Prediction models for tube feeding dependence in head and neck radiotherapy

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Chapter 7
Summarizing discussion and future perspectives
Chapter 7

7.1 General discussion and summary

The aim of the research described in this thesis is to identify prognostic factors for tube feeding use and dependence in head and neck cancer (HNC) patients treated with (chemo-) radiotherapy in order to develop prediction models for tube feeding use in the acute phase. The goal of these models was to guide intensity modulated radiotherapy treatment optimization, and to support decision-making in selecting patients for proton therapy and other preventive measures.

Following a short introduction, factors influencing tube feeding placement, their use and dependence, including the prognostic factors that were identified in a literature review, are discussed. Next, the models developed in this thesis will be discussed, including the model for tube feeding use in the acute phase, the model for tube feeding dependence at 6 months without dose volume histogram (DVH) parameters, and the model for tube feeding dependence at 6 months with DVH parameters. Finally, the ways that these models can be used for NTCP-guided plan optimization are explored.

7.2 Head and neck cancer treatment and tube feeding

With the introduction of more intensified treatment regimens, survival of patients with advanced head and neck cancer has improved [1]–[4]. In addition, the growing incidence of HPV-related oropharyngeal cancer with a less aggressive biological behaviour has contributed to a further improvement of overall survival. Consequently, this better survival rate has resulted in a higher prevalence of head and neck cancer survivors at risk of radiation-induced late toxicities. One of these toxicities is dysphagia, which may eventually result in tube feeding dependence, the most severe type of dysphagia. Tube feeding dependence is a clinically relevant side effect since it significantly decreases quality of life [5]–[10]. In addition, feeding tube use before commencing treatment and prolonged feeding tube use following treatment are associated with worse prognosis [11], [12].

The aim of the research described in this thesis is to determine the most important prognostic factors for different aspects of tube feeding dependence and to use these prognostic factors for the development of prediction models for HNC patients treated with definitive (chemo-) radiotherapy. Prediction models are essential to identify patients at high risk for prolonged tube feeding use who could be
eligible for primary or secondary preventive measures, such as proton therapy or swallowing exercises.

Some prediction models described in this thesis are so-called Normal Tissue Complication Probability (NTCP)-models, describing the relationship between three-dimensional dose distributions and the risk of radiation-induced toxicity, in our case feeding tube use (defined as tube feeding use < 6 months) or tube feeding dependence (defined as tube feeding use ≥ 6 months).

Patients were considered tube feeding dependent if oral intake was limited or not possible at all and the feeding tube was required to ensure adequate food intake. As we were primarily interested in swallowing dysfunction induced by radiation, patients that used a feeding tube at baseline were excluded from the analyses (i.e., RTOG grade 3–4).

In order to prevent weight loss, many HNC patients receiving (chemo-) radiotherapy need nutritional supplements [13], [14]. The first step is administration of high-caloric and high-protein products using soft, pureed or liquid food. The next step is additional liquid dietary supplements followed by (temporary) additional or complete enteral feeding. This final step involves the use of feeding tubes. There is ongoing debate on what should be considered the most optimal approach of enteral feeding and timing of feeding tube placement [15]. The routes that are commonly used in HNC patients are the nasogastric route and the percutaneous gastrostomy (PEG) route. A nasogastric (NG) tube is a tube which is inserted transnasally into the stomach, while a PEG tube is placed by creating an artificial tract between the stomach and the abdominal surface. The latter is an invasive method which could result in major complications [16], [17]. Nasogastric feeding is usually considered for short-to-medium-term feeding (days to weeks), whereas PEG is commonly used when long-term feeding problems (i.e., months to years) are expected [18], [19].

