Current problems and possible solutions in the treatment of nasopharyngeal carcinoma in Indonesia
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Chapter 9

Summary and Discussion
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The management of patients with Nasopharyngeal Carcinoma (NPC) in Indonesia is currently not optimal. This is, to a great extent, due to the late presentation of patients in the health care system, the limited availability and quality of radiotherapy facilities, deficient treatment protocols, and poor doctor and patient compliance. In this thesis we have presented the challenges in NPC-care in Indonesia (chapter 3) and detailed possible solutions: (1) implementation of data management (chapter 2), (2) training of General Practitioners for better awareness and knowledge of NPC for earlier recognition of the disease (chapters 4 and 5), and (3) the introduction of new treatment modalities for NPC (chapters 6, 7, and 8).

Data management (Chapter 2)

In Indonesia, where current clinical record forms and data-registration are divided among different departments, it is difficult to obtain good insight into the treatment results and follow-up history of patients. In order to improve insight into treatment results, this project started with the introduction and implementation of an online data-management system to collect necessary data for treatment analysis. This new online data-management system has been tested for quality and accuracy of clinical data. In this chapter, we have illustrated how an online clinical data management service can improve data quality in a developing country. The digital nature of our system, as well as the online availability of the data, provides fast and easy insight with adherence to treatment protocols. Therefore, we expect less loss in follow-up and increased protocol compliance for future studies. To create more efficient medical care programs and studies in developing countries, we believe that an online data system is essential.

In addition to proper data quality and better protocol compliance, the same system can serve as a tool to train and educate medical physicians, resulting in an overall improvement of treatment protocols. With this in mind, we recommend further online data systems for international training collaborations between developing and western countries regarding cancer care. To further aid this endeavour, we suggest a training course prior to departure for a developing country, by a delegation of health care workers from overseas, to analyse the treatment online and develop a custom-made training program in advance, therefore insuring more efficient training visits.

This prescribed online data system resulted in the first prospective data collection of treatment results to-date for NPC in Indonesia.

Treatment results of Nasopharyngeal Carcinoma in Indonesia (Chapter 3)

Employing the online data-system, we analysed 78 patients treated with curative intent for primary NPC. The results revealed an unfavourable outcome regarding the current treatment of NPC within the Dr. Sardjito Hospital in Yogyakarta, Indonesia. It was revealed that the cure rates were not comparable to the treatment results currently found in literature with similar treatment protocols. Internationally, the treatment of primary NPC with radiotherapy and/or concurrent chemo-radiation is reported to yield good response rates with 3-year disease-free and overall survival results of 70% and 80%. In contrast, our study in Yogyakarta exposed an initial complete response rate of only 29% within a group of 78 NPC patients.

The advanced stage of disease within the patients at presentation is probably the leading reason for this poor treatment outcome. The second factor is the limited availability of radiotherapy facilities, resulting in a long treatment delay. To overcome this negative effect of an average waiting time of 120 days, patients are now
treated with induction chemotherapy. Unfortunately, 23 (29%) of patients died before treatment response could be assessed, due to disease progression or the toxicity of the chemotherapy. The actual radiotherapy treatment delivery was another leading cause of poor treatment outcomes, with the overall treatment time appearing to be 62 days (instead of the prescribed 45) for delivering of the standard dose of 66Gy, therefore, rendering the treatment ineffective [1,2]. Reasons for this prolonged treatment time are presumably patient, doctor and hospital related. A current, on-going project focused on these factors will optimistically reveal the reasons for this prolonged treatment in more detail.

Typically, the simplest way to address the current concerns would be to establish a sufficient number of well-equipped radiotherapy facilities in Indonesia. However, given the current conditions, this would take decades. In the meantime, our goal is to assure that compliant patients with a high chance of cure are selected to receive an effective course of treatment. Early detection of NPC, new treatment regiment to overcome waiting time, a counselling system to support only those patients who have a realistic opportunity to complete the treatment, and improved maintenance for the radiotherapy facility are feasible short-term options for improving treatment outcomes in the near future.

**Knowledge of general practitioners on Nasopharyngeal carcinoma (Chapter 4 and 5)**

As previously described, earlier presentation of NPC-patients in the hospital will result in better treatment outcomes and overall survival. The knowledge and awareness of general practitioners (GPs) of NPC is crucial for patient referral to the hospital. Chapter 4 describes our methodology for testing the knowledge and awareness of GPs working within Yogyakarta. These tests revealed that GPs working in primary health care centers (PHCC) in Yogyakarta lacked sufficient knowledge on all aspects of NPC. GPs working in these PHHC are the most important providers of primary medical health care in Indonesia, therefore we enrolled these GPs in a training program to achieve earlier presentation of NPC in the treatment centers.

