Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer

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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.

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 $\geq$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:

- 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 reported in Supplement 2 [94,95,103]. The included studies by Bozec et al. were both published in 2016 and performed with the same cohort, but they had slightly different endpoints and considered different variables in the multivariate analysis for prognostic factors. Both studies were therefore included in this review.

Eighteen studies reported on prognostic factors for tube feeding placement and/or use at <6 months [50,94,95,103,107–120]. 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 [94,97–99,101,104–106]. 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].

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].

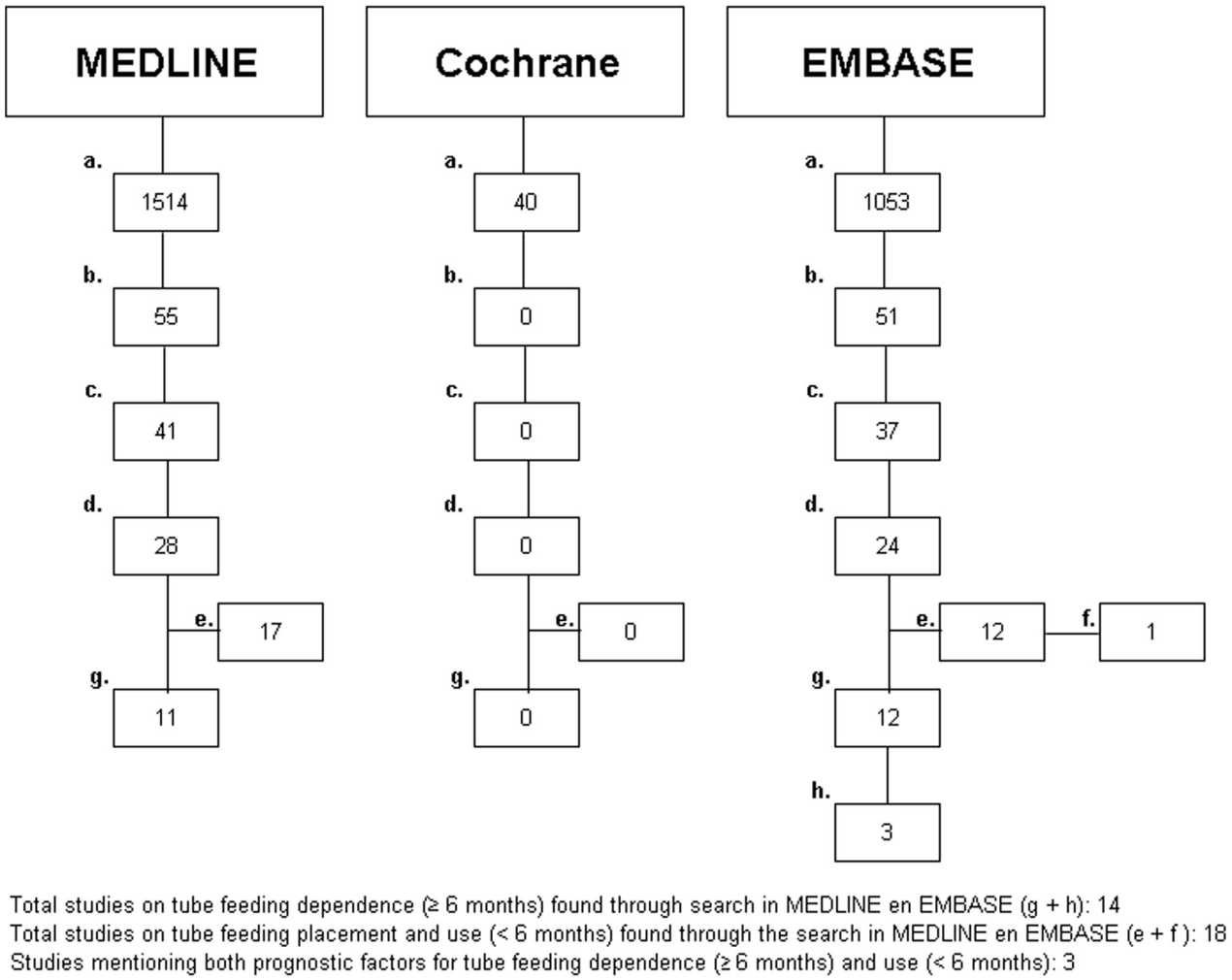

Fig. 1. Flow chart of the study selection. a. Initial search with key words, b. exclusion of studies without prognostic factors for tube feeding placement, use or dependence, foreign language or animal studies, studies in other malignancies, c. exclusion of studies on prognostic factors for tube feeding placement, use or dependence in (part of) patients treated with surgery of the primary tumor, d. exclusion of studies without a multivariate analysis on prognostic factors for tube feeding placement, use or dependence, e. total studies on prognostic factors for tube feeding placement or use before or during treatment, including those found through references, f. exclusion of studies also found through the search on MEDLINE. g. total studies with prognostic factors for tube feeding dependence, including studies found through references, h. exclusion of studies also found through the search om MEDLINE.

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

Table 1
Overview of the endpoints of the studies included for tube feeding dependence ≥ 6 months.

