Discussion and future perspectives
Persistent and recurrent nasopharyngeal cancer (NPC) is a major problem, which is largely underestimated in literature. The majority of the patients with NPC are diagnosed in low- and middle-income countries where health care budgets are limited. Therefore, diagnostic and treatment procedures are often suboptimal. Publications about NPC and the clinical outcome after treatment in these countries in world literature are rare and thus the problem remains largely unexposed. This thesis addresses the situation in Indonesia. Possible solutions for improvements are discussed. Improvement of prognosis for NPC can be obtained at different levels in the health care system, i.e. primary, secondary and tertiary prevention. Primary prevention focuses on protection of the whole population, secondary prevention targets the patients at risk, and tertiary prevention is for the patients who are diagnosed with NPC. The focus in this thesis is on treatment of NPC.

**Optimizing treatment**

The treatment of NPC, especially in low- and middle-income countries can be optimized if healthcare facilities are expanded. Reduction of waiting lists, more radiation units, diagnostic facilities and better availability of medication are needed. In many low- and middle-income countries, only outdated equipment and techniques are used and “new” techniques, like MRI-scanning, PET-scanning and IMRT are not, or only limitedly, available. This reduces the likelihood of accurate staging and subsequently results in suboptimal treatment. Besides the expansion of facilities, also more doctors, nurses and other facilitating staff have to be trained. It is expected that the growing economy in Indonesia will, in time, enable this. Nonetheless, even if money is available, it will take a long time to accomplish these advances. In the meantime other solutions are needed.

Focusing on tertiary prevention, small and easy improvements can be made by optimizing the management of currently available facilities, doctors and other medical personnel. Proper data management is mandatory for improvement. Without data management, problems stay unexposed. More radiation hours per treatment unit can be achieved by applying radiation during holidays and after working hours, and through better maintenance of the units and enhanced compliance of patients and doctors (chapter 6). It is frequently the case that patients drop out, even before treatment has initiated. Possible reasons for patients related drop out are the long waiting lists. Patients might look for alternative (traditional) medicine, go to another
hospital or simply forget their appointment. In the worst case they have disease progression, are in a too poor medical condition or even have died. Collectively, they will not show up at the appointment. Dedicated medical assistants and nurses, who guide and follow patients closely, would be very helpful in signaling problems early on and intervening when needed. This will decrease the number of drop outs and in the cases where a patient does drop out, their reserved treatment slot can be assigned to another patient. In a good working health care system, close cooperation between the different departments is mandatory, especially in NPC where the head and neck surgery, the medical oncology, the radiology, the pathology and the radiotherapy department are involved. A weekly multidisciplinary meeting, where all patients who are diagnosed, waiting for treatment and who are in treatment will be discussed, would optimize treatment and could prevent unnecessary delay.

The Epstein-Barr virus (EBV) biomarkers, discussed in chapter 2, proved to be effective in detecting treatment failures of NPC. Especially for local recurrent disease, EBV-DNA load measurement in a nasopharyngeal brush provides a good marker. Standard usage of this marker in the post treatment period can ensure early detection of persistent and recurrent disease. Although a promising tool, the actual benefit of the brush and its advantages in addition to endoscopy and imaging still needs to be examined and validated in future studies.

Especially in Indonesia, where persistent and recurrent disease is frequently seen and almost all patients have EBV related NPC, the brush could help to optimize prognosis by detecting early recurrences or persistent disease. Small local recurrent or persistent disease can effectively be treated, as shown in chapter 3 and 4. In a future study it would be interesting to brush all patients 2-3 months after treatment and give patients with a positive brush adjuvant treatment. Since radiation and surgical options are limited, photodynamic therapy (PDT) would be a good option.

