Current problems and possible solutions in the treatment of nasopharyngeal carcinoma in Indonesia
Wildeman, M.A.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 7

Temoporfin mediated photodynamic therapy in patients with local persistent and recurrent Nasopharyngeal Carcinoma after curative radiotherapy: A feasibility study

H.J. Nyst,
M.A. Wildeman,
S.R. Indrasari,
B. Karakullukcu,
R.L.P. van Veen,
M. Adham,
F.A. Stewart,
P.C. Levendag,
H.J.C.M. Sterenborg,
I.B. Tan

Summary

Background

The treatment of persistent and recurrent nasopharyngeal carcinoma (NPC) remains a challenge, especially in Indonesia. We investigated the safety and efficacy of temoporfin mediated photodynamic therapy (PDT) for patients with local persistent and recurrent NPC.

Material and Methods

Twenty-two patients with persistent and recurrent NPC (maximum tumor depth <10 mm) underwent PDT under local anesthesia with use of a nasopharyngeal light applicator. Three different drug doses and light intervals have been administered: treatment arm A: 0.15 mg/kg Foscan®; 96 h drug-light interval; B: drug dose of 0.10 mg/kg; 48 h drug-light interval; C: drug dose of 0.075 mg/kg; 24 h drug-light interval. Toxicity was measured by using the CTCAE 3.1 scale.

Results

Arm A consisted of eight patients, arms B and C consisted of seven patients. The treatment procedure was well tolerable under local anesthesia. The most common grade III toxicities for all groups is headache (n = 7; 33%). No grade IV toxicity was seen. One patient died 2 days after treatment due to a misdiagnosed pneumonia. In 17 of the 22 patients a biopsy was performed after 40 weeks and showed no tumor in all biopsies. Arm A seems, in addition to comparable toxicity, clinically more effective than arms B and C.

Conclusion

The present study demonstrated that temoporfin mediated photodynamic therapy is a relatively simple technique that can be utilized to treat residual or recurrent nasopharyngeal cancer, restricted locally to the nasopharynx.
**Introduction**

Nasopharyngeal cancer (NPC) is endemic in Southern China and most of South-East Asia with a yearly incidence reaching as high as 20—50 cases per 100,000 annually [1,2].

In Indonesia NPC is the most frequent cancer in the head and neck area and is the fourth most common tumor occurring in males. The incidence is estimated 6 per 100,000, leading to at least 14,000 new cases per year [3]. Unfortunately in Indonesia the majority of patients have advanced stage disease at initial diagnosis. In a recent study, 87% of Indonesian patients had stage III—IV disease at initial diagnosis and 18% presented with distant metastasis [4].

Radiotherapy alone or combined with chemotherapy is the treatment of choice for NPC and has a relatively high cure rate [5,6]. In 1999, Lin and Jan reported a failure rate for the primary tumor in patients with T3-4N0M0 NPC of 25% [5]. In 2000, Chang et al. reported a primary tumor control rate of 50—60% after radiotherapy in patients with advanced NPC [7]. During the last decade the treatment results have significantly improved; with disease-free and overall survival results of around 70% and 80%, respectively [8,9]. These improvements are due to the advances in diagnostic imaging, increased radiation dose [10], the different regimes of fractionation, the use of IMRT [11,12], and the use of concomitant chemotherapy [6]. These success percentages cannot be achieved in developing countries mainly due to a lack of radiotherapy facilities, imaging facilities, and poor patient compliance. In Indonesia these problems cause a high percentage of local persistent or recurrent tumor after radiotherapy [4].

Options for treatment of local recurrent NPC are brachytherapy, external re-irradiation, stereotactic radiosurgery and nasopharyngectomy. These treatment modalities can be used either alone or in combination [13—16]. Despite promising local response rates; re-irradiation causes a high incidence of major late complications, such as brain necrosis, cranial nerve palsies, and catastrophic hemorrhages [17—21]. In Indonesia re-irradiation and surgery for locally recurrent disease are not feasible because of insufficient techniques, personnel, equipment, and lack of allocated re-treatment time due to already long waiting times for treatment of primary tumors. In persistent disease, there is limited role for re-irradiation.

Photodynamic therapy (PDT) using a specially designed nasopharyngeal applicator may act as an alternative treatment option since it can be performed easily and does not require expensive equipment and extensive training of physicians and the medical staff.

PDT is a method that involves injection of a systemic photosensitizing drug that can be activated at the tumor site to produce reactive oxygen species, starting a cascade of oxidization of biomolecules and eventually causing tumor destruction. PDT has already been shown to be an effective modality for treatment of superficial lesions in previously irradiated sites [22—25].

