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

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Chapter 1

Introduction
Chapter 1

Scope

Cancer has become a leading cause of death and disability in many low and middle-income countries. In Southeast Asia one of the most frequently encountered malignancies is Nasopharyngeal Carcinoma (NPC). Fortunately, NPC is quite sensitive to radiotherapy, making treatment highly effective when given in a timely manner and according to proper protocols. Unfortunately, in contrast to high-income countries, the infrastructure for radiotherapy in these regions is often not optimal, whereby such effective treatment cannot always be delivered. The current literature in Indonesia addressing NPC has focused primarily on the incidence of the disease, without careful consideration toward additional clinical perspectives, such as public awareness, knowledge among health care providers, treatment results and survival rates. Advances in these specific clinical areas would allow better insight into the magnitude of the NPC epidemic in Indonesia and provide a more solid basis for the development of new diagnostic and treatment strategies. This thesis is intended to contribute to these areas.

Focus of this thesis

Since 1999, the Netherlands Cancer Institute's department of Head and Neck Surgery and Oncology has been involved in a KWF (Dutch Cancer Society) sponsored program with the Gadjah Mada University in Yogyakarta, Indonesia. The goal of this collaboration was to increase the capacity of the Head and Neck Surgery and Oncology department within the Dr Sardjito University Hospital in Yogyakarta to an international standard. After a few years into the exchange program, it became clear that essential requirements regarding pathology, radiology and radiotherapy were not sufficiently developed to achieve this.

The most striking obstacle in meeting these requirements was the lack of data management, making it impossible to evaluate treatment protocols and treatment results. Doctors, therefore, also lacked the essential feedback, resulting in the absence of a learning curve. This continued lack of data management made it further impossible to gain ground into the actual problems regarding general head and neck cancer care. Therefore, the decision was made to reduce the scope of generalized head and neck cancer to focus on the most prevalent disease encountered: NPC. By focusing on the most common head and neck malignancy in Indonesia, ranking number 4 in all cancers among males, a multi-disciplinary team of head and neck surgeons, radiation oncologists and medical oncologists could achieve optimal treatment outcomes. This choice for NPC has the added advantage that, if it turns out to be possible to develop optimal strategies for this cancer, this would provide a blueprint for the future development of similar strategies for other (head and neck) malignancies.

With these precedents in mind, this thesis will address the current pitfalls concerning care for patients with primary NPC in Indonesia, seek potential solutions, and create treatment options suitable for the specific local infrastructure in Indonesia.

Nasopharyngeal Carcinoma

NPC arises in the epithelial lining of the nasopharynx and is frequently found at the pharyngeal recess (Rosenmüller's fossa) posteromedial to the medial crura of the Eustachian tube opening in the nasopharynx[1]. The annual incidence of NPC is 1 per 100,000 with uneven distribution throughout the world. In western countries NPC is an orphan disease. In the Netherlands, for example, the incidence of NPC is 40-80 new cases a year [2,3]. In contrast, high incidences of NPC are found in South-East Asia and Northern Africa. In Indonesia,
NPC is the most frequent cancer of the head and neck; and, as mentioned above, is the fourth most common tumour occurring in males. Based on the incidence numbers of neighbouring countries, such as Malaysia, the incidence of NPC in Indonesia is estimated 6 per 100000[4]. However, this is likely to be an underestimation.

**Pathology**

The NPC cells are of squamous origin [5]. Histopathologically, NPC is divided into three types based on degree of differentiation, i.e. keratinizing squamous cell carcinoma (WHO type I) highly differentiated and characterized by epithelial growth patterns and keratin filaments, non-keratinizing squamous cell carcinoma (WHO type II) with retaining epithelial cell shape and growth pattern, and undifferentiated carcinoma (WHO type III), which does not produce keratin and lacks a distinctive growth pattern[6]. In endemic areas, undifferentiated type comprises the vast majority of NPC, while keratinized squamous cell carcinoma is less common [7].