Regarding the timing of PEG tube placement there are two options, named prophylactic and reactive placement [15]. Prophylactic PEG tube placement means that a PEG tube is placed before the start of treatment to prevent critical weight loss during treatment. This is mostly used in patients planned for concurrent chemoradiotherapy. In these patients more severe acute toxicity is expected, such as mucositis and xerostomia, compared to patients treated with radiotherapy alone. Reactive tube feeding refers to feeding tube insertion (either PEG tubes or NG tubes) when indicated and is usually based on weight loss or inadequate caloric intake. There is an ongoing discussion regarding the prophylactic policy, in which
the positive effects (lower medical costs and less treatment interruptions) [20]–[23] have to be balanced against the negative effects (risk of major complications and possible negative effects on long-term swallowing) [16], [17], [24]–[27]. One of the presumed negative effects of prophylactic PEG tube placement is that swallowing function is jeopardized in the long-term as a result of swallowing muscle atrophy and consequent augmentation of the severity of radiation fibrosis in the pharynx [24], [28].

As opposed to NG tubes, important advantages of PEG tubes is that they allow for higher energy intake and that this type of feeding tube is not visible, which is more comfortable for patients [29], [30].

So far, no successful randomised trials have been performed in which PEG and NG tube feeding have been directly compared regarding nutritional outcome, complications, risk of long-term dysphagia, patient satisfaction and costs. One trial was performed, but closed early due to poor accrual [31]. Recently, a randomised controlled pilot trial comparing prophylactic PEG with reactive NG tube feeding was initiated aiming to test the feasibility of an RCT. Unfortunately this trial could not be continued as the recruitment rate was again lower than expected [32]. The most optimal approach for enteral feeding in HNC patients during concurrent chemoradiation, therefore, remains to be determined.

At UMCG (University Medical Center Groningen, the Netherlands), prophylactic PEG tube placement is standard of care in all patients treated with curative concomitant chemoradiation and patients are instructed to refrain from using the PEG tube as much as possible. In patients with significant weight loss (>5% weight loss in 1 month or >10% in 6 months or BMI <18.5 kg/m2) and/or low nutritional intake (less than half of daily requirements for energy, proteins, or fluids) and/or severe swallowing dysfunction prior to treatment, PEG tubes are placed prior to treatment. These patients were, however, excluded from the analyses performed in this thesis.

In patients treated with radiotherapy alone, reactive placement of feeding tubes was used in case of significant weight loss or swallowing dysfunction during treatment. In this situation a nasogastric feeding tube was placed during treatment if swallowing problems were considered temporarily and the patient was expected to recover soon. A cut-off point of 6 weeks is used in our institution regarding the choice for a certain route of tube feeding, which is in line with most studies described in literature [19]. For severe swallowing problems early during
treatment and/or when swallowing problems are expected to persist for a longer period of time, PEG tube placement is preferred.

### 7.3 Factors influencing tube feeding placement, use and dependence

The primary endpoint in our studies was tube feeding dependence, defined as persistent PEG tube use at 6 months (or later) after treatment ($\text{TUBE}_{\text{M6}}$). In Chapter 4 of this thesis, we tested the hypothesis that $\text{TUBE}_{\text{M6}}$ was predictive for tube feeding dependence at later timepoints. Significant associations were found between $\text{TUBE}_{\text{M6}}$ and tube feeding dependence at subsequent timepoints up to 24 months after treatment. Particularly, the negative predictive values of $\text{TUBE}_{\text{M6}}$ for $\text{TUBE}_{\text{M12}}$, $\text{TUBE}_{\text{M18}}$ and $\text{TUBE}_{\text{M24}}$ were high: 97.1%, 99.1% and 98.9%, respectively, indicating that almost all patients who were not tube feeding dependent at 6 months remained independent at subsequent timepoints. However, much lower values were found regarding the positive predictive values (i.e., 50.0%, 36.8% and 40.0% for $\text{TUBE}_{\text{M12}}$, $\text{TUBE}_{\text{M18}}$ and $\text{TUBE}_{\text{M24}}$, respectively), indicating recovery from tube feeding dependence in the majority of cases [33].

