New insights into photodynamic therapy of the head and neck
Karakullukçu, Bar

Citation for published version (APA):
Karakullukçu, M. B. (2014). New insights into photodynamic therapy of the head and neck

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

mTHPC Mediated Interstitial Photodynamic Therapy of Recurrent Non-Metastatic Base of Tongue Cancers: Development of a New Method


Baris Karakullukcu,
Heike J. Nyst,
Robert L. van Veen,
Frank J.P. Hoebers,
Olga Hamming-Vrieze,
Max J.H. Witjes,
Sebastiaan A.H.J. de Visscher,
Fred R Burlage,
Peter C. Levendag,
Henricus J.C.M. Sterenborg,
I. Bing Tan.
ABSTRACT

BACKGROUND

Interstitial Photodynamic therapy (iPDT) can be an option in the management of locally recurrent base of tongue cancer after (chemo)radiation treatment. The current study aims to develop a technique to implant light sources into the tumor tissue.

METHODS

Twenty patients with previously radiated locally recurrent base of tongue cancers, who were not candidates for salvage surgery or re-radiation or who refused these therapies were included. The treatment planning was done on MRI. The light sources were implanted using modified brachytherapy techniques.

RESULTS

iPDT could be conducted in all patients without short term complications. At 6 months 9 patients had complete response with 4 patients still free of disease (46-80 months). Long term complications included pharyngocutaneous fistula in 6, serious bleeding in 1, and cutaneous metastasis in 2 patients.

CONCLUSION

The initial results are encouraging. There is room for improvement to control the destructive potential of iPDT through planning and monitoring tools.
1. INTRODUCTION

Squamous cell carcinoma (SCC) of the tongue is the most common malignancy of the head and neck region [1]. Base of tongue malignancies comprise 4-5% of all head and neck cancers [2]. Overall, disease-specific survival of SCC of the base of tongue is about 40% at 5 years, and 29% at 10 years [2]. Higher stage is associated with decreased survival [2].

There has been no significant improvement in survival for several decades for the advanced stages of head and neck carcinomas [3,4]. Around 50% of patients with locally advanced SCC develop loco-regional or distant recurrence, usually detected within the first 2 years of treatment. Recurrent and second primary tongue tumours frequently arise in previously irradiated fields [5,6].

Literature reporting outcomes for patients with persistent, recurrent, and second primary carcinoma of the base of tongue is sparse. Published series often combine base of tongue carcinoma with other oropharyngeal or head and neck tumours.

For the patients with potentially resectable loco-regional recurrence, salvage surgery is the treatment of choice. However, for many patients surgical salvage is very difficult or carries a high risk of complications due to fibrosis generated from previous treatment or tumour invasion into vital structures [7]. Barry et al. demonstrated crude local control rates of 57% for total glossectomy as a salvage strategy in 60 patients with persistent/recurrent base of tongue carcinoma [8]. Complications after salvage surgery are common. Prior irradiation impairs wound healing and predisposes to flap failure, infection, and fistulae. Many patients refuse the morbidity associated with this type of surgery.

The use of re-irradiation as a salvage strategy in this subset of patients is complicated by the need for high curative doses of radiation (60-70 Gy) to be delivered to small treatment volumes while avoiding serious morbidity [5,6]. Conventional external beam irradiation is possible but is characterised by poor outcomes and severe side effects [5,9]. Brachytherapy and intensity-modulated radiation therapy (IMRT) attenuates some of the side effects seen with external beam radiation [5,6,10-12]. For recurrent and second primary base of tongue carcinoma salvaged with brachytherapy, crude local control rates vary between 41% and 64%, and 3-year survival rate is 5-19% [5,6,10,11]. Re-irradiation with IMRT of head and neck tumors report a better 5-year survival of 29% [12].

There is a substantial group of patients who cannot receive either salvage surgery (not resectable tumour or co-morbidities preventing a comprehensive surgery) or re-radiation (too short time interval after primary radiation, already existing radiotoxicity). Salvage chemotherapy has been shown to have only a limited curative role in recurrent head and
Interstitial PDT of recurrent tongue cancer [13]. The toxicity of chemotherapy can limit its value as a palliative therapeutic option, particularly in patients where performance status is compromised after previous treatment.