Epstein-Barr virus (EBV) is consistently detected in patients with NPC from regions of high and low incidence. In nearly all tumour cells an EBV-encoded RNA signal has been demonstrated by in-situ hybridisation, whereas EBV-encoded RNA is absent from the adjacent normal tissue, except perhaps in a few scattered lymphoid cells[8]. The relation between the EBV and NPC is explained in more detail below.

**Risk factors for NPC**

Although genetic defects and epigenetic changes regulating the expression of various tumour suppressor genes are implicated in the pathogenesis of NPC, the most consistent risk factor in the tumour development of NPC EBV [9,10]. The undifferentiated carcinoma (WHO type III) is always associated with EBV [6]. High levels of volatile nitrosamines in preserved foods and butyrate in animal fat or dried meat, which are frequently consumed in high incidence regions and can trigger chronic EBV reactivation, have been shown to be putative co-carcinogen(s) for the development of NPC. Non-environmental risk factors include: gender, ethnicity and the family history [11-16].

**Presentation**

Patients with NPC present symptoms of the following categories: (1) presence of tumour mass in the nasopharynx leading to epistaxis, nasal obstruction and nasal discharge; (2) dysfunction of the Eustachian tube leading to (unilateral) otitis media with effusion, tinnitus and hearing loss; (3) skull base erosion and palsy of the 5th and 6th nerve leading to headache, diplopia, facial pain and numbness; and (4) neck mass; painless enlargement of the upper cervical lymph node.

Evaluation of 4,768 NPC subjects by Lee et al, summarized the symptoms at presentation as neck mass (76%), which related to cervical nodal metastases, nasal dysfunction (62%), headache (35%), diplopia (11%), facial numbness (8%), weight loss (7%) due to metastatic spread, and trismus (3%). Symptoms were found to be similar for both young and adult NPC subjects [17].

The early symptoms of NPC such as epistaxis, nasal obstruction, and hearing loss are not specific for NPC, which makes NPC difficult to diagnose at an early stage [18]. Accordingly, most newly diagnosed patients (75-90%) have loco-regionally advanced disease at presentation in the hospital and thus present with late stage disease[19,20].
Staging and diagnosis

NPC staging is based on two TNM classifications, by Ho and the AJCC/UICC classification respectively (American Joints Committee/International Union Against Cancer). Ho's classification is predominantly used in Asia as the highest incidence region, while AJCC and UICC are utilized more in USA and Europe [21]. Main differences are the nodal classification of the Ho's classification, which has incorporated prognostic significance, and the deviation of the t-stage in five sectors (see table 1).

