Prediction models for tube feeding dependence in head and neck radiotherapy

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Chapter 1

General introduction and outline of thesis

1.1 Head and neck cancer treatment

Head and neck cancer (HNC) is a heterogeneous group of cancers originating from the nasal cavity, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx and the larynx, and generally have a high risk to develop metastases in the lymph nodes of the neck.

In the Netherlands, about 3% of all cancer diagnoses include HNC, making it a relatively rare malignancy [1]. The most common histopathologic type (90%) is squamous cell carcinoma (HNSCC).

In the last decades the incidence of HNC in the Netherlands has risen significantly from 2,000 cases in 1990 to around 3,000 cases in 2017 [1]. This increasing incidence is probably due to the increasing population and ageing of the Dutch population. The 5-year overall survival of patients with HNC varies between 30-70% depending on the localisation and locoregional extension of the tumour [1].

The most important risk factors for the development of HNC are (previous and current) tobacco smoking and alcohol use. For oropharyngeal carcinomas at the base of the tongue or tonsillar region, HPV (human papillomavirus), and specifically HPV-16, is recognized as a causative agent in the development of this type of HNC. Patients are often relatively young and usually present with small primary tumours and advanced nodal disease [2]. The role of HPV infection in non-oropharyngeal HNC is less well defined [3]. In general, the outcome of this group of patients is considerably more favourable compared to HPV-negative disease. However, so far, treatment recommendations for HPV-positive and HPV-negative cases are similar since there is insufficient data indicating that treatment should be altered based on the HPV-status [4].

Nasopharyngeal carcinoma (NPC) is a relatively rare subtype of HNC in Western Europe and the United States compared to, for example, in China. EBV (Epstein-Barr virus) infection is the primary etiologic agent in the development of NPC. Other factors including smoking, genetics, but also dietary practices, are considered causative agents in the development of NPC [5].

Treatment of HNC requires a multidisciplinary approach including surgeons, medical and radiation oncologists, radiologists, nuclear medicine physicians but also dentists, speech and/or swallowing pathologists, dieticians, psychosocial

counsellors, prosthodontists and rehabilitation therapists. Consequently, treatment of HNC cancer is centralized in high-volume centres in the Netherlands.

Treatment may consist of surgery and/or radiotherapy with or without chemotherapy or biological agents (e.g. cetuximab). Single modality treatment is preferred in patients with limited disease [6]. In these patients treatment usually comprises either definitive radiotherapy or surgery followed by post-suoperative radiotherapy with or without chemotherapy in case of adverse prognostic factors for developing locoregional failure [7].

Most patients present with locally advanced disease, with either bulky primary tumours and/or lymph node metastases in the neck, in which case radiotherapy with or without chemotherapy or cetuximab is preferred [6]. In patients with locally advanced disease, radiotherapy is an important part of organ preservation strategies, particularly for laryngeal cancer [8,9].

The addition of chemotherapy to radiotherapy significantly improves overall survival. The benefit of chemoradiotherapy is confined to patients under 70 years of age [10,11]. Therefore, chemoradiotherapy has become the standard treatment in patients less than 70 years of age with locally advanced HNC.

For patients not fit enough for chemoradiotherapy, accelerated radiotherapy or radiotherapy with cetuximab are good alternatives. The addition of cetuximab to radiotherapy significantly improves locoregional control and overall survival in patients with advanced HNC [12]. In a subgroup analysis a potential increased effect was seen in patients aged under 65 years of age with a KPS (Karnofsky Performance Score) of 90-100 [13].

If patients are deemed not fit enough for either chemoradiotherapy or radiotherapy with cetuximab, then altered fractionation like hyperfractionated or accelerated radiotherapy are well recognised treatment options providing significantly higher rates of locoregional tumour control than conventionally fractionated radiotherapy [14,15].

First choice of treatment in a patient with locally advanced HNC who is young (< 70 years of age) and fit enough, however, remains chemoradiotherapy [16].