The aim of Chapter 2 was to provide an overview of studies reporting on the results of multivariable analyses on independent prognostic factors for (reactive) tube feeding placement, use (e.g., use < 6 months) and dependence (e.g., use ≥ 6 months after treatment) in HNC patients primarily treated with (chemo-) radiotherapy. In this review, fourteen retrospective studies were identified that fulfilled the inclusion criteria and reported on prognostic factors for tube feeding dependence at 6 months after treatment. These studies reported on patient- and disease variables, treatment variables and DVH parameters. Two of the studies reported on a model for tube feeding dependence, one including DVH parameters. Prognostic factors that were consistently associated with the risk of tube feeding dependence at 6 months after treatment for HNC patients treated with (chemo-) radiotherapy were DVH parameters, including dose to the larynx, the pharyngeal constrictor muscle (PCM) inferior and superior, and the dose to the contralateral parotid gland. Furthermore, advanced T-stage and N-stage, pre-treatment weight loss, (concomitant) chemotherapy and prophylactic gastrostomy policy were prognostic for tube feeding dependence at 6 months.
Additionally, 18 studies were identified that reported on prognostic factors for tube feeding placement and use within 6 months after treatment. For tube feeding use less than 6 months, prognostic DVH parameters included dose to the oral mucosa, contralateral submandibular gland, larynx and the pharyngeal constrictor muscle inferior and superior and cricopharyngeal muscle. Prognostic patient-, disease- and treatment-related factors for tube feeding placement and use within 6 months after treatment were similar to the prognostic factors found for tube feeding dependence at 6 months after treatment, but also included several other variables such as the use of narcotics prior to treatment and living alone at the time of treatment.

The rationale behind this review was that most published NTCP-models for severe swallowing dysfunction (including tube feeding dependence) did not systematically consider clinical and treatment-related risk factors next to dose and volume parameters. This is relevant as the risk for toxicities are not only determined by dose and volume parameters. Moreover, clinical and treatment-related risk factors may confound the relationship between radiation dose distribution parameters for tube feeding use and dependence, so it is important to consider these risk factors when developing multivariable NTCP-models. The absolute excess risk of side effects depends on both the dose to organs at risk (OARs) as well as on the baseline risk determined by other factors [34].

The systematic review of prognostic factors for tube feeding dependence revealed that next to dose volume (DVH) parameters, such as the dose to the larynx, the PCM superior, PCM inferior, cricopharyngeal muscle and the dose to the contralateral parotid gland, the most reported prognostic variables were weight and weight loss parameters before or during treatment, advanced T-stage and the use of concomitant systemic treatment and accelerated radiotherapy.

Severe dysphagia leading to tube feeding dependence is probably due to a combination of radiation-induced damage to the swallowing structures as well as to the salivary glands [35], [36]. This so-called co-toxicity is probably the result of the indirect effect of saliva production on dysphagia complaints, since reduced saliva production after radiotherapy and chemoradiotherapy may alter the perception of swallowing ability while swallowing itself is not necessarily less efficient [37]. It has also been reported that both acute xerostomia and dysphagia are important prognostic factors for swallowing dysfunction at 6 months after completing (chemo-) radiotherapy [38].
The risk of patient- and observer-rated xerostomia after (chemo-) radiotherapy is not only determined by the dose to the parotid glands, but also by the radiation dose to the submandibular and minor salivary glands lining the oral cavity [39]–[43]. Sparing of the parotid and submandibular glands with more advanced radiation techniques such as Intensity Modulated Radiotherapy (IMRT) has reduced both the incidence of xerostomia and dysphagia and improved quality of life as compared to the older 3D-CRT technique [40]–[42], [44]–[51]. Reduction in mean dose to the contralateral submandibular gland resulted in an earlier removal of the PEG tube [52]. More recently, new salivary glands were discovered located in the nasopharynx near the torus tubarius, the so-called ‘tubarial glands’. In the study describing these glands, previously unnoticed bilateral areas in the nasopharynx were visualized in patients with urological cancers by positron emission tomography/computed tomography with prostate-specific membrane antigen ligands (PSMA PET/CT). These areas corresponded with mucous glands in a histology study on human cadavers. It was shown that in HNC patients, the mean dose to tubarial glands was significantly associated with physician-rated posttreatment xerostomia and dysphagia grade≥2 at 12 months and 24 months after treatment [53].