**Table 1 | NPC staging according to Ho and AJCC**

<table>
<thead>
<tr>
<th>Tumour in the Nadopharynx (T)</th>
<th>Ho Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
<td>Tumour confined to the nasopgharynx</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>Tumour extends to soft tissues of oropharynx and/or nasal fossa</td>
</tr>
<tr>
<td>T2a</td>
<td>without parapharyngeal extension</td>
</tr>
<tr>
<td>T2b</td>
<td>with parapharyngeal extension</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>Tumour invades bony structures and/or paranasal sinuses</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Regional lymph nodes (N)</th>
<th>Regional lymph nodes (N)</th>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3a</td>
<td>greater than 6 cm in dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3b</td>
<td>extension to the supraclavicular fossa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>The American Joint Committee on Cancer Staging</th>
<th>Primary tumour (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumour confined to nasopharynx (space behind choanal orifices and nasal septum and above posterior margin of soft palate in resting position)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour extended to nasal fossa, oropharynx, or adjacent muscles or nerves below base of skull</td>
</tr>
<tr>
<td>T2a</td>
<td>without parapharyngeal extension</td>
</tr>
<tr>
<td>T2b</td>
<td>with parapharyngeal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extended beyond T2 limits and subclassified as follows:</td>
</tr>
<tr>
<td>T3a</td>
<td>Bone involvement below base of skull (floor of sphenoid sinus is included in this category)</td>
</tr>
<tr>
<td>T3b</td>
<td>Involvement of base of skull</td>
</tr>
<tr>
<td>T3c</td>
<td>Involvement of cranial nerve(s)</td>
</tr>
<tr>
<td>T3d</td>
<td>Involvement of orbits, laryngopharynx (hypopharynx), hypopharynx, or infratemporal fossa</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit</td>
</tr>
<tr>
<td>N0</td>
<td>Node palpable or thought to be benign</td>
</tr>
<tr>
<td>N1</td>
<td>Node(s) wholly in upper cervical level, bounded below by the skin crease extending laterally and backward from or just below thyroid notch (laryngeal eminence)</td>
</tr>
<tr>
<td>N2</td>
<td>Node(s) palpable between crease and supraclavicular fossa, the upper limit being a line joining the upper margin of the sternal end of the clavicle and the angle formed by the lateral surface of the neck and the superior margin of the trapezius</td>
</tr>
<tr>
<td>N3</td>
<td>Node(s) palpable in the supraclavicular fossa and/or skin involvement in the form of carcinoma en cuirasse or satellite nodules above the clavicles</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No haematogenous metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Haematogenous metastases present, and/or lymph nodal metastases below the clavicle</td>
</tr>
</tbody>
</table>
Clinical examination, with endoscopic examination, can provide valuable information about mucosal involvement and tumour extension into the nasal fossae and oropharynx. Imaging with CT scan and MRI scan give a better insight in tumour extension, skull-base erosion, or intracranial spread. Furthermore, combined (cross-sectional) imaging with MRI and CT in the treatment planning of NPC, improves the effectiveness of the radiotherapy (see below). Radiological imaging has identified para-nasopharyngeal extension as one of the most common modes of extension of NPC and has shown perineural spread through the oval foramen to be an important route of intracranial extension [22,23]. Compared with CT imaging, MRI is better for displaying both superficial and deep nasopharyngeal soft tissue invasion and for differentiating tumour from normal soft tissue. MRI is also more sensitive for assessment of retropharyngeal and deep cervical nodal metastases. Screening for distant metastasis is best achieved with positron emission tomodraphy (PET). Accordingly, the combination of PET/CT and head-and neck MRI are suggested for the initial staging of NPC patients[24]. Unfortunately, this combination is not utilized or not available in Indonesia, where only CT-imaging is used for initial loco-regional staging in combination with ultra sound and bone scans for distant metastasis screening.

**Primary treatment of Nasopharyngeal Carcinoma**

The optimal treatment modality for primary NPC is radiotherapy. Although NPC is quite sensitive to ionizing radiation, location of the tumour at the base of skull, close to the brain stem and spinal cord, requires radiation dose limitations in order to prevent radiation-induced long-term side effects.

For locally advanced NPC, the standard care is concurrent chemo-radiotherapy with cisplatin-based regimens, resulting in three-years disease-free and overall survival of 70% and 80%, respectively [25,26]. A recent meta analysis confirmed the clinical benefit of concurrent chemo- radiotherapy compared with radiation alone (RT) in the treatment of NPC in endemic areas [27].

With the introduction of intensity-modulated radiotherapy (IMRT), local and regional failure rates have declined and the biggest remaining challenge is the effective treatment of distant metastasis with occurrence
rates of 15-19% [28-31]. Besides new radiotherapy techniques, research of the Hong-Kong group also revealed improved outcomes if the staging and treatment planning is performed with MRI compared to CT-scan[29].