Author [Ref]	Relevant endpoint(s)
Bhayani [94]	Gastrostomy tube placement (see Supplement 2) and prolonged dependence (≥6 months)
Bozec [96]	Prognostic factors for oncologic (OS, SS, RFS) and functional outcomes (DOSS ≥6, permanent enteral nutrition, larynx preservation)
Bozec [95]	Impact nutritional status- and general health-status related factors on clinical outcomes including response to induction chemotherapy, toxicity of induction chemotherapy and radiotherapy, DOSS score, permanent enteral nutrition, OS, CSS and RFS
Caudell [97]	PEG tube dependence at 12 months
Chapuy [98]	Clinical, treatment and neck dissection factors associated with dysphagia measures (including PEG dependence at 12 months)
Lango [99]	Posttreatment tube feeding dependence (at 12 months) in patients treated with and without postradiotherapy neck dissections
McRackan [100]	PEG tube dependence at last follow-up
Murono [101]	Complete or almost complete gastrostomy tube dependence at 6 months after completion of treatment
Pohar [102]	PEG tube dependence at least 1 year after treatment
Sanguineti [103]	25th percentile of duration of PEG dependence at 3.3 months (see Supplement 2) and 10th percentile of duration of PEG dependence at 7 months
Setton [104]	PEG tube dependence at 1 year after treatment
Vlacich [46]	Length of PEG requirement (>12 months vs. ≤12 months)
Wopken [105]	Tube feeding dependence at 6 months after treatment
Wopken [106]	Tube feeding dependence at 6 months after treatment

Abbreviations: PEG: percutaneous endoscopic gastrostomy, DOSS: dysphagia outcome and severity scale, OS: overall survival, CSS: cause specific survival, RFS: recurrence free survival, DFS: disease free survival, CRT: chemoradiotherapy.

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 pathologists. 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 fac-

Table 2
Patient and disease variables that are predictive for tube feeding dependence ≥ 6 months at multivariate analysis

Variable	References
Smoking	
Greater number of smoking pack-years	[104]
Sex	
Male	[103]
Age	
Advanced age	[99,104]
T-stage	
T3–T4 tumor	[105,106]
Higher tumor stage	[102,98]
N-stage	
Positive nodal status	[105]
Advanced nodal stage	[104]
Primary tumor location	
Larynx/hypopharynx/base of tongue/pharyngeal wall	[97]
Posterior pharyngeal wall	[101]
BMI/weight loss	
Low or normal initial BMI (≤25 kg/m^2)	[100]
Weight loss >10% during treatment	[94]
Pretreatment weight loss	[99]
Weight loss prior to treatment (1-10% and >10%)	[105,106]
Performance status	
ECOG/WHO performance score > 1	[102]
Disease characteristics	
Symptoms at diagnosis	[103]
Abnormal pretreatment swallowing	[97]

Abbreviations: BMI: body mass index.

Table 3
Treatment variables that are predictive for tube feeding dependence ≥6 months at multivariate analysis.

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

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.

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

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

tors include patient/disease characteristics, treatment characteristics and DVH parameters. Many of the factors that are prognostic for tube feeding dependence at ≥6 months are also prognostic for tube feeding placement and tube feeding use at <6 months.

Several variables that were not reported for tube feeding dependence at ≥6 months, but were found to be prognostic for tube feeding use at <6 months, were: living alone at the time of treatment and use of narcotics prior to treatment [110], treatment field length [111], dose to the oral mucosa [103,119] and dose to the contralateral submandibular gland [50]. These prognostic factors were each reported by only one or two studies.

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 prognostic for tube feeding dependence at ≥6 months in one study [97] and also for feeding tube placement in another study [107]. Usual policy in head and neck cancer-centers is to give patients with pre-existing dysphagia and/or with pre-treatment weight loss a feeding tube prior to starting treatment. Pretreatment weight loss and decrease in body mass index were, not surprisingly, also significant for tube feeding dependence and use [99,105,106,110].

Pre-existent dysphagia is 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 (placement 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 could 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 preventive 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 chemotherapy 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.

References

[1] Murphy BA, Gilbert J. Dysphagia in head and neck cancer patients treated with radiation: assessment, sequelae, and rehabilitation. Semin Radiat Oncol 2009;19:35–42.
[2] Mittal BB, Pauloski BR, Haraf DJ, Pelzer HJ, Argiris A, Vokes EE, et al. Swallowing dysfunction–preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. Int J Radiat Oncol Biol Phys 2003;57:1219–30.
[3] Rieger JM, Zalmanowitz JG, Wolfaardt JF. Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature. Int J Oral Maxillofac Surg 2006;35:581–7.
[4] Garden AS, Harris J, Trotti A, Jones CU, Carrascosa L, Cheng JD, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99–14). Int J Radiat Oncol Biol Phys 2008;71:1351–5.
[5] Morton RP, Crowder VL, Mawdsley R, Ong E, Izzard M. Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy. ANZ J Surg 2009;79:713–8.
[6] Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia 2012;27:251–9.
[7] Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2010;78:1026–32.
[8] Shune SE, Karnell LH, Karnell MP, Van Daele DJ, Funk GF. Association between severity of dysphagia and survival in patients with head and neck cancer. Head Neck 2012;34:776–84. http://dx.doi.org/10.1002/hed.21819.
[9] Ronis DL, Duffy SA, Fowler KE, Khan MJ, Terrell JE. Changes in quality of life over 1 year in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2008;134:241–8.
[10] Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, et al. Clinical predictors of quality of life in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2004;130:401–8.
[11] Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope 2006;116:883–6.