1.2 Side effects of (chemo-) radiotherapy treatment

High dose radiotherapy (with or without systemic agents) is considered a curative treatment when the tumour receives a lethal dose of radiation, while sparing the surrounding normal tissues and preserving function as much as possible. Target volumes in HNC are generally large and surrounded by various critical structures (e.g. spinal cord, optic structures, auditory structures, salivary glands, swallowing muscles and other structures important in swallowing). Although tumour cells are more sensitive to radiation than normal cells, dose to normal tissues results in a wide variety of side effects during and after radiotherapy.

In addition to early side effects of radiation treatment of the skin (erythema, desquamation, oedema), mucous membranes (mucositis, ulceration) and larynx (cough, hoarseness), there are also early effects on the salivary glands, which cause dryness of the mouth (xerostomia) and formation of sticky saliva. Moreover, radiation to the pharynx and esophagus may cause mild or severe dysphagia and the consequent need for a feeding tube. Another important acute side effect is taste disturbance characterized by a decrease in taste acuity (i.e. a decreased sensitivity or absence of taste perception) and a change in taste quality (i.e. unpleasant taste). Taste abnormalities are caused by damage to the taste buds and hyposalivation [17,18].

Late side effects can affect the skin (atrophy, telangiectasia), subcutaneous tissues (fibrosis and loss of tissue), spinal cord (L'Hermitte syndrome), optic pathways (visual deficits), auditory structures (auditory deficits), larynx (hoarseness), thyroid gland (hypothyroidism), salivary glands (xerostomia) and pharynx and esophagus (fibrosis, aspiration and swallowing dysfunction sometimes necessitating tube feeding use).

Xerostomia and swallowing dysfunction are the side effects which most affect health-related quality of life (HRQoL) in patients after treatment [19–25]. Swallowing dysfunction may result in subsequent side effects including malnutrition and aspiration with a risk of repeated pneumonia, both of which may necessitate tube feeding use, which can consequently lead to tube feeding dependence [26].

With the clinical introduction of more intensified treatment-regimens, in particular concurrent chemoradiation, the incidence of radiation-induced swallowing dysfunction has markedly increased [27–29]. Swallowing dysfunction has been

reported in 70% of patients treated with chemoradiotherapy at even 11 years after treatment [30]. The most severe form of dysphagia - tube feeding dependence - has been reported in up to 51% of patients at 2 years after treatment [31–33].

1.3 Enteral nutrition in HNC

Patients with HNC are at high risk of malnutrition due to the location and local extension of the tumour but also by the treatment itself. Therefore, careful screening of the nutritional status by a dietician prior to treatment is of major importance [34]. Almost all patients receiving (chemo-) radiotherapy need some kind of nutritional supplementation because of the toxicity of treatment which significantly impairs adequate nutritional intake [35].

The first step in nutritional supplementation is the use of high-caloric and high-protein products. A large subset of patients require additional liquid dietary supplements. And a subgroup of these patients need (temporary) additional or complete enteral feeding.

Enteral nutrition can be delivered via an orogastric tube, a nasogastric tube, or a percutaneous gastrostomy tube. The most commonly used routes in HNC are the nasogastric route and the percutaneous gastrostomy route. A nasogastric (NG) tube is a fine tube which is inserted transnasally into the stomach. A gastrostomy is placed by creating an artificial tract between the stomach and abdominal surface. This invasive method is not without risk and can have major complications that are sometimes fatal [36,37]. A gastrostomy can be placed endoscopically in a procedure known as a percutaneous endoscopic gastrostomy (PEG), or radiologically in a procedure known as a radiologically inserted gastrostomy (RIG) or percutaneous radiological gastrostomy (PRG) [38]. A gastrostomy tube placed prior to commencement of treatment and in anticipation of requirement is called a prophylactic PEG (or PRG).

Nasogastric feeding is usually considered for short-to-medium-term tube feeding (days to weeks), whereas gastrostomy tubes are used for long-term tube feeding (months to years) [39]. An NG tube is generally placed during the course of treatment when required and is thus placed reactively. A PEG can be placed reactively but also prophylactically, for example in patients that will undergo concurrent chemoradiation which is usually associated with increased toxicity, including more severe dysphagia. PEG tube placement in patients planned

for concurrent chemoradiation is still considered standard of care in many institutions, including ours.