**Treatment of locally recurrent and persistent NPC**

Options for treatment of locally recurrent NPC are brachytherapy, external re-irradiation, stereotactic radiosurgery and (minimally invasive) nasopharyngectomy. These treatment modalities can be used either alone or in combination [32-36]. Re-irradiation is the most commonly used therapy for local recurrent NPC. Responses and new developments in technology of re-irradiation are promising, but the ‘price to pay’ is a high incidence of major late complications, such as brain tissue necrosis, cranial nerve palsies, and catastrophic haemorrhages [37-41]. Presently, locally recurrent disease re-irradiation and surgery are not feasible in Indonesia due to lack of trained personnel, proper equipment, and the absence of re-treatment time due to long waiting times for treatment of primary tumours. In persistent disease, there is limited role for re-irradiation. Locally persistent tumours after radiotherapy or chemo-radiation can sometimes be addressed surgically, either through a minimal invasive approach, or with a mandibular swing procedure [42-44]. For both surgical techniques, a well-trained surgical team and high-tech operating theatre facilities are needed. Unfortunately, both are not yet available in Indonesia.

**Photodynamic Therapy (PDT)**

PDT is an established non-invasive treatment modality for incurable head and neck cancer[45,46]. A photosensitizer is administered to the patient followed by illumination of the tumour with a specific wavelength, of 652 nM, which causes tumour destruction. Several clinical trials with first generation haematoporphrin-derived photosensitizers (HpD or Photofrin) have shown that PDT is effective in destroying NPC, with good local tumour control and complete responses in the majority of patients with limited recurrent or persistent disease, while achieving long-term palliation in cases with extensive recurrence[47-51]. Although these results were encouraging, PDT for NPC has not yet been considered as a break through in this field. The two major drawbacks of these studies were (1) the light delivery and (2) the selection of photosensitizer. First, light delivery in the nasopharynx is extremely difficult. It is almost impossible to illuminate the whole tumour area with a lens fiber, guided with endoscopes or trans-orally. This problem of proper illumination of the nasopharyngeal cavity has now been solved by the development of a special applicator, which allows one-stage illumination of the entire nasopharynx (Figure 2)[52]. The second drawback is the use of HpD/Photophrin (First generation photosensitizer). This photosensitizer has a limited depth penetration of < 5 mm and a prolonged light hypersensitivity of several months. Temoporfin (Foscan®), a second-generation photosensitizer and approved in Europe for treatment of incurable head and neck cancer, has a depth penetration of 1 cm and light hypersensitivity of only a few weeks. Research in NPC cell lines by Yow et al. confirmed that Temoporfin showed much better PDT efficiency than HpD[53]. These authors also observed significant photo destruction of the mitochondria, especially in Foscan® mediated PDT. Mitochondria are an important sub-cellular target and may play a role in cell death [54]. Temoporfin, in combination with the special designed nasopharyngeal applicator for proper illumination, has the potential to effectively treat NPC, also in the current Indonesian medical system [55].
**Treatment of metastatic NPC**

For the treatment of metastatic NPC several chemotherapeutic schedules have been tested, showing that NPC has high level of response and enduring responses [56]. The first-line treatment consists of platin-based regimens; after progression under platinis, the most frequently tested second-line drugs are gemcitabine, capecitabine or taxanes, all with acceptable results.

A recent review by Bensouda et al. showed that gemcitabine (GCb) is one of the most effective single agent therapies in NPC [57]. The largest study with 32 patients treated with GCb, after platinum-based chemotherapy failed, showed 43.8% partial response and 28.1 % stable disease with minimal side effects [58].

**Epstein Barr Virus (EBV)**

EBV is a ubiquitous human gamma herpes virus with a persistent infection ranging from 80 to 99 % of the worldwide population. Infection is via direct salivary contact. In developing countries, primary infection occurs in early infancy and is asymptomatic in most cases. In western countries primary infection is more often delayed until adolescence and then causes infectious mononucleosis in up to 25% of the cases [59].

In 1997 WHO recognized EBV as “Class 1 human carcinogenic virus.”[60]. EBV is also associated with a variety of lymphoid (Burkitt’s lymphoma, Hodgkin’s Lymphoma, Lymphoepthelioma-like carcinoma, extranodal NK/T-cell lymphoma) and gastric cancer [61].