[12] Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 2008;118:39–43.
[13] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys 2012;83:210–9.
[14] van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia 2011;26:155–70.
[15] Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg 2013;139:1127–34.
[16] Shinn EH, Basen-Engquist K, Baum G, Steen S, Bauman RF, Morrison W, et al. Adherence to preventive exercises and self-reported swallowing outcomes in post-radiation head and neck cancer patients. Head Neck 2013;35:1707–12.
[17] Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol 2015;272:3521–31.
[18] Lazarus CL, Husaini H, Falciglia D, DeLacure M, Branski RC, Kraus D, et al. Effects of exercise on swallowing and tongue strength in patients with oral and oropharyngeal cancer treated with primary radiotherapy with or without chemotherapy. Int J Oral Maxillofac Surg 2014;43:523–30. http://dx.doi.org/10.1016/j.ijom.2013.10.023.
[19] Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg 2012;138:376–82. http://dx.doi.org/10.1001/archoto.2012.187.
[20] Mortensen HR, Jensen K, Aksglæde K, Lambertsen K, Eriksen E, Grau C. Prophylactic swallowing exercises in head and neck cancer radiotherapy. Dysphagia 2015;30:304–14. http://dx.doi.org/10.1007/s00455-015-9600-y.
[21] van den Berg MGA, Kalf JG, Hendriks JCM, Takes RP, van Herpen CML, Wanten GJA, et al. Normalcy of food intake in patients with head and neck cancer supported by combined dietary counseling and swallowing therapy: a randomized clinical trial. Head Neck 2016;38:E198–206. http://dx.doi.org/10.1002/hed.23970.
[22] van der Molen L, van Rossum MA, Rasch CRN, Smeele LE, Hilgers FJM. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Oto-Rhino-Laryngology 2014;271:1257–70. http://dx.doi.org/10.1007/s00405-013-2640-8.
[23] Tang Y, Shen Q, Wang Y, Lu K, Wang Y, Peng Y. A Randomized Prospective Study of Rehabilitation Therapy in the Treatment of Radiation-induced Dysphagia and Trismus. Strahlentherapie Und Onkol 2011;187:39–44. http://dx.doi.org/10.1007/s00066-010-2151-0.
[24] Virani A, Kunduk M, Fink DS, McWhorter AJ. Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. Head Neck 2015;37:162–70. http://dx.doi.org/10.1002/hed.23570.
[25] Ahlberg A, Engstrom T, Nikolaidis P, Gunnarsson K, Johansson H, Sharp L, et al. Early self-care rehabilitation of head and neck cancer patients. Acta Otolaryngol 2011;131:552–61. http://dx.doi.org/10.3109/00016489.2010.532157.
[26] Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60:1425–39.
[27] Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys 2011;81:e93–9.
[28] Webster GJ, Rowbottom CG, Ho KF, Slevin NJ, Mackay RI. Evaluation of larynx-sparing techniques with IMRT when treating the head and neck. Int J Radiat Oncol Biol Phys 2008;72:617–22.
[29] Schwartz DL, Hutcheson K, Barringer D, Tucker SL, Kies M, Holsinger FC, et al. Candidate dosimetric predictors of long-term swallowing dysfunction after oropharyngeal intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:1356–65.
[30] Caglar HB, Tishler RB, Othus M, Burke E, Li Y, Goguen L, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:1110–8.
[31] Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol 2010;28:2732–8.
[32] Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, Worden FP, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007;68:1289–98.
[33] Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, de Kruijf WJ, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol 2007;85:64–73.
[34] Li B, Li D, Lau DH, Farwell DG, Luu Q, Rocke DM, et al. Clinical-dosimetric analysis of measures of dysphagia including gastrostomy-tube dependence among head and neck cancer patients treated definitively by intensity-modulated radiotherapy with concurrent chemotherapy. Radiat Oncol 2009;4:52.
[35] Fua TF, Corry J, Milner AD, Cramb J, Walsham SF, Peters LJ. Intensity-modulated radiotherapy for nasopharyngeal carcinoma: clinical correlation of dose to the pharyngo-esophageal axis and dysphagia. Int J Radiat Oncol Biol Phys 2007;67:976–81.
[36] Caudell JJ, Burnett 3rd OL, Schaner PE, Bonner JA, Duan J. Comparison of methods to reduce dose to swallowing-related structures in head and neck cancer. Int J Radiat Oncol Biol Phys 2010;77:462–7.
[37] van der Laan HP, Christianen ME, Bijl HP, Schilstra C, Langendijk JA. The potential benefit of swallowing sparing intensity modulated radiotherapy to reduce swallowing dysfunction: an in silico planning comparative study. Radiother Oncol 2012;103:76–81.
[38] van der Laan HP, Gawryszuk A, Christianen ME, Steenbakkers RJ, Korevaar EW, Chouvalova O, et al. Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: treatment planning optimization and clinical introduction. Radiother Oncol 2013;107:282–7.
[39] Peponi E, Glanzmann C, Willi B, Huber G, Studer G. Dysphagia in head and neck cancer patients following intensity modulated radiotherapy (IMRT). Radiat Oncol 2011;6:1.
[40] Popovtzer A, Cao Y, Feng FY, Eisbruch A. Anatomical changes in the pharyngeal constrictors after chemo-irradiation of head and neck cancer and their dose-effect relationships: MRI-based study. Radiother Oncol 2009;93:510–5.
[41] Dornfeld K, Simmons JR, Karnell L, Karnell M, Funk G, Yao M, et al. Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. Int J Radiat Oncol Biol Phys 2007;68:750–7.
[42] Bhide SA, Gulliford S, Kazi R, El-Hariry I, Newbold K, Harrington KJ, et al. Correlation between dose to the pharyngeal constrictors and patient quality of life and late dysphagia following chemo-IMRT for head and neck cancer. Radiother Oncol 2009;93:539–44.
[43] Anand AK, Chaudhoory AR, Shukla A, Negi PS, Sinha SN, Babu AAG, et al. Favourable impact of intensity-modulated radiation therapy on chronic dysphagia in patients with head and neck cancer. Br J Radiol 2008;81:865–71. http://dx.doi.org/10.1259/bjr/31334499.
[44] Frowen J, Cotton S, Corry J, Perry A. Impact of demographics, tumor characteristics, and treatment factors on swallowing after (chemo) radiotherapy for head and neck cancer. Head Neck 2010;32:513–28. http://dx.doi.org/10.1002/hed.21218.
[45] Prameela C, Ravind R, Renil Mon P, Sheejamol V, Dinesh M. Radiation dose to dysphagia aspiration-related structures and its effect on swallowing: comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy plans. J Cancer Res Ther 2016;12:845–51. http://dx.doi.org/10.4103/0973-1482.163676.
[46] Vlacich G, Spratt DE, Diaz R, Phillips JG, Crass J, Li CI, et al. Dose to the inferior pharyngeal constrictor predicts prolonged gastrostomy tube dependence with concurrent intensity-modulated radiation therapy and chemotherapy for locally-advanced head and neck cancer. Radiother Oncol 2014;110:435–40.
[47] Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.
[48] Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12:127–36.
[49] Roe JWG, Carding PN, Drinnan MJ, Harrington KJ, Nutting CM. Swallowing performance and tube feeding status in patients treated with parotid-sparing intensity-modulated radiotherapy for head and neck cancer. Head Neck 2016;38:E1436–44. http://dx.doi.org/10.1002/hed.24255.
[50] Gensheimer MF, Nyflot M, Laramore GE, Liao JJ, Parvathaneni U. Contribution of submandibular gland and swallowing structure sparing to post-radiation therapy PEG dependence in oropharynx cancer patients treated with split-neck IMRT technique. Radiat Oncol 2016;11:151. http://dx.doi.org/10.1186/s13014-016-0726-3.
[51] Beadle BM, Liao K-P, Giordano SH, Garden AS, Hutcheson KA, Lai SY, et al. Reduced feeding tube duration with intensity-modulated radiation therapy for head and neck cancer: A Surveillance, Epidemiology, and End Results-Medicare Analysis. Cancer 2017;123:283–93. http://dx.doi.org/10.1002/cncr.30350.
[52] Bhayani MK, Hutcheson KA, Barringer DA, Roberts DB, Lewin JS, Lai SY. Gastrostomy tube placement in patients with hypopharyngeal cancer treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck 2013;35:1641–6. http://dx.doi.org/10.1002/hed.23199.
[53] Ishiki H, Onozawa Y, Kojima T, Hironaka S, Fukutomi A, Yasui H, et al. Nutrition support for head and neck squamous cell carcinoma patients treated with chemoradiotherapy: how often and how long? ISRN Oncol 2012;2012:274739.

