Summary
(English, Dutch, Indonesian)
Nasopharyngeal cancer (NPC) is sensitive to radiotherapy and chemotherapy. In literature, the reported treatment results are rather good; 5-year survival rates are around 70-80% or even higher. These results, however, are presumably only reached in high-income countries with well-equipped hospitals. Since the majority of patients with NPC are diagnosed in low- and middle-income countries, the actual survival rates for NPC are likely less positive. In Indonesia, NPC is one of the most frequently observed types of cancer with more than 15,000 people diagnosed each year. One study showed that half of the patients diagnosed with NPC in Yogyakarta died as soon as 2 years after diagnosis. It is expected that many of these patients died due to persistent or recurrent disease after treatment with curative intent, which underscores the need for improvements in treatment in Indonesia.

When NPC persists or reoccurs, treatment options are limited since full dose chemotherapy and radiotherapy were already administered. These tumors have already shown poor response to these modalities making success of a second course of the same modalities doubtful. Moreover, retreatment will be accompanied by serious side effects. If persistent or recurrent disease is detected at an early stage, it has the highest chance to cure. Nevertheless, early detection can be difficult, since tumors can mimic post-treatment scar tissue. In part I of this thesis new diagnostic tools that can detect and predict persistent or recurrent NPC are discussed. In addition, two relatively new treatment modalities for NPC, i.e. photodynamic therapy and Epstein-Barr virus targeted therapy are explored. Part II of this thesis focuses on Indonesia, aiming to reveal the reasons for the poor outcome of NPC treatment and give suggestions for improvement.

Part I: Early diagnosis of persistent and recurrent NPC, and new treatment modalities

Epstein-Barr virus (EBV) is strongly associated with NPC. Especially in the high endemic regions, EBV is consistently detected in the tumor cells of NPC. Also in the non-endemic regions, in more than half of the patients EBV is detected in NPC. It is hypothesized that EBV stimulates the oncogenic growth and modulates the tumor microenvironment, enabling tumor cells to evade the immune response, which are important features of EBV-associated tumor development. Patients with EBV positive NPC have strong and specific immunoglobulin reactivity to EBV. The quantity and diversity of this response can be measured. Also, high levels of EBV
DNA can be detected in peripheral blood and in the nasopharyngeal region. These measurements have shown to be useful in detecting new cases of NPC. In chapter 2 the benefit of these measurements after treatment is assessed. The goal was to find out if they could predict and detect persistent and recurrent disease. The results showed that at diagnosis, none of the markers could predict survival or treatment failure. When EBV DNA load in blood was high after treatment, however, a significantly increased likelihood for persistent or recurrent disease was found. Additionally the brush had a high sensitivity (90%) and specificity (98%) for local residual of recurrent disease. It was therefore concluded that the EBV- DNA load in blood and especially in the brush could be helpful to detect recurrent or persistent disease in an early stage.

Chapter 3 and chapter 4 focus on the treatment of local failures of NPC. Chapter 3 is a review and chapter 4 presents the results of photodynamic therapy for NPC. Local recurrent disease occurs in 10–30 % of the patients. Worldwide, local recurrence is more frequently seen than local persistent disease, but in Yogyakarta persistent local disease after curative intent therapy is a major problem. Different modalities can be used in the treatment of local residual disease. Interestingly, the treatment of persistent disease has better outcomes than treatment of recurrent disease. This is in contradiction to other head and neck tumors. Surgery (endoscopic or open), brachytherapy (interstitial or intracavitary), external or stereotactic beam radiotherapy, all have very good and comparable response rates. Choice should depend on the extension of disease, feasibility of the treatment, and the doctor and patient’s preferences and experience, as well as the risks of the adverse events. For the more extended tumors, choice of treatment is more difficult, because complete response rates are lower and severe side effects are commonly seen. The results of external beam re-irradiation and stereotactic radiotherapy are better than brachytherapy for T3-4 tumors.

Since persistent and residual disease is a problem in countries with limited radio therapeutic and surgical facilities, it should be understood that most of the above mentioned therapeutic modalities (radiotherapy and surgery) are not readily available and thus not realistic options. Alternatives are urgently needed. Photodynamic therapy (PDT) can be a good alternative. Photodynamic therapy is a one hit treatment. A light sensitive drug is administered intravenously, making all cells in the patient sensitive to light. Then the tumor is illuminated by special laser
light, which destroys the tumor cells. Chapter 4 presents the results of a phase II trial of PDT for local failures after treatment of NPC with a tumor depth of less than 10 mm. Twenty-one patients were treated. All patients were treated under local anesthesia. Local control for 2 years was reached in 75% of the patients and 2-year overall survival was 65%. Please note that these results are better compared to the previously presented survival rates of treatment for primary NPC. Pain was the most common side effect, and could be managed with analgesics. No treatment related deaths or other serious adverse events where seen. Moreover, during the intervention no complications were encountered. These results showed that PDT was an effective and safe treatment for persistent and recurrent local failures of NPC.

Chapter 5 is a phase I–II study, aiming to use EBV in the tumor cells as a target for the treatment of patients with recurrent or metastatic NPC. In NPC, EBV is present in a latent state and only non-immunogenic viral antigens are produced. Therefore, they are not recognized by the immune system. Besides, active immune evasion strategies are operational in the tumor microenvironment due to the EBV. Consequently, EBV tumor cells can escape elimination by the immune system effectively. In this study, EBV was triggered (by gemcitabine and valproic acid) to a lytic (more active) state wherein viral kinases are produced. Rational was that this makes EBV visible again for the immune system, and therefore trigger an immune response to eliminate the NPC tumor cells. Here besides, in the lytic state, EBV will also be susceptible for antiviral therapy. Valganciclovir, an anti-viral drug, was therefore added to the therapy for an even more effective strategy to attack NPC.