Given the association between salivary function and dysphagia, it is likely that preventive measures against xerostomia, such as salivary gland sparing IMRT, sparing of the stem cell-containing region of the parotid gland in IMRT [54], and stem cell therapy [55] may also contribute to the prevention of dysphagia and consequent tube feeding use in HNC patients.

Many HNC patients present with dysphagia as a direct result of the location and extension of the primary tumour [56]. Dysphagia is a major contributing factor to critical weight loss, defined as loss of weight of ≥5% in 1 month or ≥10% in 6 months. At time of diagnosis, critical weight loss is already present in 30-55% of HNC patients [57]. During treatment, the severity of malnutrition may increase due to treatment-related side effects, such as alteration or loss of taste, mucositis, xerostomia, fatigue, nausea and vomiting, especially in those treated with concurrent chemoradiotherapy [58], [59]. Weight loss is considered a clinically relevant phenomenon for this patient population, since it is associated with a higher risk of complications, decreased treatment tolerance and possibly a lower response to treatment, decreased quality of life, and higher morbidity and mortality [60]–[62]. Therefore, enteral feeding is indicated in this category of patients.
Chapter 7

7.4 Modelling

7.4.1 Modelling for prognostic factors for tube feeding use and dependence

In Chapter 3, the results of the development of NTCP models for tube feeding use during and immediately after chemoradiotherapy treatment were presented, developed in a prospective cohort managed with a prophylactic PEG tube. For one model, we used ‘total duration of feeding tube use’ (\(TF_{\text{duration}}\)) as the endpoint. A second model was developed for the endpoint ‘feeding tube use > 6 weeks’ (\(TF_{>6\text{weeks}}\)) as a cut-off point for future decisions regarding either installation of a nasogastric tube (< 6 weeks feeding tube use) or a PEG tube (> 6 weeks feeding tube use).

For \(TF_{>6\text{weeks}}\) we found a significant association with the mean dose to the contralateral submandibular gland. For \(TF_{\text{duration}}\) we found significant associations with the mean dose to the contralateral parotid gland, use of pain medication before treatment and percentage baseline weight loss. Unfortunately, both models were not very robust, reflected in a poor AUC (area under the curve) and calibration.

As mentioned in the previous section, the results of this study support the hypothesis that xerostomia plays a role in the development of dysphagia, since the contralateral submandibular and parotid gland were the only DVH parameters predicting for \(TF_{>6\text{weeks}}\) and \(TF_{\text{duration}}\) respectively.

Pre-treatment weight loss > 5%, decrease in body mass-index and use of analgetics prior to treatment were identified as predictors for the duration of tube feeding use in previous studies [11], [63]. One of these studies presented a pre-therapeutic risk score to support the selection of HNC patients at risk for enteral feeding during (chemo-) radiotherapy who may benefit from prophylactic PEG tube placement [63]. Patients with significant baseline weight loss are prone to develop critical weight loss earlier, resulting in nutritional supplementation and ultimately enteral feeding at an earlier stage during treatment [57].

An interesting finding was that all patients with nasopharyngeal cancer used their feeding tube for over 6 weeks. Nasopharyngeal cancer is associated with more severe acute and late dysphagia [64] as compared to oropharyngeal carcinoma [65]. And swallowing function in patients with nasopharyngeal carcinoma continues to deteriorate for years after treatment [66]. In our cohort, eleven out
of thirteen patients with nasopharyngeal cancer were treated with three-weekly cisplatin followed by adjuvant cisplatin and 5-fluoro-uracil (5-FU). Other studies have shown that this three-weekly regimen of concomitant chemotherapy is associated with a higher incidence of severe mucositis (grade 3-4) as compared to concomitant weekly cisplatin, especially in nasopharyngeal carcinoma [67], [68].