[54] van den Broek GB, Balm AJM, van den Brekel MWM, Hauptmann M, Schornagel JH, Rasch CRN. Relationship between clinical factors and the incidence of toxicity after intra-arterial chemoradiation for head and neck cancer. Radiother Oncol 2006;81:143–50. http://dx.doi.org/10.1016/j.radonc.2006.09.002.

[55] Tulunay-Ugur OE, McClinton C, Young Z, Penagaricano JA, Maddox AM, Vural E. Functional outcomes of chemoradiation in patients with head and neck cancer. Otolaryngol Head Neck Surg 2013;148:64–8.

[56] Shiley SG, Hargunani CA, Skoner JM, Holland JM, Wax MK. Swallowing function after chemoradiation for advanced stage oropharyngeal cancer. Otolaryngol Head Neck Surg 2006;134:455–9.

[57] Meirovitz A, Kuten M, Billan S, Abdah-Bortnyak R, Sharon A, Peretz T, et al. Cytokines levels, severity of acute mucositis and the need of PEG tube installation during chemo-radiation for head and neck cancer–a prospective pilot study. Radiat Oncol 2010;5:16.

[58] Hatoum GF, Abitbol A, Elattar I, Lewin A, Troner M, Kronberg F, et al. Radiation technique influence on percutaneous endoscopic gastrostomy tube dependence: Comparison between two radiation schemes. Head Neck 2009;31:944–8.

[59] Homma A, Hatakeyama H, Mizumachi T, Kano S, Sakashita T, Kuramoto R, et al. A retrospective study of G-tube use in Japanese patients treated with concurrent chemoradiotherapy for hypopharyngeal cancer. PLoS One 2016;11. http://dx.doi.org/10.1371/journal.pone.0161734.

[60] McLaughlin BT, Gokhale AS, Shuai Y, Diacopoulos J, Carrau R, Heron DE, et al. Management of patients treated with chemoradiotherapy for head and neck cancer without prophylactic feeding tubes: The University of Pittsburgh experience. Laryngoscope 2010;120:71–5. http://dx.doi.org/10.1002/lary.20697.

[61] Lohia S, Rajapurkar M, Nguyen SA, Sharma AK, Gillespie MB, Day TA. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2014;140:331–7.

[62] Jeffery E, Sherriff J, Langdon C. A clinical audit of the nutritional status and need for nutrition support amongst head and neck cancer patients treated with radiotherapy. Australas Med J 2012;5:8–13. http://dx.doi.org/10.4066/AMJ.2012.910.