PDT has been studied in the past to treat locally recurrent/persistent NPC. The results from studies with first generation photosensitizers like hematoporphyrin and without a nasopharyngeal applicator for proper illumination, although quite promising, did not lead to established protocols for PDT for NPC [26]. Temoporfin mediated photodynamic therapy (PDT) is a registered treatment in Europe for incurable head and neck cancer [22,24]. Temoporfin mediated PDT in combination with a specially designed nasopharyngeal applicator for proper illumination of the nasopharyngeal cavity might be a suitable therapy for local persistent or recurrent NPC, especially in developing countries where advanced radiotherapy options are limited [27].
Yow et al. has shown in nasopharyngeal cancer cell lines that the uptake of second generation photosensitizer temoporfin is higher and the photodynamic reactions are more efficient compared with hematoporphyrin [28]. Since there are no data reported in the literature on temoporfin mediated PDT in NPC, we planned a study to investigate the feasibility of three different treatment regimens to be able to select one of these treatment regimes and conduct a phase II trial.

**Methods**

**Patients**

Eligible patients were aged 18 years or older with pathologically proven locally recurrent or residual nasopharyngeal carcinoma (type I, II or III), a discrete tumor ≤10 mm in depth measured by CT imaging (surface illumination with temoporfin has an effective penetration of 10 mm), which is endoscopically visible and accessible for unrestricted surface illumination using a nasopharyngeal applicator. Other eligibility criteria included a Karnofsky performance status of at least 70%. Local ethics committee approval was obtained for the study, and each patient gave written informed consent. All patients had previously been treated with in onset curative radiotherapy for their primary NPC.

Exclusion criteria were any disease which is caused or exacerbated by light and treatment within the prior 30 days with a light-activated therapy. Patients with distant metastasis and lymph-node involvement were also excluded from the study protocol.

**Treatment regimes**

Three treatment regimes were investigated to select the most safe and efficacious treatment scheme. Besides the standard dose for Head and neck tumors of 0.15 mg/kg, two lower drug doses were evaluated. The possible loss in effectiveness by reducing the drug dose was compensated by reducing the drug-light interval. The lower drug doses were evaluated to see if these would give less side effects and lower the costs with the same effectiveness. Any grade IV and V adverse event (according to CTC 3.1) was considered as SAE (serious adverse event). In case of two SAE from one dose group these parameters were considered too toxic.

**Arm A**: Eight patients received the dose level and the drug light interval that are recommended for the treatment of patients with squamous cell carcinoma of the head and neck. These parameters are drug dose: 0.15 mg/kg Foscan®; drug-light interval: 96 h; light dose: 20 J/cm².

**Arm B**: 7 patients were treated at a drug dose of 0.10 mg/kg and a drug-light interval of 48 h.

**Arm C**: 7 patients were treated at a drug dose of 0.075 mg/kg and a drug-light interval of 24 h.

**Drug administration**

A dose of 0.15 mg, 0.10 mg or 0.075 mg of Foscan® per kilogram of body weight was administered by slow intravenous injection into a proximal deep vein in at least 6 min, according to the producers instructions. Patients remained in a light-restricted room for 24 h after administration of temoporfin and then made a gradual return, with an increase of 100 lx per day, to unrestricted indoor light exposure over a period of 2 weeks. Guidelines for light exposure and a lux-meter to monitor light exposure were given to the patients, and treating physicians advised both patients and their families and friends about the importance of complying with a gradual return to normal light exposure. A booklet was also available for the patient to optimize adherence to these guidelines.
**Laser Illumination**

To ensure homogeneous light administration to the entire nasopharynx, a specially designed nasal light applicator (Rotterdam Nasopharyngeal Light Applicator; type 625, Wacker Chemie, Krommenie, The Netherlands) was used [27] (Fig. 1). The inner diameter of the silicon tubing can accommodate two linear light diffusers for light delivery and dosimetry.

After decongestion (R/xylometazoline hydrochloride 1%) and topical anesthesia, the applicator was introduced into the nasopharynx transorally over 2 guiding tubes (four French). By using a small silicone flange, the applicator remains fixed in a stable position during illumination.

The surface of the tumor was illuminated with 652 nm light, emitted from a 6-W Applied Optronics diode laser, inserted into one channel catheter [27]. The length of the diffuser is 5 cm, and the diameter of the catheter is 0.4 cm. The light dose administered was 20 J/cm at a fluence rate of 100 mW/cm. The total illumination time is 400 s for 2 diffusers.

**Study Assessments**

Following treatment with PDT, patients were evaluated on day 1 and 2, and week 1, 2, 4, 6, 8, 12 and 16 post PDT. Patients subsequently entered a followup phase, with visits every 4 weeks up to 40 weeks post-PDT. Thereafter, they were followed annually until death or lost to follow-up. The following assessments were performed to evaluate safety: physical examination including vital signs, Karnofsky performance status and weight, recording of adverse events according to CTCAE 3.1, concomitant medication (in particular use of analgesics).