The policy of prophylactic PEG placement in chemoradiotherapy patients is under debate [40–42]. The main question is as to whether the positive effects (less weight loss, fewer treatment interruptions and lower medical costs) [43–45] outweigh the negative effects (complications and unused PEG tubes) [36,37,41]. Additionally, there are some reports suggesting a negative effect of prophylactic PEG placement on long-term swallowing function [46–49]. It has been hypothesised that prophylactic placement of a PEG leads to earlier use, due to pain and dysgeusia, and consequent reduction in swallowing frequency, which may ultimately lead to swallowing muscle atrophy and augmentation of the severity of radiation fibrosis in the throat [46,50].

Radiation-induced dysphagia has been investigated for many years. Initial research merely focussed on the swallowing process [29]. Swallowing was found to be a complex process involving multiple muscles, cranial nerves, and other structures of the oral cavity, pharynx, larynx and esophagus [26]. Swallowing takes place in four phases: the oral preparation phase, oral phase, pharyngeal phase and esophageal phase. All phases have their own set of muscles and other structures that are needed for optimal swallowing.

The first phase of oral preparation, which is a voluntary phase, consists of grinding the food with the teeth and, by alternate contraction and relaxation of the intrinsic and extrinsic muscles of the oral tongue, mixing the food with saliva to form a food bolus. Sensory receptors in the tongue relay information to the brain stem and cortex regarding the viscosity of the bolus and the need for additional mastication [26,51].

In the second phase, the oral phase, the bolus is propelled posteriorly in the oral cavity stimulating pharyngeal pressure receptors mainly located at the base of the tongue and the roof of the mouth. The tongue can apply variable pressure to the most anterior part of the bolus depending on the thickness of the bolus. This stimulation of the pressure receptors initiates the non-voluntary pharyngeal phase [26,51].

Several important structures are involved in the smooth functioning of the third phase, the pharyngeal phase, which is the phase in which the swallowing reflex is triggered. The first structure, the velopharyngeal valve, consisting of the soft

palate and the pharyngeal walls, prevents food from entering the nose and also enables pressure to build up in the pharynx [51]. The next structure, the base of the tongue, contacts the posterior pharyngeal wall during swallowing by contraction of the glossopharyngeal muscle. The base of the tongue drives the bolus through the pharynx by also generating pressure. Tongue base retraction is an important event in propulsion of the entire bolus through the pharynx and assuring that no residue remains in the vallecula [26,51]. The role of the next important structure, the larynx, is to ensure that the bolus enters the esophagus and does not enter the airway, which would cause aspiration. This process is marked by hyolaryngeal elevation or HLE, which is caused by the retraction of the tongue base to contact the posterior pharyngeal wall. HLE is characterised by the forward and upward movement of the hyoid bone and the larynx, which, in turn, provokes the biomechanical downward movement of the epiglottis ensuring closure of the laryngeal entrance [51,52]. Meanwhile, by contraction of the pharyngeal constrictor muscles from superior to inferior, the food moves downward toward the esophagus [26]. The last event in the pharyngeal phase is initiated by the relaxation of the cricopharyngeal region or upper esophageal sphincter. This sphincter is comprised of cricoid cartilage and the cricopharyngeal muscle. In rest, the sphincter is in a state of contraction, preventing air from entering the esophagus. When a food bolus approaches, the cricopharyngeal muscle relaxes, thereby loosening the tension on the cricoid cartilage. This allows the larynx to elevate. Due to this elevation the sphincter opens and allows the food bolus to pass [51].

During the final phase, the esophageal phase, the peristalsis of the esophageal muscles results in movement of the bolus to the stomach through the muscular lower esophageal sphincter [26,51].

The duration of these phases vary, with 1-2 seconds for the oral phase, under 1 second for the pharyngeal phase and 8-10 seconds for the esophageal phase [51].

If any of the phases are disrupted somehow, a patient can experience dysphagia. Radiation-induced dysphagia in HNC patients is thought to be the result of structural, mechanical and neurological deficits due to radiation-induced fibrosis of tissues in combination with the acute side effects of radiotherapy promoting muscular disuse and atrophy [53,54].

