CHAPTER 1

General Introduction
1.1 Introduction

Head and neck cancer (HNC) originating from the oral cavity, larynx and pharynx is responsible for about 0.83 million new cancer cases and 0.43 million cancer deaths worldwide every year. These are predominantly squamous cell carcinoma (SCC) [1,2]. Much progress has been made in the treatment of HNC in the last two decades. The introduction of chemotherapy, better understanding of human papillomavirus (HPV)-related oropharynx SCC, and multidisciplinary management, has resulted in improved overall survival (OS) rates [3–5].

Based on data from the Surveillance, Epidemiology and End Results (SEER) program and the Netherlands Cancer Registry, the 5-year OS rate for HNC patients is approximately 60%. For patients with early stage disease, the 5-year OS rate can even reach 70-90% [6]. However, 30%-50% of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) still experience treatment failures, predominantly occurring at the site of the primary tumour, followed by regional failures and distant metastases [7]. The prolonged life expectancy of HNC patients has consequently increased the number of patients with acute and late toxicity following treatment. To enable more personalised treatment approaches for HNC patients, there is a rising demand for adequate prediction of treatment failure, as well as complications [5,8–11].

Normal tissue complication probability (NTCP) models and tumour control probability (TCP) models are used for the prediction of treatment outcome, this can mean treatment-related side effects and/or tumour control. For HNSCC patients, the most common treatment-related side effects are xerostomia, dysphagia and tube feeding dependence, while the main treatment failures are local failure, regional failure, distant metastasis and death. The current NTCP models of the most frequently reported side effects and TCP models of the main treatment failures of HNSCC are mainly based on classic prognostic factors such as tumour stage, performance status, age, baseline toxicity scores, dose-volume parameters, etc. [7,10,12–15]. However, patients with similar prognostic factors may still have different outcomes. In other words, these TCP and NTCP models need to be further improved before they can be used for future personalised medicine [16].

New emerging data in the form of radiomics, also called image biomarkers (IBM), reflect
the intensity, shape and textural heterogeneity of the region of interest derived from medical images. Such imaging data has shown significant associations with survival and complications in HNSCC patients [17,18]. An important question that has remained unanswered in previous publications is about the extent to which the addition of these radiomic features improves the predictive power of models consisting only of classical prognostic factors, such as TNM staging, performance status and baseline toxicity scores.

The additional role of radiomic features in predicting radiation-induced toxicities for HNSCC patients has been explored in a thesis by LV van Dijk (UMC Groningen, 2018) and associated publications [18–20]. This thesis focused on improving the prediction of treatment failures.

The overarching aim of this thesis was to evaluate the prognostic ability of radiomic features and to test whether the performance of prediction models for different treatment failures could be improved by the addition of radiomics to the classical prognostic factors for HNSCC patients primarily treated with radiotherapy.

1.2 Candidate features

Classic prognostic factors such as clinical and biological factors have been shown to influence treatment response, and new emerging radiomics (image biomarkers) have also demonstrated their prognostic values in a series of studies [21–27]. All of them are included as candidate parameters in the analyses described within thesis.

Clinical features

Currently, clinical factors are most frequently used in routine clinical practice to estimate local control (LC), regional control (RC), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) rates of individual patients. The clinical factors can be categorised as follows: (a) tumour-related and (b) patient-related prognostic factors.

TNM classification is the most important tumour-related feature and has been used in routine clinical practice to guide treatment decision-making [8,22,28]. Generally, systemic therapy is recommended for patients with advanced TNM stage to improve tumour control. Other similar features such as tumour volume, tumour diameter and overall
stage have also frequently been reported [21,22,29,30]. Besides TNM classification, large variations in OS and LC can be found in patients with HNSCC from different tumour subsites [28]. Despite being centimeters apart, nasopharyngeal and laryngeal cancer have a higher radio-sensitivities than oral cavity and hypopharynx cancer [7,10,25,31]. In addition to tumour-related prognostic factors, patient-related features such as high alcohol intake, active smoking status, presence of co-morbidities, advanced age, poor WHO performance score, instance of weight loss and male gender all showed significant associations with worse LC, RC, DFS and OS [11,22,28,32]. These factors are currently taken into consideration when treatment decisions are made. For example, patients with a poor WHO performance score who are older than 70 years are not considered candidates for systemic treatment, while surgery is not preferred for patients with severe co-morbidities [8].