The tumor response was monitored with endoscopic examination of the nasopharynx and biopsies of the nasopharynx. Overall survival was calculated from the time of illumination to death.

**Table 1 | Patient characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n = 8) mean (range)</th>
<th>Arm B (n = 7)</th>
<th>Arm C (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 (19–68)</td>
<td>53 (45–61)</td>
<td>41 (43–57)</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/2</td>
<td>5/2</td>
<td>2/5</td>
</tr>
<tr>
<td>Persistent/ recurrent</td>
<td>8/0</td>
<td>6/1</td>
<td>7/0</td>
</tr>
</tbody>
</table>
In case of a partial response or recurrence, based on endoscopic examination and if pathologically proven, the patient was eligible for re-treatment with PDT.

**Results**

**Patient characteristics**

Most patients had pathologically proven residual NPC. Only one patient had recurrent disease. Tumor evaluation after the initial treatment, 12 weeks after finishing radiotherapy treatment, showed in the cases with persistent disease tumor in the nasopharynx and were included in this study. The patient with disease recurrence had, during regular follow up, a visible mass at endoscopy which after evaluation showed to be a local recurrence and was included. Tumor size was measured by CT-scan and all patients had a discrete tumor depth of 1 cm or less (Table 1).

**Safety/adverse events/tolerability**

All included patients were able to complete the treatment procedure. The treatment procedure was well tolerable under local anesthesia. There were no short term adverse events.

All grade I—IV adverse events scored, until 16 weeks after treatment, are presented in Table 2. All possible adverse events were scored but only the post treatment adverse events are presented in Table 2.

Three of eight patients in arm A had grade III toxicities for headache; no grade IV toxicity was seen in arm A. One patient in arm A died due to pneumonia 2 days after illumination of the tumor. This is considered a grade V adverse event. A chest X-ray prior to the treatment already showed pneumonia but this was misinterpreted by the radiologist and despite fever the patient was enrolled in the study.

In arm B two grade III toxicities were seen in three of seven patients; one patient had a grade III headache, one patient had a grade III tinnitus. There were no grade IV toxicities seen.

Arm C had a total of four grade III toxicities in three of the seven patients. Three patients had a grade III headache; one of these patients already suffered a grade II headache before treatment. One patient had a grade III musculoskeletal myositis of the neck muscles causing a grade III headache. There were no grade IV toxicities seen. One patient arm C started with a cranial neuropathy grade III that completely resolved one week after treatment.

The most common grade III toxicities for all groups is headache (n = 7; 33%). None of the patients had skin burns or other skin adverse reaction caused by the photosensitizer.
Table 2 | All grade I—IV adverse events till 16 weeks post treatment for all patients; *one patient died due to pneumonia 2 days after illumination of the tumor and is considered a grade V adverse event, despite a chest X ray before treatment already showed pneumonia but was misinterpreted by the radiologist.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Arm A ($n = 8$)*</th>
<th>Arm B ($n = 7$)</th>
<th>Arm C ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I</td>
<td>Grade II</td>
<td>Grade III</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Xerostomie</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Orbital damage</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal/ myositis neck</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genealized muscle weakness</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Otitis external Ear</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders; effusion of the middle ear</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trismus</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiation recall reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis/ pharyngitis</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>35</td>
<td>3</td>
</tr>
</tbody>
</table>
Clinical results

In 17 of the 22 patients a biopsy was performed after 40 weeks and showed no tumor in all 17 biopsies. The patients who did not receive a biopsy after 40 weeks already died \( (n = 3) \) or the biopsy could not be performed because the patient did not show up \( (n = 1) \) or was postponed \( (n = 1) \) because of the big earthquake in 2006 and the patient died before the biopsy could be performed [30].

In arm A one of eight patients died. One patient was lost to follow up but at his last visit, 32 months after treatment, he had no complaints and no signs of disease progression. In arm B six of seven patients died, three related to disease, one with unknown reason and two not related to the tumor. In arm C three out of seven patients died, all related to disease and four patients are still alive without any sign of disease.

Survival for all patients is shown in Figs. 2 and 3. With a mean follow up of 37.8 months (range: 2 days to 71 months), 10 patients are alive; two of them had a local recurrence and were successfully re-treated with PDT.

In total 10 patients died, two not related to disease or treatment, one of unknown cause, one treatment related and six related to disease. The 10 patients who are still alive have a mean follow up of 58 months (min 37 to max 71 months).