This creates a serious need for new treatment alternatives. Photodynamic therapy (PDT) is a method that involves injection of a systemic photosensitizing drug which can be activated at the tumour site to produce reactive oxygen species, starting a cascade of oxidation of biomolecules and eventually causing tumour destruction. PDT has already been shown to be an effective modality for treatment of superficial lesions in previously irradiated sites [14-17]. Based on the data, recently, meta-tetrahydroxyphenylchlorin (mTHPC, temoporfin; Foscan®, Biolitec Pharma, Edinburgh, Scotland)-mediated PDT has been approved by European Medicine Agency (EMEA) as a treatment method of recurrent head and neck tumours. One of the main limitations of PDT for larger tumours is the penetration of light in tissues. Clinical benefit is only achieved in tumours that can be completely illuminated [17]. mTHPC has an activation wavelength of 652 nm which penetrates around 10 mm in tissues (depending on the optical properties of the tissues). Interstitial Photodynamic Therapy (iPDT), which is a method of implanting the light source in the tumour, can potentially overcome this restraint. Multiple fibres can be inserted directly into the tumour under image guidance and large volumes of tumour can be destroyed in sites that are inaccessible to surgery or where re-irradiation and surgery would cause damage to vital adjacent structures. There are studies showing promising results with ultrasound guided interstitial photodynamic therapy of head and neck tumours [18-20]. We have elected to carry out a Phase I/II study of iPDT, which incorporates brachytherapy techniques. The main aim of the study is to evaluate the safety and feasibility of iPDT for treatment of non-metastatic recurrent base of tongue carcinomas. The setup of the study was dynamic with the treatment method evolving with experience and new technical developments.

2. MATERIALS AND METHODS

2.1. PATIENTS

The study is conducted in three centers between 1993 and 2010: Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, University Medical Center Groningen, Erasmus University Medical Center. The target population was patients with non-metastatic recurrent squamous cell carcinomas of the base of tongue after (chemo)radiotherapy. All patients were evaluated by the multidisciplinary tumour board and considered for eligibility for salvage surgery and/or re-irradiation treatment. The patients ineligible for salvage surgery and/or re-irradiation, were offered to take part in the study. Additionally patients who
declined total glossectomy as a salvage procedure were also offered iPDT as an alternative to palliative care. The experimental nature of the iPDT was thoroughly explained to the patients and informed consent was obtained. The study was reviewed and approved by institutional protocol review board.

2.2. WORK–UP AND PLANNING

The diagnosis of recurrent base of tongue squamous cell carcinoma was established by tissue biopsy obtained under general anaesthesia. In addition to obtaining tissue samples examination under general anaesthesia gave us the chance of evaluating the dimensions of the tumour and technical feasibility of placing catheters to perform iPDT. All patients received magnetic resonance imaging (MRI) to assess the extent of tumour and estimate the number and length of light sources needed to ensure full light coverage (Figure 1).

Figure 1. MRI images are helpful to delineate the gross tumor volume (GTV) and plan the number and location of light sources necessary to treat. a) The GTV is delineated. b) The number, location and length of light sources are planned marked on the images. c) The simulation of the planning is done with placing 8 mm radius light cylinders around the planned light sources to ensure theoretical full coverage of the GTV. With this approach the light sources are approximately at 15 mm distance to each other.
For the 5 most recent iPDT procedures we have used a customized version of a brachytherapy planning program (Oncentra, Nucletron, Netherlands) to delineate the gross tumor volume (GTV) and plan and simulate the illumination. This technique is still in development and will be described in detail in future publications. A safety margin of 5 mm beyond the GTV was taken into account when planning the treatment. The light sources are planned maximum 15 mm distant to each other to ensure full coverage of the tumour. Earlier planning was done on the MRI images as estimations without simulations.

The patients were informed about light avoidance measures by a specialized nurse and provided with written material, protective clothing and a lux-meter to measure ambient light.

Regional disease was evaluated with ultrasound of the neck and fine needle aspiration biopsy as indicated. If nodal disease was detected, patients were managed by selective neck dissection before the iPDT procedure. Patients with distant metastasis or inoperable regional disease were not treated with iPDT.