An extensively investigated preventive measure for radiation-induced dysphagia are the so-called prophylactic swallowing exercises. These are exercises aimed

at training swallowing structures and are performed before, during and/or after treatment with radiotherapy. Examples of swallowing exercises are the Mendelsohn manoeuvre and the Shaker exercise; the first aims to strengthen the HLE and the second is used to train the muscles above and underneath the hyoid bone by sustained and repetitive head lifting [55,56]. Several randomised trials have been performed to investigate the potential benefit of these and other prophylactic swallowing exercises in the prevention of severe long-term dysphagia in HNC patients treated with (chemo-) radiation [54,57–62]. A meta-analysis of available trials has shown benefit of prophylactic swallowing exercises in HNC patients [63].

Damage by radiation to any of the anatomical structures involved in swallowing, the so-called Swallowing Organs at Risk (SWOARs), has also been the topic of extensive research. This research first focussed on identifying which SWOARs are responsible for radiation-induced dysphagia [64]. An example is the clear dose effect relationship found between the dose to the pharyngeal constrictor muscles (PCM) and the risk of swallowing dysfunction, including prolonged feeding tube use [65–74].

By identifying the relationships between radiation dose to these structures and the risk of swallowing dysfunction, primary preventive strategies can be developed. This includes reducing the dose to these SWOARs in radiotherapy treatment planning optimization, but also by using new radiation technologies which allow better normal tissue sparing, such as proton therapy [75].

1.4 Radiotherapy developments in HNC

Since the introduction of linear accelerators allowing high-energy external beam treatment and the use of CT-scans for radiotherapy treatment planning in 3D treatment planning systems (TPS), radiotherapy treatment of HNC has developed rapidly. By using CT-scanning for radiotherapy treatment planning, both target volumes and organs at risk can be contoured. And with the use of intensity-modulated radiotherapy (IMRT) over the past 20 years, and the more recently developed technique of volumetric modulated arc therapy (VMAT), considerable improvements have been made in the treatment of HNC patients. Using IMRT (and VMAT) the radiation beams can be optimized to deliver a high dose to specified target volumes, while reducing the dose to adjacent normal tissue, thus improving the conformity of the dose to the volume to be treated [76].

As IMRT allows highly conformal dose distributions to very complex shaped target volumes, accurate delineation of the target volumes and organs at risk became increasingly important. Consensus guidelines have been proposed for the delineation of organs at risk and clinical target volume (CTV) for the primary tumour and nodal areas in the neck [64,77].

Based on the results of some clinical trials, IMRT is currently considered the standard technique in HNC treatment in particular to reduce the risk of xerostomia by reducing the dose to the salivary glands, without jeopardising tumour control rate compared to older techniques, such as 2D-RT and 3D-CRT [75,78–81].

A recent advancement in HNC radiotherapy has been proton therapy. With proton therapy the dose to normal tissues can be reduced by allowing more precise dose delivery because of the unique physical properties of heavy particles. A benefit of proton therapy over standard photon therapy is that there is no exit dose beyond the target and the lateral dose distribution is sharper [82]. The sharp dose fall-off of protons can be explained by the fact that protons penetrate tissue to a variable depth, depending upon their energy, and then deposit that energy in the tissue in a sharp peak, known as a Bragg peak. By this property of proton therapy the dose to normal tissue can be reduced.

In the Netherlands, proton therapy treatment is insured care in the paediatric populations, due to superior normal tissue sparing and lower chance of secondary cancer induction [83,84]. Other standard insured indications for proton therapy are intra-ocular tumours [85] and chordomas and chondrosarcomas [86,87].

Several other indications, such as HNC, breast cancer, lung cancer and prostate cancer, are known as model-based indications. Patients with these types of cancer, who will benefit in terms of prevention of side effects, are selected for proton therapy on an individual basis by performing planning comparative studies. When comparing the photon and proton treatment plans, the chance of developing a certain complication is predicted by filling out the dose to selected organs at risk given in both treatment options in a so-called normal tissue complication probability model (NTCP) model. If the predicted chance of developing a certain side effect is significantly lower with proton therapy the patient qualifies for proton therapy treatment and treatment is reimbursed by the insurance company of the patient [88].