In Chapter 4, we described a large multicentre prospective cohort study to identify which patient-, disease- and treatment-related factors were associated with tube feeding dependence at 6 months after treatment. The main purpose of this study was to develop a prediction model for tube feeding dependence after curative (chemo-) radiotherapy in HNC based on pre-treatment characteristics that would support better selection of patients for preventive measures already prior to treatment. These measures could include new radiotherapy treatment techniques and/or preventive swallowing exercises during (chemo-) radiotherapy. They could also support decision making regarding the general treatment strategy, such as the choice between definitive (chemo-) radiotherapy or surgery as the primary treatment modality. This prediction model was validated in an external and independent prospective cohort to further support its general applicability [69].

The group LASSO (least absolute shrinkage and selection operator) analysis that was performed resulted in a model consisting of six variables, comprising weight loss prior to treatment, advanced T-stage, positive N-stage, bilateral neck irradiation, accelerated radiotherapy and chemoradiation.

These findings are in line with those obtained by other authors who reported on the relationship between tube feeding dependence after radiotherapy or chemoradiotherapy [70]–[73]. In all these studies, multivariable analyses were used. However, the added value of our study was that we used this analysis to develop a prediction model. The nomogram we present in Chapter 4 allows for an integration of different prognostic variables in estimating the risk on radiation-induced tube feeding dependence in individual patients.

Given that we excluded patients who were tube feeding dependent prior to treatment, it is important to notice that this prediction model is only applicable to patients not using feeding tubes at baseline. In other words, the model only applies for patients with RTOG grade 0-2 swallowing dysfunction. Two of the studies that reported on the same prognostic variables as used in our model, did not exclude patients with pre-treatment dysphagia (including tube feeding use) [70], [73].
In Chapter 5, we present an NTCP model for tube feeding dependence at 6 months after treatment developed in a prospective cohort of 355 patients. The aim of this study is to develop a multivariable NTCP-model including dose volume parameters, that can be used for treatment planning optimization in patients planned for definitive (chemo-) radiotherapy. This analysis resulted in a multivariable NTCP-model consisting of advanced T-stage, moderate to severe weight loss at baseline, accelerated radiotherapy, chemoradiation, radiotherapy plus cetuximab, and the mean dose to the superior and inferior PCM, the cricopharyngeal muscle, and to the contralateral parotid gland. Other authors also found that the dose to the superior and inferior pharyngeal constrictor muscles are prognostic factors for tube feeding dependence after (chemo-) radiotherapy [74]–[76]. The mean dose to the contralateral parotid gland and cricopharyngeal muscle has never been reported as a prognostic factor for tube feeding dependence prior to our publication. However, in a recent publication, reporting on the development of an NTCP-model for acute radiotherapy-related dysphagia (CTCAE v.4.0 grade ≥ 3) and indication for PEG insertion (according to a nutritional stepped-wedge protocol), the mean dose to the cricopharyngeal muscle was an independent prognostic factor for acute radiotherapy-related dysphagia [77]. And, as we already mentioned on page 5 of this discussion, acute xerostomia is significantly associated with grade 2-4 swallowing dysfunction at 6 months after completing (chemo-) radiotherapy, which includes tube feeding dependence [38].

The dose volume parameters included in the model presented in Chapter 5 can be used to guide radiotherapy treatment planning optimization. Treatment planning optimization is a valuable strategy to prevent late dysphagia [78]–[84], xerostomia [44], [45], and tube feeding dependence [52]. This model can also be used to identify patients at high risk of persistent severe swallowing problems which may benefit from preventive measures, such as swallowing rehabilitation. Moreover, this model can be used for selection of HNC patients who may benefit from more advanced radiotherapy techniques, such as proton therapy. In the Netherlands, the model-based approach is used for the selection of HNC patients for proton therapy [85].

The model-based approach is considered an evidence-based alternative to randomised controlled trials comparing photon and proton therapy in HNC patients, where protons are primarily used to reduce the dose to OARs to prevent radiation-induced toxicities [86]. To estimate the reduction in the risk of toxicities, a plan comparison study is performed, comparing the use of protons to standard photon techniques, to determine the difference in dose in the most relevant OAR (i.e., delta-dose). NTCP-models are then used to translate delta-dose into a delta-
NTCP, which refers to the expected reduction in the risk of a given side effect. Patients qualify for proton therapy if the pre-defined delta-NTCP values are met [87]. The model presented in Chapter 5 has been used in the first National Indication Protocol for Proton therapy to select HNC patients for proton therapy [88].