2.3. IPDT PROCEDURE

mTHPC (4mg/ml, 5 ml flacon) was administered to a proximal arm vein with slow injection, at a dose of 0.15 mg /kg. The injection procedure is in compliance with the recommendations of the producer. mTHPC cannot be administered as an infusion and has to be administered slowly over a minimum time frame of 6 minutes. The injection procedure is performed in an outpatient setting. Light avoidance measures are employed immediately after the injection. The patients were discharged home after the injection. Four days later the patients were admitted for the iPDT. All procedures were carried out under general anaesthesia. Due to expected oedema after iPDT post-operatively, the airway patency was managed with elective tracheotomy. Before percutaneous insertion of the light sources, the skin was disinfected with alcohol. Hollow brachytherapy needles (ProGuide needle 6F, sharp, 200 mm, Nucletron, Netherlands) were inserted via the submental skin, through the base of tongue into the oropharynx. Guidewires were introduced through the needle and retrieved from the oral cavity (Figure 2a). Transparent flexible brachytherapy catheters (Flexible Implant Tube, 6F, Single leader, 50cm, Nucletron, Netherlands) were attached to the guidewires and pulled through the needles from the oropharynx to the skin. The insertion needles were removed. The catheters were secured in place by color-coded rubber beads (Figure 2b). The correct placement and length of the catheters were checked by introducing optically coded radiodense dummy afterloaders in the catheters and imaging with 2D C-bow X-Ray (Figure 2c). These images were used to verify the inter spacing of the implants and to determine the length of each individual light source (figure 2d). The light source diffusers are available at different light diffusing lengths: 1,2,3,4,5, and 6 cm. The length of the diffusing portion
can further be adjusted by applying a black tube over the diffuser. Additional catheters were introduced as necessary. The noninvolved mucosal surfaces of the pharynx and oral cavity were shielded from treatment light by placing pliable black wax over these surfaces. The skin side was not shielded. Each catheter was then filled with a corresponding linear diffuser (Ceram Optec, Bonn, Germany), after which light was delivered at 100mW cm\(^{-1}\) for 300 seconds (30 J cm\(^{-1}\)) (Figure 3). The linear diffusers were connected to a single port or four-port 652 nm 2W diode laser (Ceralas PDT, Biolitec, Germany) that was used as the light source. After sequentially illuminating all locations, the catheters were removed. To ensure post-operative feeding nasogastric feeding tubes were introduced.

2.4. POST-OPERATIVE CARE

Postoperatively the patients were kept hospitalized until post-operative pain was under control. Most of the patients were discharged with tracheotomy and nasogastric tube in place. Arrangements were done to provide home-healthcare for tracheotomy and tube feeding management. If the home conditions were not favourable the patients were discharged to nursing homes.

Figure 2. The treatment catheters are placed under general anesthesia. a) Hollow brachytherapy needles (ProGuide needle 6F, sharp, 200 mm, Nucletron, Netherlands) are inserted via the submental skin, through the base of tongue into the oropharynx. Guidewires are introduced through the needle and retrieved from the oral cavity. Transparent flexible brachytherapy catheters (Flexible Implant Tube, 6F, Single leader, 50cm, Nucletron, Netherlands) are attached to the guidewires and pulled through the needles from the oropharynx to the skin. b) The catheters are secured in place by color-coded rubber beads. c) The correct placement and length of the catheters are checked by introducing optically coded radiodense dummy afterloaders in the catheters and imaging with 2D C-bow X-Ray. d) X-Ray images are used to verify the inter spacing of the implants and to determine the length of each individual light source. Each marking on the dummy afterloader corresponds to one centimeter. The light source diffusers are available at different light diffusing lengths: 1, 2, 3, 4, 5, and 6 cm. The length of the diffusing portion can further be adjusted by applying a black tube over the diffuser.
Figure 3. Linear light diffusers (Ceram Optec, Bonn, Germany) of pre-planned lengths are loaded in the catheters and sequentially turned on to deliver 652 nm light, 100 mW cm\(^{-1}\) for 300 seconds (30 J cm\(^{-1}\)). The mucosal surface of the pharynx and oral cavity is protected from treatment light by black shielding wax.

2.5. ASSESSMENT AND FOLLOW UP

The patients were followed every two weeks for the first 2 months and thereafter every month until the time of death. An MRI was obtained after 3 months and 6 months and compared to the pre-treatment MRI. RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria were used to evaluate tumor response. Complications, management of complications, tube feeding and time to closure of tracheotomy were noted. Progression free interval and overall survival were evaluated with Kaplan-Meier method.

3. RESULTS

3.1. PATIENT CHARACTERISTICS

Between 2003 and 2010 a total of 20 patients with recurrent SCC of the tongue were treated with salvage iPDT. Thirteen patients were men, and 7 were women, and their median age was 64 years (range 55-93). Fourteen patients were considered inoperable; six patients refused salvage total glossectomy. All the patients had received prior radiotherapy, either alone or adjuvant to surgery or combined with concomitant chemotherapy. Prior therapies to the head and neck region are summarized in Table 1. The tumors were not tested for HPV positivity. No patients were lost to follow-up.
3.2. TUMOUR RESPONSE

At the three month response evaluation point, judging clinical response proved to be difficult. The way the tumour responded to iPDT was with necrosis. When measured with RECIST criteria there was progression. At 6 months after the treatment it was observed that the necrotic portions of the tumour had disappeared in 14 patients, creating tissue defects (figure 4) (in 6 patients through and through defects from the oropharynx to the submental area). Therefore the 3-month tumour evaluation was abandoned after the initial 5 patients and the 6-month evaluation was recorded as tumour response.