[63] Lee S-Y, Kim BH, Park YH. Analysis of dysphagia patterns using a modified barium swallowing test following treatment of head and neck cancer. Yonsei Med J 2015;56:1221–6. http://dx.doi.org/10.3349/ymj.2015.56.5.1221.

[64] Rutter CE, Yovino S, Taylor R, Wolf J, Cullen KJ, Ord R, et al. Impact of early percutaneous endoscopic gastrostomy tube placement on nutritional status and hospitalization in patients with head and neck cancer receiving definitive chemoradiation therapy. Head Neck 2011;33:1441–7.

[65] Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiother Oncol 2006;78:152–8.

[66] Gardine RL, Kokal WA, Beatty JD, Riihimaki DU, Wagman LD, Terz JJ. Predicting the need for prolonged enteral supplementation in the patient with head and neck cancer. Am J Surg 1988;156:63–5.

[67] Sachdev S, Refaat T, Bacchus ID, Sathiaseelan V, Mittal BB. Age most significant predictor of requiring enteral feeding in head-and-neck cancer patients. Radiat Oncol 2015;10:93–6.

[68] Mays AC, Moustafa F, Worley M, Waltonen JD, D'Agostino RJ. A model for predicting gastrostomy tube placement in patients undergoing surgery for upper aerodigestive tract lesions. JAMA Otolaryngol Head Neck Surg 2014;140:1198–206. http://dx.doi.org/10.1001/jamaoto.2014.2360.

[69] Iseli TA, Kulbersh BD, Iseli CE, Carroll WR, Rosenthal EL, Magnuson JS. Functional outcomes after transoral robotic surgery for head and neck cancer. Otolaryngol Head Neck Surg 2009;141:166–71. http://dx.doi.org/10.1016/j.otohns.2009.05.014.

[70] Miyamoto S, Sakuraba M, Nagamatsu S, Kayano S, Kamizono K, Hayashi R. Risk factors for gastric-tube dependence following tongue reconstruction. Ann Surg Oncol 2012;19:2320–6. http://dx.doi.org/10.1245/s10434-012-2298-2.

[71] Fujiki M, Sakuraba M, Miyamoto S, Hayashi R. Predictive factors of dysphagia after lateral and superior oropharyngeal reconstruction with free flap transfer. J Surg Oncol 2016;113:240–3. http://dx.doi.org/10.1002/jso.24105.

[72] Gourin CG, Starmer HM, Herbert RJ, Frick KD, Forastiere AA, Eisele DW, et al. Short-and long-term outcomes of laryngeal cancer care in the elderly. Laryngoscope 2015;125:924–33. http://dx.doi.org/10.1002/lary.25012.

[73] Breunig C, Benter P, Seidl RO, Coordes A. Predictable swallowing function after open horizontal supraglottic partial laryngectomy. Auris Nasus Larynx 2016;43:658–65. http://dx.doi.org/10.1016/j.anl.2016.01.003.

[74] Yang W, McNutt TR, Dudley SA, Kumar R, Starmer HM, Gourin CG, et al. Predictive factors for prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement and use in head and neck patients following intensity-modulated radiation therapy (IMRT) treatment: concordance, discrepancies, and the role of gabapentin. Dysphagia 2016;31:206–13. http://dx.doi.org/10.1007/s00455-015-9679-1.

[75] Magnuson JS, Durst J, Rosenthal EL, Carroll WR, Ritchie CS, Kilgore ML, et al. Increased likelihood of long-term gastrostomy tube dependence in head and neck cancer survivors without partners. Head Neck 2013;35:420–5.

[76] Sayan M, Cassidy RJ, Switchenko JM, Kayode OA, Saba NF, Steuer CE, et al. Development of late toxicities in patients with oral tongue cancer treated with surgical resection and adjuvant radiation therapy. Front Oncol 2017;6. http://dx.doi.org/10.3389/fonc.2016.00272.

[77] Dean JA, Wong KH, Gay H, Welsh LC, Jones A-B, Schick U, et al. Functional data analysis applied to modeling of severe acute mucositis and dysphagia resulting from head and neck radiation therapy. Int J Radiat Oncol Biol Phys 2016;96:820–31. http://dx.doi.org/10.1016/j.ijrobp.2016.08.013.

[78] Sinclair CF, McColloch NL, Carroll WR, Rosenthal EL, Desmond RA, Magnuson JS. Patient-perceived and objective functional outcomes following transoral robotic surgery for early oropharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 2011;137:1112–6. http://dx.doi.org/10.1001/archoto.2011.172.

[79] Matuschek C, Bolke E, Geigis C, Kammers K, Ganswindt U, Scheckenbach K, et al. Influence of dosimetric and clinical criteria on the requirement of artificial nutrition during radiotherapy of head and neck cancer patients. Radiother Oncol 2016;120:28–35. http://dx.doi.org/10.1016/j.radonc.2016.05.017.

[80] Williams GF, Teo MT, Sen M, Dyker KE, Coyle C, Prestwich RJ. Enteral feeding outcomes after chemoradiotherapy for oropharynx cancer: a role for a prophylactic gastrostomy? Oral Oncol 2012;48:434–40.

[81] Shinozaki T, Hayashi R, Miyazaki M, Tomioka T, Zenda S, Tahara M, et al. Gastrostomy dependence in head and neck carcinoma patient receiving post-operative therapy. Jpn J Clin Oncol 2014;44:1058–62.

[82] Jack DR, Dawson FR, Reilly JE, Shoaib T. Guideline for prophylactic feeding tube insertion in patients undergoing resection of head and neck cancers. J Plast Reconstr Aesthet Surg 2012;65:610–5.