To conclude, the prediction models developed in this thesis can be used to identify patients at risk for feeding tube dependence who may benefit from preventive measures, such as preventive swallowing exercises or more advanced radiotherapy techniques, such as proton therapy. To enhance the generalizability of the developed models, external validation is required [89], [90].

7.4.2 Modelling: need for validation

Prediction models are developed to support health care providers in estimating the probability that a condition/disease is present (diagnostic models) or that a specific event will occur in the future (prognostic models) [91]. NTCP-models that are developed in radiation oncology are examples of prognostic models. Radiation-oncology is a rapidly evolving field of investigation, and NTCP-models, such as the models developed in this thesis, are commonly used to estimate if a reduction in dose to relevant critical structures using new treatment techniques (for example proton therapy) results in a reduction of observed toxicity.

To test whether an NTCP-model is generalizable to patients treated with more advanced radiotherapy techniques or to patients treated at different institutions, external validation is (ideally) used. To avoid overly optimistic performance estimates of the model, the databases used for validation should ideally be independent from the database used for development of the model. Another important requirement in validation is that the estimate of the performance should take the uncertainty of the model into consideration [34].

The TRIPOD statement (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) was developed because many reported prediction models were of a poor quality. In this statement, a checklist of 22 items is given with which studies aimed at developing, validating, or updating a prediction model can be evaluated [91]. In addition, several types of analysis are discussed in this statement. In a type 1 analysis, a single dataset is used for development of the prediction model and the predictive performance is then directly evaluated using the same data (type 1a analysis) or the dataset is resampled by using resampling techniques (e.g., bootstrapping or cross-validation) to evaluate the performance
and optimism of the model (type 1b analysis); this type of analysis is recommended when data are limited. In a type 2 analysis the dataset is either randomly (type 2a) or non-randomly (type 2b) split (e.g., by location) into two sets; one set is used to develop the prediction model and one set is used to evaluate its predictive performance. This type of analysis requires a larger dataset than type 1 analysis to avoid lack of power during development and validation. Type 3 analysis uses one dataset to develop the prediction model and a separate dataset (e.g., data from a different study) to evaluate the performance of the model. Type 4 analysis is used to evaluate the predictive performance of an existing prediction model on separate data; both type 3 and 4 analyses are referred to as external validation studies [91], [92].

The model presented in Chapter 4 is an example of a type 3 analysis, in which the prediction model developed in a dataset based on a cohort treated at our institution was externally validated in an independent patient cohort with patients that were treated with photon radiotherapy with or without chemotherapy at a different institution. The model performed excellent at external validation [69].

Another option, when external validation in an entirely new dataset is not possible, is internal validation by means of a resampling technique (type 1b analysis). The model presented in Chapter 5 was cross-validated, which is an example of such a resampling technique. In this type of analysis, a single dataset is used for both model development and model validation. The data are randomly split into training and test sets. The training set is then used for development of the model, while model performance is assessed a specified number of times in new test sets (which is all available data minus the data used for model development). This procedure provides a reliable estimate of the errors of the modelling procedure but also the prediction performance of the model. This procedure results in a more generalizable model [92]. One issue with this type of cross-validation is that prediction performance is probably too optimistic because the model development and validation is performed on the same dataset. To avoid this overly optimistic estimate of model performance, double cross-validation can be introduced as a validation method. This means that, when the dataset is split in both a training and test cohort, both samples are used for model building and validation while the sets are resampled. This type of cross-validation with a double resampling loop has the advantage that the stability of model performance can be assessed [34]. The model performance at double cross-validation was excellent. The model presented in Chapter 5 was also externally validated, needing only an adjustment to the intercept [89].
The model in Chapter 5 is currently being used to select patients by means of the model-based approach for proton therapy. The model was also externally validated in a proton cohort [93] and showed robustness and validity for proton therapy patients.

For model-based selection of future patients, validation of the models would ideally be done regularly when new patient data becomes available, with the aim of reoptimizing the model.