Standard adjuvant PDT after chemo-radiotherapy is also a suggestion for the improvement of NPC prognosis. In chapter 4, PDT was given to patients with proven persistent or recurrent disease. The overall survival of patients receiving adjuvant PDT after chemo-radiotherapy was better than that of newly diagnosed NPC patients in Yogyakarta (1). Although a bias exists when comparing these survival rates, these results suggest that an additional course of PDT can improve prognosis.
PDT can also be given as neo-adjuvant treatment in order to prevent or reduce tumor growth during the waiting time. Nowadays, chemotherapy is given to overcome the waiting time for radiotherapy. However, many patients who had neo-adjuvant chemotherapy are physically not strong enough to get another course of chemotherapy during concurrent chemo-radiotherapy. They can only receive radiotherapy, which is shown to be less effective than concurrent chemo-radiotherapy (2-5). PDT in a neo-adjuvant setting can be an alternative to overcome the waiting time for concurrent chemo radiotherapy, a future study should proof this benefit.

Also, other alternatives in the treatment for NPC should be explored. These treatments are needed when chemo-radiotherapy has failed, or in an attempt to overcome the waiting time before treatment. For instance, today, the molecular biology of cancer and its effects on the immune system has gained much attention in the hope of finding novel treatment modalities. Also in NPC this is a hot topic (6-9). The main approaches of novel molecular therapies in NPC are; targeting of signal transduction and angiogenesis, modulation of gene expression, and cancer immunotherapy. Although a firm number of pre-clinical studies have booked interesting success, large clinical studies on these topics are limited. A few trials with epidermal growth factor receptor inhibitors and angiogenesis inhibitors showed clinical benefit, however, serious adverse events occurred (10).

Immunotherapy can involve a broad range of strategies. Roughly, their goals can be categorized in; increased tumor antigenicity (making the tumor cells more recognizable to the immune system), increased immunological response (for a stronger and longer lasting immune response), and a decreased immune escape of tumor cells. The presence of EBV in NPC makes it a potential target for immunotherapy. One of the strategies to improve tumor antigenicity is presented and discussed in chapter 5, the EBV cytolytic virus activation therapy. In the lytic phase of EBV, more immunogenic proteins are expressed, making the tumor more susceptible for immunological elimination and susceptible for anti-viral drugs, like valganciclovir. Despite initial promising results, this phase-I/II trial did not result in a clinical breakthrough, probably due to a more complex strategy of tumor escape (11). A strategy for a more direct immune effect is the administration of or expansion of EBV-specific cytotoxic T lymphocytes (CTL). Expansion of the EBV-specific CTL in NPC has been achieved, but the lack of actual clinical effects on tumor response
means more research is needed. Hypothesized problems are that NPC tumor cells are not recognized by the CTL and that the CTL might not reach their target place (nasopharynx or place of metastatic disease) in an active state (8, 10). Currently, several clinical trials are being performed in the aim of improving the strategy of EBV specific CTL therapy in NPC (12). In immune-checkpoint blockades, one of the promising targets is the Programmed cell death pathway. Programmed death-1 (PD-1) is a cell-surface receptor that is expressed on lymphocytes. After it binds with PD-1 ligands (PD-L1) located on the cell surface of the tumor, the lymphocyte proliferation program and its effector functions are inhibited. It is assumed that in this way PD-1 plays an important role in the immune escape of tumor cells. In a “normal” immune response, this pathway prevents damage to collateral tissue during an inflammatory response. In NPC, both PD-L1 and PD-1 are highly expressed, and associations have been found between the extent of expression and the stage of disease, and the interval to recurrent disease and overall survival. This implies its role in tumor growth and supports its potential as a target in treatment (7, 13, 14). Studies with anti-PD-1 in the treatment of melanomas showed promising results (15). Currently, two anti-PD-1 agents are being studied for patients with recurrent and/or metastatic NPC, i.e.; Nivolumab and Pembrolizumab. Preliminary results of Pembrolizumab showed tumor reduction in two-thirds of the patients. Additionally, the influence of the extent to which PD-1 and PD-L1 are expressed in the tumor microenvironment on clinical outcome is studied (7, 14-17).