In chapter 5, we confirmed the results presented within Chapter 4, evaluated improvements post-training and compared the effectiveness of two different training formats: a centralized symposium versus local lectures in the PHCC. Both educational formats appeared equally effective in increased knowledge about key symptoms, in particular early-stage symptoms. In addition to raising the level of knowledge in primary health care workers, we will aim to raise public awareness about the importance of early-stage cancer recognition and how and when to consult a GP in all economic levels within Indonesian society. Similar campaigns to educate society on breast and cervical cancer have proven to be highly effective. Continued education of the local GPs and their surrounding society will ideally result in earlier detection of NPC, better treatment outcomes, and improved overall prognosis. Currently the NPC awareness program takes place in Yogyakarta, Jakarta, Surabaya and Makassar. In the future, we hope to expand this program to the rest of Indonesia.

**Development of new treatment modalities for NPC**

In Chapter 3 we demonstrated the poor prognosis rate for NPC patients in Indonesia. Most of these patients have persistent, progressive or metastatic disease after initial treatment, with limited realistic treatment options. This signifies an evident need for new treatment modalities, such as photodynamic therapy (PDT) and lytic induction chemotherapy.
Photodynamic therapy

Review: Photodynamic therapy in the therapy for recurrent/persistent nasopharyngeal cancer (Chapter 6)

Locally persistent or recurrent NPC is a recurring epidemic across Indonesia. As described in Chapter 3, 12 of the 48 NPC patients, who finished their treatment, continued to have persistent disease in the nasopharynx. In these circumstances, treatment options are limited. Re-irradiation of recurrent disease is not a realistic option to implement in a country with scarce radiotherapy facilities and the high risk of severe soft and osseous tissue damage. Surgical procedures are also complicated and require vast experience, which is not currently available.

Conversely, PDT has the potential to be a highly effective local treatment modality for recurrent or persistent nasopharyngeal cancer, without the severe side effects after re-irradiation. In this review, all reported results of PDT as an alternative treatment for NPC are summarized. Despite promising results with first generation photosensitizers, no new clinical studies have been enrolled in the past decade.

Temoporfin mediated photodynamic therapy in patients with local persistent and recurrent Nasopharyngeal Carcinoma: a feasibility study (Chapter 7)

In a feasibility study with 21 patients with locally-persistent NPC and one patient with locally-recurrent NPC, we investigated the safety and efficiency of temoporfin mediated PDT. PDT with the nasopharyngeal applicator is a relatively simple technique, which can be utilized to treat residual or recurrent NPC, restricted to the nasopharynx. The treatment is a suitable option for Indonesia because of the short waiting and treatment procedure times. Patients were treated under local anaesthesia with the use of a dedicated nasopharyngeal applicator. Three different drug doses and light intervals were administered. Overall the results are very promising; in 17 of the 22 patients a biopsy was performed 40 weeks after therapy and showed no tumor. One patient died two days after treatment due to a misdiagnosed pneumonia.

Based on our experiences and taking into account the poor treatment results currently for primary NPC in Indonesia, it is reasonable to assume that PDT can successfully be used in the future as part of the primary treatment. We hypothesize that PDT can be applied for NPC during the waiting time for radiotherapy, without compromising the options for all other possible treatment modalities. A current ongoing phase II study will hopefully confirm the effectiveness of PDT treatment for patients with locally persistent or recurrent NPC.

Cytolytic Virus Activation Therapy (Chapter 8)

NPC is causally linked to Epstein-Barr virus (EBV). In EBV positive NPC all tumour cells carry EBV. This virus is a potential target for therapy. EBV hides in a latent state and expresses only a few non-immunogenic viral proteins essential for EBV maintenance, contributing to tumour growth. We developed a cytolytic virus activation (CLVA) therapy for NPC treatment, reactivating latent EBV by epigenetic modulation, triggering immune recognition and inducing susceptibility to antiviral therapy. CLVA therapy combines gemcitabine (GCb) and valproic acid (VPA) for virus activation and tumour clearance with (val)ganciclovir (GCV) as antiviral drug to block virus replication and kill proliferating virus infected cells. The CLVA treatment was optimized and validated in NPC cell lines and subsequently tested in three Dutch patients with recurrent NPC, refractory to conventional treatment. These patients developed increased levels of viral DNA in the circulation originating from apoptotic tumour cells, witnessed stabilization of the disease, and experienced improved quality of life.
Our results in the first CLVA treated patients indicate that this therapy had a biological effect and was well tolerated.

This new virus specific therapy could open a generic approach for treatment of other EBV-associated malignancies. The effect of CLVA therapy on tumour behaviour remains to be proven in a phase I/II trial, which started in 2010 (Eudract nr: 2010-022444-20). In addition to a treatment option for other EBV-associated malignancies, it has the potential to be a valuable treatment modality during the waiting time for radiotherapy.

**Future perspectives and projects**

At present, the answer to locally advanced NPC, which is one of the most common cancers in Indonesia, is concurrent chemo-radiation. Chemotherapy can be administered in most well equipped hospitals within Indonesia, whereas radiotherapy for most patients is not a realistic option due to limited availability of radiotherapy facilities throughout the country. Although in several centres radiotherapy can be administered according to international standards, the scarcity makes this only available for a very limited number of patients. In 2008 there were 18 linear accelerators and 17 Cobalt-60 teletherapy available in Indonesia with a population of 229 million, whereas 6 machines were under commission, resulting in 0.13 accelerators per million inhabitants [3]. This is in stark contrast to Europe, where 5.5 accelerators are available per million inhabitants in high-resource countries, 3.5 in medium-resource countries, and 2 per million in low resource countries [4]. The recommended number of treatment units per population differs widely; European guidelines recommend on average 5.9 units per million inhabitants [5].