![Figure 2](image) | Disease specific survival.
Discussion

The present study demonstrated that temoporfin mediated photodynamic therapy is a relatively simple technique that can be utilized to treat residual nasopharyngeal cancer, restricted locally to the nasopharynx. All patients tolerated PDT under local anesthesia in an outpatient clinic setting. Since this procedure takes less than half an hour, it has a significant advantage over other treatment options, which require extensive setups and experienced personnel. The treating physician can administer the PDT alone or with minimal nursing support. Furthermore PDT is a one-time treatment which makes patient compliance to treatment a non-issue, unlike re-radiation where the patient has to show up for multiple radiation sessions. In Indonesia it is frequently observed that patients do not comply with the radiation treatment schedules. Moreover, there is already a long waiting time for radiation treatment even for primary tumors. The same advantage applies over nasopharyngectomy approaches which require a time consuming specified surgical expertise, operating room facilities, time and a longstanding postoperative recovery.

Although this feasibility study is encouraging it is too early to talk about clinical efficacy, which needs to be demonstrated in a larger phase II trial. Considerable data is available over temoporfin mediated PDT of head and neck cancers [22—25]. However, this was not previously tested on NPC, which has a very different biological behavior than squamous cell cancers of the head and neck. The undifferentiated histological subtype, NPC WHO III, is the most prevalent NPC type in South-East Asia and Indonesia. This type of cancer is causally associated with the Epstein—Barr virus (EBV) [31]. Therefore we have compared the standard treatment regimen with two other regimens, which are in theory less toxic, to be able to select a regimen for a phase II trial. Regarding toxicity, there was no significant difference between the treatment groups. The adverse events are mostly local and could be disease related, as well as treatment-related. The most common grade III adverse events was headache. The headache seen in the patients can be caused by irritation of the deep neck muscles by PDT, since the prevertebral muscles are close to the nasopharynx and headache symptoms were

Figure 3 | Overall survival.
accompanied by stiff neck feelings. The complaints of headache all disappeared eventually and irreversible
damage of the prevertebral muscles is not likely since surface illumination has a penetration depth of 1 cm.
The effusion of the middle ear, seen in 16 patients, was caused by massive edema of the nasopharynx after
illumination, which caused occlusion of the Eustachian tube; around 6—8 weeks after illumination the edema
disappeared and the effusion resolved. The death of one patient two days after treatment was probably
caused by a missed pneumonia, which the patient already had before the injection of temoprofin.

Arm A seems, in addition to comparable toxicity, clinically more effective than arms B and C. Although clinical
complete responses can also be observed in arms B and C, arm A seems to have a better overall survival and
disease specific survival, but the numbers are too small to draw this conclusion. Except for the patient lost
to pneumonia, all the patients in arm A are alive and disease free. Arms B and C both have three mortalities
due to disease progression. At 40 weeks the biopsies taken from the nasopharynx did not show viable tumor
cells. This suggests that all three treatment regimens are effective on the nasopharyngeal surface, but arms B
and C might be less penetrating than arm A and missing deeper tumor tissues. The difference in effectiveness
could be due to concentration of the photosensitizer. Lower doses of temoprofin might not provide sufficient
concentration in the tumor tissues. Because the depth of the tumor receives a lower light fluence than the
surface, the amount of activated photosensitizer might not be sufficient to cause cellular damage at certain
deeps. Whereas with higher concentrations, even though the activation percentage remains the same, the
absolute amount of activated photosensitizer could be higher. Another consideration is the location of the
photosensitizer in the tissues. Earlier research suggests that the maximal tumor intracellular concentration
is reached 4 days after temoporfin injection and in shorter time points, temoporfin is located more in blood
vessels [32]. Therefore in arms B and C the treatment effect could be necrosis due to vascular shutdown and
in arm A more apoptosis due to intracellular damage. This could explain the better long-term disease control.

Whatever the reason might be, treatment arm A has a longer overall survival and disease-free survival with
comparable toxicity/adverse events. Therefore this regimen is chosen to conduct the ongoing phase II study.
Once this study is concluded we will be able to determine and compare the clinical efficacy of PDT in patients
with small local residual/ recurrent NPC.

Based on our experiences so far it is not illogical to assume that temoporfin mediated PDT can also successfully
be used in the future as primary treatment modality for superficially growing NPC, with still the availability of
all other treatments and PDT for retreatment of small recurrences.

Conclusion

PDT could be a very suitable/attractive option for treatment of NPC, in terms of short waiting time, short
procedure time which can be conducted under local anesthesia in the outpatient clinic; a simple procedure
that can be learned and carried out easily by medical personnel.

Acknowledgements

The authors would like to thank Winrich Rauschning for helping with the study design. This project was
supported by Biolitec Pharma Ltd., Dublin, Ireland.
References