1.5 Normal Tissue Complication Probability

Multivariable Normal Tissue Complication Probability (NTCP) models are prediction models describing the relationship between 3D-dose distributions in organs at risk and the probability of a certain complication or side effect [89]. These models may consist of a combination of dose-volume parameters, patient-, tumour- and treatment characteristics. In addition to estimating the risk of developing certain complications and side effects, NTCP models can also be used for several other purposes such as defining dose constraints for radiotherapy treatment planning optimization. But also for the selection of the most appropriate treatment technique for individual patients [90].

Proper selection of patients for proton therapy, radiotherapy treatment planning optimization and prophylactic swallowing exercises is only possible with adequate NTCP models.

The aim of this thesis was to develop NTCP models for tube feeding use and dependence in HNC patients treated with radiotherapy with or without chemotherapy.

To this aim we first performed a literature review (Chapter 2) aimed at identifying prognostic factors for feeding tube placement, use and dependence in HNC patients treated with (chemo-) radiotherapy. These prognostic factors for tube feeding dependence were used in NTCP modelling for tube feeding dependence, which was the aim of chapter 3, 4 and 5. In Chapter 3 we developed a multivariable prediction model for feeding tube use in the acute phase and in Chapter 4 and 5 for tube feeding dependence in HNC patients treated with (chemo-) radiotherapy. Chapter 6 reports on a retrospective study we did on the feasibility of direct use of the developed NTCP model in Chapter 5 in the treatment planning system (TPS) for inverse treatment planning optimization.

1.6 Aims of this thesis

To identify prognostic variables for tube feeding placement, use during treatment and dependence after treatment by a review of literature

To develop multivariable prediction models for long-lasting tube feeding use in the acute phase of concurrent CRT **($LLTFD_{acute}$) defined as use > 6 weeks** and for **total length of feeding tube use ($TFD_{duration}$)**

To develop multivariable prediction models for tube feeding dependence at 6 months after treatment

First a baseline model in which a preselection can be made **before radiotherapy treatment planning**

Secondly an advanced model in which patients can be selected **based on the radiation dose to SWOARs**

Lastly, to test the feasibility of direct use of the NTCP model in the treatment planning system for inverse treatment planning optimization

To summarize:

Chapter 2 reports on a review on prognostic factors for feeding tube placement, feeding tube use and feeding tube dependence in HNC patients treated with primary (chemo-) radiotherapy. The aim of this chapter is to gain better knowledge about prognostic factors found to be predictive for (prolonged) use of a feeding tube in HNC patients treated with (chemo-) radiotherapy. With this knowledge, the correct prognostic factors can be incorporated in predictive modelling.

Chapter 3 presents NTCP models developed in a cohort of HNC patients treated with chemoradiotherapy for whom acute and late toxicity of treatment including tube feeding use was prospectively scored. The aim of these models is to predict which HNC patient would need a prophylactically placed PEG (e.g. would be feeding tube dependent for months to years) and other prophylactic measures or could be managed reactively with a nasogastric tube. The resulting multivariable prediction models for long-lasting tube feeding use in the acute phase of concurrent CRT ($TF_{>6\ weeks}$) defined as use > 6 weeks and for total length of feeding-tube use ($TF_{duration}$) aid in the selection of patients for prophylactic or reactive feeding tube placement.

In Chapter 4 and 5 NTCP models are presented that predict the chance for a patient to become feeding-tube dependent after treatment (at 6 months). The rationale behind the basic model without DVH parameters is that a patient can be selected for preventive measures before starting radiotherapy treatment planning

optimization. The advanced model includes DVH parameters that can be used for radiotherapy treatment planning optimization and patient selection for proton therapy.

Chapter 6 describes how the DVH parameters from the NTCP model developed in Chapter 5 can be used in the TPS for treatment planning optimization by using inverse treatment planning.

The findings of this thesis are discussed and summarized in Chapter 7. A Dutch translation of the summary is provided in Chapter 8.

1.7 References

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