### 7.5 Preventive measures

#### 7.5.1 Treatment optimization and modern radiotherapy techniques

In recent years, dose volume parameters that are found to be predictive for the risk of late-xerostomia and late-dysphagia have been used in IMRT treatment planning optimization and it has been shown that reducing the dose to these structures indeed results in less late xerostomia and dysphagia [44], [45], [47], [78]–[84], [94], [95]. In these studies, the dose distributions are optimized by minimizing an objective function based on dose-volume parameters that are dictated to the treatment planning system (TPS) before start of the optimization process. The objective function is a single numerical value which scores the quality of the treatment plan. As well as physical dose constraints for targets and OARs, biological indices, such as the gEUD (generalized equivalent uniform dose), are also used in treatment optimization. The gEUD uses the physical dose distribution and a tissue-dependent parameter to describe tumour and healthy tissue properties [96]. Addition of gEUD parameters for OARs in treatment optimization has been shown to provide better protection of OARs [97]. However, these gEUD parameters only include dose information for separate OARs and, unlike NTCP-models, are not proportional with clinical responses. Therefore, in Chapter 6 we describe the use of the NTCP-model developed in Chapter 5 in NTCP-objective function-based automated planning in the TPS.

The objective of this in-silico planning study was to assess whether NTCP-guided plan optimization for tube feeding dependence results in clinically acceptable treatment plans with improvement of the NTCP-estimates for tube feeding dependence, as compared to the original clinical plan which was planned according to the aforementioned strategy.
The tube feeding dependence (TFD) based NTCP-guided optimized plans were compared against the original clinical plan and an NTCP-guided optimized plan for grade 2-4 swallowing dysfunction (DYS) [98]. The reason behind the comparison of the TFD-based plan against the DYS-based plan, was that the use of automated planning itself may have contributed to a lower dose in OARs which overlap with the targets, such as the parotid glands. By comparing the TFD-based and DYS-based plans against each other, the effect of NTCP-objective based autoplanning versus conventional (manual) IMRT planning was discounted.

The NTCP-objective based autoplanned plans resulted in a 5% reduction in predicted NTCP value for tube feeding dependence in 5% of patients as well as an improved dose conformity. No improvements were found when the OAR dose in the clinical plan was already low (i.e., < 20 Gy). This was expected since the NTCP model for TFD requires a relatively large dose change in OARs to achieve a substantial NTCP-reduction. Additionally, the clinical plans were already optimized for sparing certain swallowing structures [99], so there was relatively little gain to be expected, especially in patients with an already low dose in OARs.

One limitation of this study was the use of generalized equivalent uniform dose, or gEUD-based objectives for OARs that were not included in the NTCP-model for TFD. This may have limited the true exploration of the NTCP-based objectives in the TPS. However, not incorporating gEUD-based objectives for OARs in the optimization process resulted in clinically unacceptable plans.

In Chapter 6 we showed that plan optimization using NTCP-based objective functions for tube feeding dependence resulted in clinically acceptable plans with slightly lower predicted NTCP values for tube feeding dependence, especially in patients with considerable risk factors.

Besides using the NTCP models either indirectly or directly in IMRT treatment planning optimization, they can also be used for the selection of patients for new treatment strategies such as proton therapy.

7.5.2 Swallowing exercises
Next to advanced radiotherapy techniques, swallowing exercises are also an option in the prevention of late dysphagia.

The benefit of preventive swallowing rehabilitation is a reduction in the loss of muscle mass with swallowing exercises. Results of a randomised trial show that
swallowing rehabilitation reduces structural loss of muscle of the tongue and the floor of the mouth (e.g. the genioglossus, hyoglossus and mylohyoid muscles) and reduces deterioration in swallowing ability at 6 weeks after treatment in a group of patients treated with (chemo-) radiotherapy who performed swallowing exercises during treatment [100]. Limitations of this study were the limited study size and the fact that, due to withdrawal rates, no meaningful analysis could be performed at 6 months posttreatment. Furthermore, no information could be given regarding the muscle structure of the pharyngeal constrictor muscles due to movement artifacts of the MRI.