[83] Lee JY, Suresh K, Nguyen R, Sapir E, Dow JS, Arnould GS, et al. Predictors of severe long-term toxicity after re-irradiation for head and neck cancer. Oral Oncol 2016;60:32–40. http://dx.doi.org/10.1016/j.oraloncology.2016.06.017.

[84] Ward MC, Bhateja P, Nwizu T, Kmiecik J, Reddy CA, Scharpf J, et al. Impact of feeding tube choice on severe late dysphagia after definitive chemoradiotherapy for human papillomavirus-negative head and neck cancer. Head Neck 2016;38:E1054–60. http://dx.doi.org/10.1002/hed.24157.

[85] Truong MT, Lee R, Saito N, Qureshi MM, Ozonoff A, Romesser PB, et al. Correlating computed tomography perfusion changes in the pharyngeal constrictor muscles during head-and-neck radiotherapy to dysphagia outcome. Int J Radiat Oncol Biol Phys 2012;82:e119–27. http://dx.doi.org/10.1016/j.ijrobp.2011.04.058.

[86] Starmer HM, Tippett D, Webster K, Quon H, Jones B, Hardy S, et al. Swallowing outcomes in patients with oropharyngeal cancer undergoing organ-preservation treatment. Head Neck 2014;36:1392–7. http://dx.doi.org/10.1002/hed.23465.

[87] Mortensen HR, Overgaard J, Jensen K, Specht L, Overgaard M, Johansen J, et al. Factors associated with acute and late dysphagia in the DAHANCA 6 & 7 randomized trial with accelerated radiotherapy for head and neck cancer. Acta Oncol 2013;52:1535–42. http://dx.doi.org/10.3109/0284186X.2013.824609.

[88] Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–9.

[89] Machtay M, Moughan J, Farach A, Martin-O'Meara E, Galvin J, Garden AS, et al. Hypopharyngeal dose is associated with severe late toxicity in locally advanced head-and-neck cancer: an RTOG analysis. Int J Radiat Oncol Biol Phys 2012;84:983–9. http://dx.doi.org/10.1016/j.ijrobp.2012.03.005.

[90] Koiwai K, Shikama N, Sasaki S, Shinoda A, Kadoya M. Risk factors for severe Dysphagia after concurrent chemoradiotherapy for head and neck cancers. Jpn J Clin Oncol 2009;39:413–7.

[91] Hutcheson KA, Abualsamh AR, Sosa A, Weber RS, Beadle BM, Sturgis EM, et al. Impact of selective neck dissection on chronic dysphagia after chemo-intensity-modulated radiotherapy for oropharyngeal carcinoma. Head Neck 2016;38:886–93. http://dx.doi.org/10.1002/hed.24195.

[92] Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2009;75:385–92.

[93] Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;73:410–5.

[94] Bhayani MK, Hutcheson KA, Barringer DA, Lisec A, Alvarez CP, Roberts DB, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck 2013;35:1634–40.

[95] Bozec A, Benezery K, Chamorey E, Ettaiche M, Vandersteen C, Dassonville O, et al. Nutritional status and feeding-tube placement in patients with locally advanced hypopharyngeal cancer included in an induction chemotherapy-based larynx preservation program. Eur Arch Otorhinolaryngol 2016;273:2681–7. http://dx.doi.org/10.1007/s00405-015-3785-4.

[96] Bozec A, Benezery K, Ettaiche M, Chamorey E, Vandersteen C, Dassonville O, et al. Induction chemotherapy-based larynx preservation program for locally advanced hypopharyngeal cancer: oncologic and functional outcomes and prognostic factors. Eur Arch Otorhinolaryngol 2016;273:3299–306. http://dx.doi.org/10.1007/s00405-016-3919-3.

[97] Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA. Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2010;76:403–9.

[98] Chapuy CI, Annino DJ, Snavely A, Li Y, Tishler RB, Norris CM, et al. Swallowing function following postchemoradiotherapy neck dissection: review of