**Epstein Barr Virus (EBV) and NPC**

In case of undifferentiated NPC there is a causative link with EBV. The relation between EBV infection and NPC is complex and, based on the observation that the presence of EBV in the tumour cells is associated with faster cell growth, less differentiation, and a higher metastasis rate of NPC, in comparison to tumours which do not contain EBV DNA [62].
EBV-markers for screening, diagnostic and monitoring

Prior studies have shown that EBV-related markers can be used for early detection (screening) and prognostic monitoring. These markers include EBV (IgA) serology and EBV-DNA load since NPC patients have characteristic elevated IgG and IgA antibody titres to several EBV encoded antigens as well as increased EBV-DNA derived from shed (apoptotic) fragments from the tumour into the circulation. Increased IgA antibody levels are found against early antigen (EA), viral capsid antigen (VCA) and the latent Epstein-Barr nuclear antigen 1 (EBNA1) as well as inhibitory antibodies to the EBV specific DNase[63,64]. These antibody responses against defined viral antigens are the basis of a proposed screening test for NPC in high risk populations[65-67]. Recent insight in the molecular basis and diversity of anti-EBV IgA and IgG responses allowed the development of more defined serological tools[68-72]. EBV DNA load in the circulation and in nasopharyngeal brushings can be used in addition as independent NPC-related EBV markers, since both have been detected in a higher proportion of NPC patients than controls[73-77]. EBV IgA serology testing especially appears to fulfill criteria as a possible screening tool in the future, since the cost is relatively low and easy to use when combined with finger-prick blood sampling [71,78]. Patients with elevated EBV-IgA serology plus defined chronic symptoms suggestive of NPC may be selected for more costly EBV-DNA testing in the nasopharyngeal brushing to make early-stage NPC diagnosis possible [79].

EBV genes

The genome of EBV is a linear double stranded DNA molecule of 172,000 base pairs and encodes for 80 proteins. In most cases of EBV malignancies the viral genome is not integrated into the cellular DNA but forms circular episomes that replicate aside the host chromosomes. The integrated form of EBV DNA is occasionally found in B cell lymphoma and especially in high grade B cell lymphoma [80].

EBV infection can be latent or lytic (figure 2). In latent infected cells only a few proteins are transcribed and the genes coding for these proteins are therefore referred as 'latent genes'[81]. These latent genes of EBV are EBNA1, EBNA2, LMP1, LMP2, EBNA3, and LP. Only EBNA1 is expressed in all latent infected cells[82]. Another group of genes, the lytic genes, are involved in viral DNA replication and formation of new virions. These genes are classified in three different types: immediate-early genes (IE genes), early genes (E genes) and late genes (L genes).

Immediate-early genes

The lytic cascade starts with activating the expression of IE genes like in all other herpes viruses. These genes are BZLF1 and BRLF1 and encode the transactivators ZEBRA (Zta) and Rta, which are responsible for activation of the other lytic phase genes. The BZLF1 gene encodes a sequence specific DNA-binding protein ZEBRA. ZEBRA can bind many ZEBRA-responsive elements (ZRE’s), which are present in the BZLF1 promoter (positive regulation) and in promoters of EBV early genes[83]. The promoter of the BZLF1 gene is called Zp (ZEBRA promoter), and this promoter is thus very important in regulating the switch from latent to lytic phase. The BZLF1 gene can also be activated by the Rta, but the main expression of the BZLF1 gene is due to activation via Zp[84]. It has been demonstrated that in some of EBV-associated malignancies, sporadic tumour cells show detectable ZEBRA expression. Since true late gene transcription in these tumour cells is mostly absent, these levels of ZEBRA expression probably reflect partial (abortive) activation of the lytic phase[85]. The other IE gene, BRLF1, encodes for the protein Rta, which acts together with ZEBRA to activate the E genes.
Early genes

The E genes are also called replication factors. These genes encode enzymes that are involved in DNA synthesis and nucleotide metabolism or interfere with the apoptosis pathway to ensure prolonged cell survival. Therefore, these proteins/enzymes encoded by these genes (like EBV-PK) can be potential targets for anti-viral drugs and are therefore important for the development of new anti-tumour therapies[86].