**Primary and secondary prevention**

Besides the above mentioned suggestions for tertiary prevention, also at the level of primary and secondary prevention improvements can be made. A first improvement can be made by increasing the awareness of the population at risk of developing NPC or cancer in general. Major shifts in awareness can be achieved, like; quit smoking, quit eating preserved/salted food (especially the ones that were soaked in formaldehyde), eat fresh fruits and vegetables, ventilate the house and wear protection if exposed to occupational hazards (18). However, these easy-appearing plans can be more challenging than expected. Take the tobacco industry for instance; in some regions they have substantial political influence, making anti-tobacco campaigns less likely to succeed. In the past decade, in many NPC-high-incidence regions, the incidence of NPC has decreased. This is thought to be
the consequence of urbanization, improved tobacco control, changes in diet and economical development (19). Therefore, not just in Indonesia, primary prevention programs should get prioritized. Not only NPC, but also other types of cancer could benefit from these prevention programs.

In secondary prevention there is also room for improvement. For example in an attempt to prevent doctor delay, awareness programs, including education of general practitioners about the prevalence, symptoms and referral procedures of NPC, can be introduced (20). Patient delay is also a problem in NPC. Patients often only seek medical help when they already have an advanced stage of the disease. In one ongoing study, interviews with patients were performed to discover the reasons for these delays. From experience we know that traditional, complementary and alternative medicine have an important place in the Indonesian society, but their actual contribution is uncertain. Hopefully, this study will shed light on this and help in understanding and subsequently preventing such patient’s delays. Another improvement in secondary prevention is screening of high-risk populations using EBV-based markers which have been proven to be effective. This has been shown repeatedly in high incidence regions. Also for Indonesia, where many people at high-risk for NPC live, these markers can help for early stage referral to the hospital. However, with all the interventions just mentioned, ethical questions also arise. For instance, the health care system already encounters problems in the available capacity. What will happen if the number of patients asking for medical needs increases further? If appropriate treatment is not available, early diagnosis may not make sense and might even harm the patient and the family.

In 2014 the Indonesian government changed the health care system. By introducing a new health care insurance system. They aim to provide national health care insurance coverage by 2018. The mission to provide health care for everyone is a very noble and fair aspiration, and accomplishment thereof would be a major achievement for Indonesia. The estimated population of Indonesia is 253 million, with >10% of the population living in poverty. Therefore, if they succeed, Indonesia could be a great example for other countries. Unfortunately, due to the increased number of patients asking for medical need, the balance with the available capacity for diagnosis and treatment will become even more strained. This misbalance is for example displayed by the increased waiting time for radiotherapy in Yogyakarta, ie. from a median of 4 month in 2009-2013 to over two years nowadays in 2016.
Breast, lung and prostate cancer care have to cope with the increasing number of patients as well. Radiotherapy is required in more than half of all patients with cancer at some stage of the treatment (21-24). In 2008, Gondhowiardjo et al. raised their concerns regarding the shortness of radiation facilities in Indonesia (25). At that time, 35 radiation units were available. Datta et al. calculated a lack of 380 radiation units in Indonesia in 2014. In 2020 this number will increase up to 474 units (22).

The problems discussed in this thesis are not specific for NPC in Indonesia. As mentioned before, the majority (>90%) of the patients with NPC are diagnosed in low- and middle-income countries (26-27). And, also in the treatment of other types of cancer it is likely that similar problems are encountered. Cancer is the leading cause of death worldwide, and the distribution of cancer mortality is gravitating towards the low- and middle-income countries (28-29). Currently, two-thirds of cancer deaths occur in these countries and this burden increases every year. Since data management is frequently poor in these regions large studies are lacking, therefore full exposure of the actual problem is hardly possible. Fortunately, recently more attention is being given to cancer care in low- and middle-income countries (21-29).
References