The vast lack of equipment in Indonesia results in excessive waiting lists, inadequate treatment procedures and preferential treatments for the elite. Many wealthy patients receive their treatment in hospitals abroad, resulting in an outflow of substantial health care dollars to adjacent countries such as Malaysia, Singapore, and Australia. The less fortunate individual therefore cannot receive this quality of treatment. Currently the Indonesian government offers a reimbursement for lower incomes, placing greater pressure on waiting lists. It is not unusual to wait 6 months or more before treatment. With radiotherapy remaining the cornerstone of cancer treatment today, this implies that many cancer patients, including NPC, cannot be treated effectively.

The best way to address these growing concerns would be to create sufficient radiotherapy facilities in Indonesia with well-trained staff, raise medical and public awareness, and provide proper health care insurance for all patients. The growing economy in Indonesia will expectantly, in time, enable these solutions, but in the meantime small-scale solutions can improve care for patients with NPC. For this reason, the main initiative in Yogyakarta for the coming years is to build an internationally supported cancer-training centre. By introducing health care at the international standard level, supported by committed overseas faculty, Indonesian doctors can be trained according to these international standards. This would reduce the need for higher income brackets to seek care abroad, therefore investing their money in the local and national medical systems and providing better overall heath care for the underprivileged (i.e. the "Robin Hood principle"). The minister of Health, the medical faculty, the University Hospital in Yogyakarta and foreign investors support this initiative, leading to the onset of international standards for cancer care in Indonesia.

Above and beyond the realization of an internationally supported cancer-training centre, clinical research projects must still be performed. The Dutch Cancer Society has granted two novel research projects. The first grant for a phase II study on cytolytic virus activation for NPC patients with distant metastasis or patients beyond cure. The effectiveness of lytic induction will hopefully be proven in this phase II trial. Future research will be needed in regard to other lytic inducing agents, which have even less side effects and can be taken
orally. The role of lytic induction can be a very promising research line, since we expect less side effects compared with conventional chemotherapy regimes.

The second research grant will investigate how to decrease the number of patients presenting with late stage disease. One of the objectives of this study is to evaluate the effect of the training programmes for the GPs working in the PHCCs within Indonesia. Besides expected earlier presentation of NPC patients to the ENT-specialists, the incidence and the number of unnecessary referred patients will be evaluated. Study-specific questionnaires will be developed for the assessment of the reasons for patient’s delay in consulting the GP, and this information will be used to facilitating future customized public awareness campaigns.

The studies under this research grant will additionally focus on counselling and monitoring of NPC patients. This project will start with extensive monitoring of the patients during the waiting period and the radiotherapy treatment, providing further insight into the reason patients do not return to the hospital in time, or do not return at all. As the patients start the daily radiotherapy treatment, we will evaluate their return rate. In the case of a “no show”, the patient will be questioned to find out the reason for this non-compliance. Therefore, home visits will be part of this study. To prevent unnecessary treatments in the future, this project will analyse any necessary current diagnostic system adjustments. From this analysis it can be expected that patients will be screened (again) for distant metastasis after a long waiting time before radiotherapy. By only treating patients who still have a fair chance for cure, the overall waiting time will shorten and unnecessary use of the limited resources can be prevented. The final phase of this project will combine the above-mentioned projects and will optimistically lead to a new referral protocol, improved counselling structure, and an enhanced diagnostic system.

Furthermore, EBV markers can also be used for early-stage detection in defined populations, which, in combination with doctor’s awareness, may improve more effective treatment (better treatment response at early stage). The GP education program should include referencing the availability of improved diagnostic procedures for early detection. Improved education, combined with new diagnostic tests based on EBV, could be a cheap and sensitive method for detecting NPC in Indonesia and other high incidence countries. Importantly, the decision for serological diagnostic testing or EBV-DNA based analysis has to be based on complaints and duration of complaints registered and interpreted by the GP. Our on-going research is focussed on finding the best decision process to accomplish effective early stage testing in defined NPC risk groups, being either NPC family members or patients with characteristic head and neck complaints [6].

Another important issue to remember is the lack of proper data collection on a regular basis among local physicians, causing a lack of awareness regarding their treatment failures and complications. Because of this unawareness, there is no cause for self-evaluation or improvement of current treatments, creating a greater learning curve. This issue can hopefully be addressed with a newly funded program, making it possible to implement an online data-management system in all cancer centres across Indonesia, leading to better national insight and training programs.

Additional funding will be raised to investigate the role of PDT in primary treatment of NPC. In a phase I-II trial we hope to evaluate this treatment modality for NPC patients, taking the most advantage of the prolonged waiting time for standard (chemo)-radiation in developing countries like Indonesia. Patients who receive induction PDT during the waiting period for radiotherapy have the potential to increase the state of their health and limit further tumour progression.
Reference List