Late genes

After activation of both IE and E genes, the L genes are activated. These L genes are mainly structural proteins and the expression of these genes relies on new linear genomic templates. These genes do not only encode structural proteins of the virion, but also a few non-structural genes. Among the structural proteins are VCA-p18, a small capsid protein, and VCA-p40 and Gp125, nuclear membrane proteins. These proteins are strongly immunogenic in humans and serve as targets for sero-diagnosis, because almost all EBV carriers develop antibodies to these proteins. A non-structural late protein is vIL-10, which has been shown to be correlated with a poor prognosis.

![Diagram of EBV infection and gene expression phases](image)

**Figure 2** | Epstein-Barr virus infection can be latent or lytic. Both states are associated with their own profile of gene expression. The lytic state consists of 3 phases, the immediate early (IE), the early (E), and the late (L) phase.

Indonesia

Indonesia is a democratic republic, proclaimed by President Soekarno on the Declaration of Independence of Indonesia on August 17th 1945. The country is one of the largest archipelagos in the world consisting of 17,508 islands totalling 248 million inhabitants. Islam is the major religion (85.2% of the population), designating

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Indonesia as the largest Muslim country in the world. The remaining population consists of Protestants (8.9%); Catholics (3%); Hindus (1.8%); Buddhists (0.8%); and other religions (0.3%).

**Economy**

Indonesia has abundant natural resources including crude oil, natural gas, tin, copper and gold. Despite being the second largest exporter of natural gas and an abundance of crude oil, Indonesia has recently needed to import crude oil for increased consumption. The agriculture products of Indonesia include rice, tea, coffee, spices and rubber. The major trade partners of Indonesia are Japan, the United States of America and neighbouring countries Malaysia, Singapore and Australia. Despite its wealth in natural resources, the country is still facing crucial issues of poverty because of the uneven distribution of the national income.

Since the 1990s, Indonesia had experienced an improvement in socioeconomic indicators. The proportion of population living in poverty dropped. There was a setback in mid-1997 due to the Southeast Asian economic crisis, which affected the Indonesian economy the hardest in comparison with other countries in the region. The economic crisis resulted in the departure of president Soeharto, who had been in power for 31 years. Most recently the proportion of people living in poverty has further declined. In 2006, an estimated 17.8% of the population lives below the poverty line, 49.0% of the population lives on less than US$2 per day, and the unemployment rate was 9.75%. As of 2010, an estimated 13.3% of the population was living below the poverty line, and the unemployment rate was 7.1%.

**Health care system**

Health expenditure in Indonesia is 5.5 % of Gross Domestic Product (GDP). This is low compared to other countries in the region, with neighbouring Malaysia at 8% of GDP. It is comparatively worse when factored against western countries such as the Netherlands, which is currently at 10.4% of GDP. The primary health care level is generally regarded as having relatively adequate levels of provision, with an average of one public health centre for every 30 000 people. However, the quality of the health workforce, deficiencies in human resources and reportedly low productivity still remain a problem. For many decades the main health problem was related to communicable disease, whereas currently an epidemiological shift towards non-communicable diseases, cancer among them, is ranking high. According to the WHO, this will become is an increasing a major problem and an additional challenge for Indonesia. Cancer is becoming a burden in terms of cost, suffering and human lives. Unfortunately these diseases are affecting not only wealthy people but also poor people, which will reduce their ability to generate adequate income and again lead to further impoverishment. Even in cases where insurance is available for the poor, it rarely covers all expenses and frequently the entire community spends all their savings for one patient. Unfortunately, in most cases, this spending is wasted due to poor treatment results, insufficient counselling, patient’s delay, doctor’s delay and long waiting periods.
**Brief outline Thesis**

To address the major questions regarding the improvement of treatment and diagnosis of NPC in Indonesia, we performed a prospective study and a survey among GPs. The results are the fundaments of the described current problems on NPC-care in Indonesia (chapter 3 and 4). The other chapters describe possible solutions: implementation of data management (chapter 2), training of General Practitioners for better awareness and knowledge of NPC, and thus for earlier recognition of the disease (chapters 5), and the introduction of new treatment modalities for NPC to eventually improve treatment outcome (chapters 6, 7, and 8).