The treatment proved safe with manageable and reversible side effects. The best observed clinical response was partial response in 25% (n=2) and stable disease in 37.5% (n=3). Three patients (37.5 %) had progressive disease despite the treatment. The treatment did not show the desired clinical response, although the proof of principle was shown in some patients and no severe adverse events were encountered. To assess the clinical efficacy of the treatment, the number of patients in this study might have been too low. Additionally, the majority of the patients were heavily pretreated. They had rapid recurrent disease or even progression during previous treatments, which might reflect the aggressiveness of the tumors and resistance to chemotherapeutics. More studies are needed to analyze and optimize this potential therapy for NPC.
Part II: Nasopharyngeal cancer in Indonesia: problems and possible solutions

As stated earlier, persistent and recurrent NPC is a major problem in the treatment of NPC in Indonesia, resulting in poor survival rates. Problems are encountered at different levels in health care. Patients often come to the hospital with advanced stage disease, the start of the treatment is regularly delayed due to a lack of treatment facilities, and treatment schedules are suboptimal due to frequent interruptions.

At present, the primary treatment for locally advanced NPC is concurrent chemoradiation. Chemotherapy can be administered in most well equipped hospitals within Indonesia. Radiotherapy can be administered in several centers, but the scarcity makes this only available for a very limited number of patients. In 2015, forty-one radiation units (accelerator and cobalt) were available in Indonesia, for a population of 250 million, resulting in 0.16 units per million inhabitants. This results in the availability of radiation treatment for approximately 29,300 patients. According to the WHO, 199,940 patients should have been treated with radiotherapy for cancer. In comparison to 2008, there is an evident growth in radiation facilities, although only less than 15% of the patients could be treated in 2015. For comparison, in Europe in high-resource countries, 5.5 accelerators per million inhabitants are available, in medium-resource countries 3.5, and 2 in low resource countries. The recommended number of treatment units per population differs widely; European guidelines recommend on average 5.9 units per million inhabitants.

Chapter 6 shows that the waiting time and the overall treatment time for radiotherapy in Indonesia are long compared to international standards. The waiting time to start treatment was 3.5 months. It is inevitable that the tumor progresses during this period, making cure less likely. Standard radiotherapy consists of a total dose of 66 to 70 Gray, delivered in 33 to 35 fractions. The optimal therapy response is achieved when the total dose is administered in 45 to 47 days. Each interruption during treatment causes a prolongation of the overall radiotherapy treatment time. During the interruptions tumor cells can repopulate and prolongation will therefore influence the treatment success to a great extent. In this study the overall treatment time was 57 days, which is 10–12 days longer than recommended. The main reasons for the interruptions were the radiotherapy facilities being intermittently
operational (due to power black outs, malfunctioning radiotherapy machines or treatment planning systems and the long time before they were properly up and running again). Other reasons were the patient’s poor condition and public holidays. With radiotherapy remaining the cornerstone in the treatment of NPC, the results presented in this chapter imply that patients with NPC cannot be treated effectively in this setting.

In **chapter 7** the actual effect of a long overall treatment time on clinical outcome was investigated. One-hundred-and-forty-two patients treated with curative intent for primary NPC were included. It was expected that a prolonged treatment time was related to unfavorable clinical outcome, but results showed no correlation between overall treatment time and clinical outcome. However, it would be shortsighted to conclude that the interruptions do not affect therapy outcome for NPC. The study furthermore confirmed that problems are encountered at more levels during treatment. Therefore, the overall treatment time might not be the weakest link in the treatment.

**Chapter 8** is an observational study about young people diagnosed with NPC in Jakarta. Cancer care and clinical outcome for young patients with NPC in Jakarta was considered poor compared to international standards. In the literature, 1–4% of the young patients with NPC have distant metastasis at initial diagnosis. In this study, however, 14% of the patients presented with distant metastasis. The 5-year overall survival for patients without distant metastasis was between 16–38% in Jakarta, compared to 52–77% in the literature. These results might be caused by the late stage of presentation at the hospital, insufficient treatment (compliance) and poor follow-up. These results were comparable to the results found in the study in Yogyakarta among adults. This confirms the suggestion that these results reflect the reality for patients diagnosed with NPC in Indonesia.

Recently, healthcare has become one of the priorities of the Indonesian government. The mission is to make health care accessible for everyone. This is a very noble and fair aspiration and accomplishment would be a major achievement for Indonesia, since Indonesia has an estimated population of 253 million people, of which >10% living below the poverty line. This said, Indonesia could be a great example for other developing countries. Nevertheless, providing access to healthcare for everyone can create new problems, like an increased number of patients asking for medical
care. This problem might be reflected by the increased delay to treatment. At the beginning of our studies (2009-2013), the median waiting time for radiotherapy was 4 months, in Yogyakarta. Since 2014 the waiting time increases progressively, nowadays (2016) the planned waiting time exceeds 2 years. This might have its consequences on prognosis for patients with NPC.

An efficient healthcare system should be able to provide the appropriate treatment within a certain timeframe. Incomplete treatments, or treatments when cure is no longer possible are not useful and maybe even only do harm. Universal healthcare coverage can only become successful when the treatment capacity is in balance with the demand. The need for expansion of the treatment facilities, especially the radiotherapy capacity, is evident. However, it will take many years before Indonesia can build the capacity needed for cancer care. New innovative treatment modalities or more effective usage of the existing facilities are needed to bridge the gap in the coming years. The data presented in this thesis give insight in the actual problems in the treatment of NPC in Indonesia and give suggestions for improvement and alternative treatment modalities.