Other randomised trials have shown conflicting results [101]–[106]. A recent review including most of these randomised trials concluded that undertaking therapeutic exercises before, during and/or immediately after HNC treatment does not lead to improvement in swallowing after treatment. However, all randomised trials performed until now have been relatively small studies with possibly insufficient power to detect any difference. Furthermore, the data from the studies included in this review could not be combined due to differences in inclusion criteria, measurement tools that were used, and differences in primary outcome [107].

Recently, a meta-analysis was performed to assess the benefit of exercise therapy on swallowing physiology, function and quality of life [108]. All patients of the included studies were treated with (chemo-) radiotherapy as the primary treatment modality for their HNC. Most of the included studies investigated early swallowing interventions, while some studies focused on late interventions. The most performed swallowing exercise was the Mendelsohn manoeuvre, which is a manoeuvre that has been used for many years to treat patients with pharyngeal dysphagia, in which the duration of submental muscle contraction is increased during swallowing. This increases the extent and duration of laryngeal elevation during the swallow and thereby increases the duration and width of the opening of the upper esophageal sphincter [109], [110]. Other commonly used exercises included tongue strength and jaw function exercises.

Functional outcomes were obtained using highly diverse subjective and objective measures. The most commonly reported subjective clinician-rated measure was the Functional Oral Intake Scale (FOIS). This is a 7-point scale of oral dietary tolerance, which ranges from complete feeding tube dependence (score 1) to a total oral diet without restrictions [111]. Most commonly-used objective measures included the presence or absence of either a PEG or other feeding tube, or duration
of PEG tube use. Four of the seven studies reporting on objective swallowing measures, including duration of feeding tube use, had used a prophylactic PEG tube policy [28], [100], [106], [112]. The results of the meta-analysis showed that early rehabilitation is beneficial for the intermediate (up until 3 months after treatment) and late (from 3 months to 6 years after treatment) mean FOIS score, but does not alter outcome in terms of the presence of a feeding tube. Quality of life, as measured by diverse quality of life questionnaires, including the European Organization of Research and Treatment of Cancer Core Quality of Life Questionnaire/Module for Head and Neck Cancer (EORTC QLQ-30/H&N35), was not significantly improved in patients with early interventions at intermediate or late timepoints [108].

In conclusion, there is limited evidence that swallowing rehabilitation is beneficial for swallowing function after treatment. High-quality randomised trials are needed to support clear recommendations regarding the most effective moment to start rehabilitation, the most effective type of swallowing exercises and the required intensity of swallowing rehabilitation for HNC patients treated with curative (chemo-) radiotherapy.

### 7.6 Conclusions and future perspectives

We identified prognostic factors for tube feeding use and dependence and developed and validated NTCP models for tube feeding use and dependence. We also performed plan optimizations using NTCP-based objective functions for swallowing dysfunction and tube feeding dependence resulting in clinically acceptable plans and leading to lower predicted NTCP values for tube feeding dependence.

For an optimal balance between tumour control and toxicity in individual patients, detailed information is needed on the relationship between normal tissue irradiation and the risk of a wide range of radiation-induced toxicities including tube feeding dependence. To achieve this, we need externally validated models with reliable dose-response estimates to organs at risk. These models need to have a high predictive performance and should accurately describe the relationship of normal tissue radiation dose and the risk of the complication. Currently, such models are lacking for a wide range of toxicities in HNC patients. Using these optimal models, we can come to a comprehensive individual toxicity risk profile that can be used to minimize the overall toxicity burden of radiation treatment.
for an individual HNC patient by treatment planning optimization and by selecting patients at highest risk for new treatment strategies.

Prediction models are currently primarily based on radiation dose parameters and clinical factors. By adding image biomarkers extracted from organs at risk that have been segmented on medical imaging (e.g., CT, FDG-PET and MR images) and by using machine learning approaches, the prediction of toxicities may possibly improve even further.
7.7 References


Summarizing discussion and future perspectives


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Chapter 7


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