**Histopathological/molecular biological features**

Many histopathological and molecular biological markers that are associated with prognosis have been previously studied and reported. Extranodal extension (ENE) and p16 are the most important biomarkers identified for HNSCC. These have therefore been included in the AJCC 8th TNM classification to guide treatment decisions [5,8,33–35]. Additionally, the over-expression of epidermal growth factor receptor (EGFR) showed an association with a poor response to radiotherapy. Also, the concurrent use of anti-EGFR monoclonal antibody cetuximab with radiotherapy has been shown superior to radiotherapy alone, with improved survival [36]. There are many other potential biological factors, such as gene mutations related to hypoxia, intrinsic radio-sensitivity and apoptosis, that are likely to play a role in determining a patient’s radiation response. However, none have yet entered routine clinical practice [22,37].

A main concern with histopathological/molecular biological features is that the tests are not always available and feasible in the clinic. For patients treated with primary non-surgical modalities (the patient population discussed in this thesis), such as (chemo) radiotherapy, only limited pathological information is available. Furthermore, tests based on the limited biopsy specimen might not be reliable and representative for the whole tumour [22,34].

**Radiomics**
Radiomics, or IBM, refers to the comprehensive quantification of tumour phenotypes based on medical images. A wide variety of medical images is already available for diagnostic, staging and radiotherapy treatment planning purposes. Radiomic features can be extracted from these medical imaging modalities (computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) or ultrasound) without the need for additional image acquisition [38,39]. For HNSCC patients primarily treated with radiotherapy (RT) at the University Medical Centre Groningen (UMCG), a pre-treatment planning CT scan is always acquired and saved for every patient. Therefore a large dataset is available to study CT-based radiomic features. Compared with the histopathological/molecular biological features based on the limited and invasive needle biopsy specimens, radiomics is able to capture the phenotype of the whole tumour non-invasively [38]. Moreover, radiomic features are objectively calculated by using standard formulas, providing quantitative information regarding intensity, shape and textural characteristics of a region of interest. This transforms three-dimensional morphological tumor information into multi-dimensional and mineable data [16,17,40–44]. Together, the advantages of radiomic features make them very promising candidates for the prediction of patient-specific treatment outcome.

1.3 Study cohort
It is important to study prognostic factors in a well-defined patient group treated with the same modalities [12]. In this thesis, with respect to this criterion, we focused on the HNSCC patients who were primarily treated with definitive radiotherapy, which accounts for two-thirds of new HNSCC patients [45,46]. All studies in this thesis are retrospective analyses, which was composed of 707 consecutive, prospectively collected, nonsurgically treated HNSCC patients from University Medical Centre Groningen (UMCG), the Netherlands, 113 HNSCC patients from department of radiation oncology in Maastricht (MAASTRO), the Netherlands, and 289 nasopharyngeal cancer patients from Shantou University Medical College (SUMC), China with a standardised follow-up programme [47].

1.4 Outline of the thesis
The first part of this thesis (Chapter 2 and 3) focussed on improving the prediction of different prognostic endpoints with CT-based radiomic features. We tested the hypothesis that the prediction of overall survival (OS) could be improved by adding radiomic features to clinical features in Chapter 2. Furthermore, the ability to generalise the prognostic value of radiomics for different tumour types was investigated by training a model on nasopharyngeal cancer patients and externally validating this model on other HNC sub-types.

With the knowledge gained in Chapter 2, we subsequently tested the performance of radiomic features in a systematic and thorough analysis using local control (LC), regional control (RC), distant metastasis-free survival (DMFS) and disease-free survival (DFS) rate as endpoints in Chapter 3.

We expected that prognostic models including radiomic and clinical features could be used to identify patients with a high risk of treatment failures prior to treatment, and consequently could support more effective personalised treatment approaches.

The second part of this thesis (Chapter 4 and Chapter 5) focused on advanced HNSCC patients with pathological lymph nodes (N+). Instead of identifying patients who are at high risk of treatment failures, in this study we tried to estimate the failure risk of each individual pathological lymph node. If we can identify those lymph nodes with high failure risk prior to treatment, intensified radiation schedules could be applied to the specific high-failure risk node to improve nodal control without increasing the dose to normal tissue. Alternatively, pre-treatment lymph node-targeted dissection could be arranged to avoid severe post-operative complications.

Chapter 4 explored the predictive clinical and radiomic features that could be used to identify pathological lymph nodes that have a large risk of persistence or recurrence. A pre-treatment prediction model for nodal failures was developed and internally validated in Chapter 4. Before this model is introduced into the clinic, a TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) type 4 level model validation [48] would be required. Therefore, we validated the model in an external cohort of HNSCC patients from the MAASTRO clinic in Chapter 5.

The findings of this thesis are summarised and future perspectives are discussed in Chapter 6.
REFERENCES