findings and analysis of contributing factors. Otolaryngol Head Neck Surg 2011;145:428–34. http://dx.doi.org/10.1177/0194599811403075.
[99] Lango MN, Egleston B, Ende K, Feigenberg S, D'Ambrosio DJ, Cohen RB, et al. Impact of neck dissection on long-term feeding tube dependence in patients with head and neck cancer treated with primary radiation or chemoradiation. Head Neck 2010;32:341–7.
[100] McRackan TR, Watkins JM, Herrin AE, Garrett-Mayer EM, Sharma AK, Day TA, et al. Effect of body mass index on chemoradiation outcomes in head and neck cancer. Laryngoscope 2008;118:1180–5.
[101] Murono S, Tsuji A, Endo K, Kondo S, Wakisaka N, Yoshizaki T. Factors associated with gastrostomy tube dependence after concurrent chemoradiotherapy for hypopharyngeal cancer. Support Care Cancer 2015;23:457–62.
[102] Pohar S, Demarcantonio M, Whiting P, Crandley E, Wadsworth J, Karakla D. Percutaneous endoscopic gastrostomy tube dependence following chemoradiation in head and neck cancer patients. Laryngoscope 2015;125:1366–71.
[103] Sanguineti G, Rao N, Gunn B, Ricchetti F, Fiorino C. Predictors of PEG dependence after IMRT+/-chemotherapy for oropharyngeal cancer. Radiother Oncol 2013;107:300–4.
[104] Setton J, Lee NY, Riaz N, Huang SH, Waldron J, O'Sullivan B, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. Cancer 2015;121:294–301.
[105] Wopken K, Bijl HP, van der Schaaf A, Christianen ME, Chouvalova O, Oosting SF, et al. Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer. PLoS One 2014;9:e94879.
[106] Wopken K, Bijl HP, van der Schaaf A, van der Laan HP, Chouvalova O, Steenbakkers RJ, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer. Radiother Oncol 2014;113:95–101.
[107] Lango MN, Galloway TJ, Mehra R, Ebersole B, Liu JC-J, Moran K, et al. Impact of baseline patient-reported dysphagia on acute gastrostomy placement in patients with head and neck squamous cell carcinoma undergoing definitive radiation. Head Neck 2016;38:E1318–24. http://dx.doi.org/10.1002/hed.24220.
[108] Strom T, Trotti AM, Kish J, Rao NG, McCaffrey J, Padhya TA, et al. Risk factors for percutaneous endoscopic gastrostomy tube placement during chemoradiotherapy for oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2013;139:1242–6.
[109] Zauls AJ, Watkins JM, Lucas J, Shirai K, Sharma AK. Requirement of percutaneous endoscopic gastrostomy tube placement in head-and-neck cancer treated with definitive concurrent chemoradiation therapy: An analysis of clinical and anatomic factors. Pract Radiat Oncol 2013;3:e61–9.
[110] Jang JW, Parambi RJ, McBride SM, Goldsmith TA, Holman AS, Chan AW. Clinical factors predicting for prolonged enteral supplementation in patients with oropharyngeal cancer treated with chemoradiation. Oral Oncol 2013;49:438–42.
[111] Poulsen MG, Riddle B, Keller J, Porceddu SV, Tripcony L. Predictors of acute grade 4 swallowing toxicity in patients with stages III and IV squamous carcinoma of the head and neck treated with radiotherapy alone. Radiother Oncol 2008;87:253–9.
[112] Baschnagel AM, Yadav S, Marina O, Parzuchowski A, L Jr TB, Warner JN, et al. Toxicities and costs of placing prophylactic and reactive percutaneous gastrostomy tubes in patients with locally advanced head and neck cancers treated with chemoradiotherapy. Head Neck 2014;36:1155–61.
[113] Lawson JD, Gaultney J, Saba N, Grist W, Davis L, Johnstone PA. Percutaneous feeding tubes in patients with head and neck cancer: rethinking prophylactic placement for patients undergoing chemoradiation. Am J Otolaryngol 2009;30:244–9.
[114] Romesser PB, Romanyshyn JC, Schupak KD, Setton J, Riaz N, Wolden SL, et al. Percutaneous endoscopic gastrostomy in oropharyngeal cancer patients treated with intensity-modulated radiotherapy with concurrent chemotherapy. Cancer 2012;118:6072–8.
[115] Al-Mamgani A, van Rooij P, Verduijn GM, Mehilal R, Kerrebijn JD, Levendag PC. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope 2013;123:386–93. http://dx.doi.org/10.1002/lary.23699.
[116] Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? Cancer 2001;91:1785–90.
[117] Otter S, Schick U, Gulliford S, Lal P, Franceschini D, Newbold K, et al. Evaluation of the risk of grade 3 oral and pharyngeal dysphagia using atlas-based method and multivariate analyses of individual patient dose distributions. Int J Radiat Oncol Biol Phys 2015;93:507–15. http://dx.doi.org/10.1016/j.ijrobp.2015.07.2263.
[118] Barnhart MK, Ward EC, Cartmill B, Robinson RA, Simms VA, Chandler SJ, et al. Pretreatment factors associated with functional oral intake and feeding tube use at 1 and 6 months post-radiotherapy (+/- chemotherapy) for head and neck cancer. Eur Arch Otorhinolaryngol 2017;274:507–16. http://dx.doi.org/10.1007/s00405-016-4241-9.
[119] Sanguineti G, Gunn GB, Parker BC, Endres EJ, Zeng J, Fiorino C. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2011;79:52–9.
[120] Amin N, Reddy K, Westerly D, Raben D, DeWitt P, Chen C. Sparing the larynx and esophageal inlet expedites feeding tube removal in patients with stage III-IV oropharyngeal squamous cell carcinoma treated with intensity-modulated radiotherapy. Laryngoscope 2012;122:2736–42.
[121] Sanguineti G, Endres EJ, Gunn BG, Parker B. Is there a "mucosa-sparing" benefit of IMRT for head-and-neck cancer? Int J Radiat Oncol Biol Phys 2006;66:931–8.
[122] Sanguineti G, Adapala P, Endres EJ, Brack C, Fiorino C, Sormani MP, et al. Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys 2007;68:741–9.
[123] Christianen ME, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. Radiother Oncol 2011;101:394–402.
[124] van de Water TA, Bijl HP, Westerlaan HE, Langendijk JA. Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia. Radiother Oncol 2009;93:545–52.
[125] Dawes C. Rhythms in salivary flow rate and composition. Int J Chronobiol 1974;2:253–79.
[126] Tabak LA. In defense of the oral cavity: structure, biosynthesis, and function of salivary mucins. Annu Rev Physiol 1995;57:547–64. http://dx.doi.org/10.1146/annurev.physiol.57.1.547.
[127] Logemann JA, Smith CH, Pauloski BR, Rademaker AW, Lazarus CL, Colangelo LA, et al. Effects of xerostomia on perception and performance of swallow function. Head Neck 2001;23:317–21.
[128] Mortensen HR, Jensen K, Aksglæde K, Behrens M, Grau C. Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters. Radiother Oncol 2013;107:288–94. http://dx.doi.org/10.1016/j.radonc.2013.06.001.
[129] Tribius S, Sommer J, Prosch C, Bajrovic A, Muenscher A, Blessmann M, et al. Xerostomia after radiotherapy. What matters–mean total dose or dose to each parotid gland? Strahlentherapie Und Onkol Organ Der Dtsch Rontgengesellschaft 2013;189:216–22.
[130] Vainshtein JM, Samuels S, Tao Y, Lyden T, Haxer M, Spector M, et al. Impact of xerostomia on dysphagia after chemotherapy-intensity-modulated radiotherapy for oropharyngeal cancer: Prospective longitudinal study. Head Neck 2016;38:E1605–12. http://dx.doi.org/10.1002/hed.24286.
[131] Baredes S, Behin D, Deitch E. Percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. Ear Nose Throat J 2004;83:417–9.
[132] Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FKL, Barasch A, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer 2008;113:2704–13. http://dx.doi.org/10.1002/cncr.23898.
[133] Nguyen NP, Vos P, Moltz CC, Frank C, Millar C, Smith HJ, et al. Analysis of the factors influencing dysphagia severity upon diagnosis of head and neck cancer. Br J Radiol 2008;81:706–10. http://dx.doi.org/10.1259/bjr/98862877.
[134] King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of radiation-induced dysphagia in head and neck cancer. Dysphagia 2016;31:339–51. http://dx.doi.org/10.1007/s00455-016-9710-1.
[135] van der Laan HP, Bijl HP, Steenbakkers RJHM, van der Schaaf A, Chouvalova O, Vemer-van den Hoek JGM, et al. Acute symptoms during the course of head and neck radiotherapy or chemoradiation are strong predictors of late dysphagia. Radiother Oncol 2015;115:56–62. http://dx.doi.org/10.1016/j.radonc.2015.01.019.
[136] Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MWS, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer 2012;118:5793–9. http://dx.doi.org/10.1002/cncr.27631.
[137] Epstein JB, Wilkie DJ, Fischer DJ, Kim Y-O, Villines D. Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. Head Neck Oncol 2009;1:26. http://dx.doi.org/10.1186/1758-3284-1-26.
[138] Bar AdV, Weinstein G, Dutta PR, Dosoretz A, Chalian A, Both S, et al. Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. Cancer 2010;116:4206–13. http://dx.doi.org/10.1002/cncr.25274.
[139] Bar AdV, Weinstein G, Dutta PR, Chalian A, Both S, Quon H. Gabapentin for the treatment of pain related to radiation-induced mucositis in patients with head and neck tumors treated with intensity-modulated radiation therapy. Head Neck 2010;32:173–7. http://dx.doi.org/10.1002/hed.21165.
[140] Starmer HM, Yang W, Gourin CG, Kumar R, Jones B, McNutt T, et al. One-year swallowing outcomes in patients treated with prophylactic gabapentin during radiation-based treatment for oropharyngeal cancer. Dysphagia 2017. http://dx.doi.org/10.1007/s00455-017-9783-5.
[141] Nguyen NP, North D, Smith HJ, Dutta S, Alfieri A, Karlsson U, et al. Safety and effectiveness of prophylactic gastrostomy tubes for head and neck cancer patients undergoing chemoradiation. Surg Oncol 2006;15:199–203. http://dx.doi.org/10.1016/j.suronc.2006.12.002.
[142] Wiggenraad RGJ, Flierman L, Goossens A, Brand R, Verschuur HP, Croll GA, et al. Prophylactic gastrostomy placement and early tube feeding may limit loss of weight during chemoradiotherapy for advanced head and neck cancer,