Data collection by Electronic Medical Record (EMR) systems has been proven to be helpful in data collection for scientific research and in improving healthcare. This study shows that the introduction of a Clinical Trial Data Management service (CTDMS) composed of electronic Case Report Forms (eCRF) results in effective data collection and treatment monitoring. The digital nature of the CTDMS, as well as the online availability of that data, gives fast and easy insight in adherence to treatment protocols. As such, the CTDMS can serve as a tool to train and educate medical doctors and can improve treatment protocols.


Treatment of primary Nasopharyngeal Carcinoma (NPC) with radiotherapy and/or concurrent chemoradiation shows good response rates, as reported in many series in the literature. We present a prospective cohort of patients with curable NPC who have been treated in 2009 till 2011. In contrast to the literature, the treatment results found in this series are very disappointing. The identification of the causes for the high rate of treatment failures will hopefully lead to a series of interventions, which will eventually lead to improvement of these results.

**Chapter 4: Knowledge of general practitioners about nasopharyngeal cancer at the Puskesmas in Yogyakarta, Indonesia** (Fles R, Wildeman MA (contributed equally), Sulistiono B, Haryana SM, Tan IB. BMC Medical Education 2010, 10:81.)

This study reveals that general practitioners (GPs) in the Primary Health Care Centres (PHCC) in Yogyakarta lack knowledge on all aspects of Nasopharyngeal Carcinoma (NPC). This is an important finding as NPC is endemic in Indonesia and the PHCC are the institutions that provide primary medical health care in the country.


This study confirms our findings from Yogyakarta regarding GPs insufficient knowledge of NPC and proves that lectures in the Primary Health Care Centre by a team of two GPs and a symposium by local head and neck surgeons have both been proven to be effective training tools in the education of GPs on NPC.
Chapter 6: Photodynamic therapy in the therapy for recurrent/persistent nasopharyngeal cancer
(Wildeman MA, Nyst HJ, Karakullukcu B, Tan BI. Head & Neck Oncology 2009, 1:40)

A review of five studies conducted in the past with Photodynamic therapy for recurrent/persistent NPC; these studies were all with first generation photo sensitizer and without a local application device tailored for optimal delivery of the laser light to the nasopharynx. Despite this, the results of these studies are very promising.

Chapter 7: Temoporfin mediated photodynamic therapy in patients with local recurrent nasopharyngeal carcinoma

A feasibility study with Temoporfin mediated PDT in 22 patients with persistent (n=21) and recurrent (n=1) Nasopharyngeal Carcinoma. This novel treatment with a special designed nasopharyngeal applicator and second-generation photo sensitizer showed no severe side effects and a good clinical response.

Chapter 8: Cytolytic virus activation therapy for Epstein-Barr virus driven tumours

Since all NPC tumour cells carry EBV, the virus itself is a potential target for therapy. In these tumour cells EBV “hides” in a latent state and expresses only few non-immunogenic viral proteins essential for EBV maintenance and contributing to tumour growth. We developed a cytolytic virus activation (CLVA) therapy, which activates virus gene expression in tumour cells by epigenetic modulation, triggering immune recognition and induces susceptibility to antiviral therapy.

Our results in the first CLVA treated patients indicate that induction therapy had a biological effect and was well tolerated. Virus specific tumour therapy will open a generic approach for treatment of multiple EBV-associated malignancies both in developed and developing countries worldwide.

Chapter 9: Summary and future perspectives

Chapter 10: Summary in Dutch

Reference List

2. Dutch Association of Comprehensive Cancer Centres, i.e. VIKC. 2012.


