consistently associated with the risk of tube feeding dependence for head and neck cancer patients treated with (chemo-) radiotherapy were the dose–volume parameters: dose to the larynx, pharyngeal constrictor muscle inferior and superior, and the dose to the contralateral parotid gland. Patient and disease variables, including advanced tumor and nodal stage and pretreatment weight loss, and the treatment variables chemoradiotherapy and prophylactic gastrostomy policy, were also found to be associated with the risk of tube feeding dependence at ≥6 months (Tables 2–4). Comparable prognostic factors were found to be prognostic for feeding tube placement and use at < 6 months (Supplement 2).

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Conflicts of interest statement

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.08.022.

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