a preliminary study. Clin Otolaryngol 2007;32:384–90. http://dx.doi.org/10.1111/j.1749-4486.2007.01533.x.

[143] Madhoun MF, Blankenship MM, Blankenship DM, Krempl GA, Tierney WM. Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)? World J Gastroenterol 2011;17:1004–8.

[144] Hughes BGM, Jain VK, Brown T, Spurgin A-L, Hartnett G, Keller J, et al. Decreased hospital stay and significant cost savings after routine use of prophylactic gastrostomy for high-risk patients with head and neck cancer receiving chemoradiotherapy at a tertiary cancer institution. Head Neck 2013;35:436–42. http://dx.doi.org/10.1002/hed.22992.

[145] Grant DG, Bradley PT, Pothier DD, Bailey D, Caldera S, Baldwin DL, et al. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. Clin Otolaryngol 2009;34:103–12. http://dx.doi.org/10.1111/j.1749-4486.2009.01889.x.

[146] Sethugavalar B, Teo MT, Buchan C, Ermis E, Williams GF, Sen M, et al. Impact of prophylactic gastrostomy or reactive NG tube upon patient-reported long term swallow function following chemoradiotherapy for oropharyngeal carcinoma: a matched pair analysis. Oral Oncol 2016;59:80–5. http://dx.doi.org/10.1016/j.oraloncology.2016.06.007.

[147] Shaw SM, Flowers H, O'Sullivan B, Hope A, Liu LWC, Martino R. The effect of prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement on swallowing and swallow-related outcomes in patients undergoing radiotherapy for head and neck cancer: a systematic review. Dysphagia 2015;30:152–75. http://dx.doi.org/10.1007/s00455-014-9592-z.

[148] Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. In: Perry A, editor. Cochrane Database Syst. Rev.. Chichester, UK: John Wiley & Sons, Ltd; 2016. http://dx.doi.org/10.1002/14651858.CD011112.pub2.