![Image](image.png)

**Figure 4.** The volume treated with iPDT becomes necrotic 4-16 weeks after the procedure. In this case the necrotic tissue at the base of tongue is visible at 12 weeks after the iPDT. The necrotic tissue can be removed with a resulting tissue defect. The patient illustrated here, refused surgical options and opted for iPDT. There was a complete response that is sustained for 46 months and he is still free of disease.
Table 1. Characteristics of patients and summary of previous treatments to the head and neck area.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Maximum tumor radius (cm)</th>
<th>Previous treatments to the head and neck region time before PDT</th>
<th>indication</th>
<th>procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>male</td>
<td>2.0</td>
<td>1 year</td>
<td>bilateral T1N0 oropharynx cancer</td>
<td>RT</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>female</td>
<td></td>
<td>3 years</td>
<td>Neck metastasis from unknown primary</td>
<td>MRND and RT</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>male</td>
<td>1.0</td>
<td>1 year</td>
<td>T1N0 larynx cancer</td>
<td>RT</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>female</td>
<td>3.5</td>
<td>5 months</td>
<td>T2N0 tongue cancer</td>
<td>RT</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>female</td>
<td></td>
<td>2 years</td>
<td>T2N0 tongue cancer, T2N0 tonsil cancer left</td>
<td>RT</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>male</td>
<td>1.5</td>
<td>1 year</td>
<td>T1 N0 supraglottic larynx cancer</td>
<td>RT</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>male</td>
<td>1.2</td>
<td>4 years</td>
<td>T2 tonsil, T1 N2c epiglottis cancer</td>
<td>CRT</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>male</td>
<td>4.3</td>
<td>1 year</td>
<td>T2N0 tongue cancer</td>
<td>RT</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>female</td>
<td>1.6</td>
<td>1 year</td>
<td>T2 N1 oropharynx cancer</td>
<td>Commando procedure and MRND</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>male</td>
<td>2.5</td>
<td>1 year</td>
<td>T4 N2b tongue cancer</td>
<td>CRT</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>male</td>
<td>1.3</td>
<td>3 years</td>
<td>T4 N0 oral cancer</td>
<td>Commando procedure, MRND, reconstruction with crista iliaca free flap and RT sequestrectomy and PMMF</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>female</td>
<td>2.9</td>
<td>6 years</td>
<td>T4N1 larynx cancer</td>
<td>TL, MRND, PMMF</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>female</td>
<td>4.5</td>
<td>8 years</td>
<td>T4N2c tongue cancer, dysfunctional larynx</td>
<td>CRT</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>male</td>
<td>2.1</td>
<td>1 year</td>
<td>T2N1 tongue cancer</td>
<td>CRT</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>male</td>
<td>6.0</td>
<td>1 year</td>
<td>persistent neck node</td>
<td>MRND</td>
</tr>
<tr>
<td>16</td>
<td>71</td>
<td>male</td>
<td>3.0</td>
<td>15 years</td>
<td>T2N0 Esophagus cancer</td>
<td>excision with gastric pull-up</td>
</tr>
<tr>
<td>17</td>
<td>58</td>
<td>male</td>
<td>3.0</td>
<td>13 years</td>
<td>T4N0 larynx cancer</td>
<td>TL, bilateral SND and RT</td>
</tr>
<tr>
<td>18</td>
<td>63</td>
<td>male</td>
<td>3.5</td>
<td>2 years</td>
<td>T4N2c tongue cancer</td>
<td>CRT</td>
</tr>
<tr>
<td>19</td>
<td>66</td>
<td>female</td>
<td>4.9</td>
<td>1 year</td>
<td>recurrent tongue cancer</td>
<td>palliative chemotherapy</td>
</tr>
<tr>
<td>20</td>
<td>61</td>
<td>male</td>
<td>4.2</td>
<td>1 year</td>
<td>T4N0 tongue cancer</td>
<td>CRT</td>
</tr>
</tbody>
</table>

**Abbreviations**: PDT, photodynamic therapy; RT, radiotherapy; MRND, modified radical neck dissection; TL, total laryngectomy; CRT, concomitant chemoradiation; PMMF, pectoralis major myocutaneous flap; SND, selective neck dissection.
3.2.1. Tumour response according to RECIST 1.1 criteria at 6 months post-iPDT

Two patients are not evaluable. One patient was lost due to pneumonia and the other due to stroke before completion of 6 months. Nine tumours had complete response with complete disappearance of the treated tumour (Figure 5). Four of these patients are still free of disease after a follow-up range of 46-80 months. The other five developed new lesions in the head and neck area. One patient developed tonsil carcinoma on the left side, 8 months after complete response of T4 N0 base of tongue tumour. This was treated with iPDT with complete response. Three months later right tonsil cancer was detected and treated with iPDT. These could be considered marginal misses of iPDT or less likely new primary tumours. The patient died 14 months after initial iPDT due to lung metastasis. Four patients had recurrences at the treatment borders (8-15 months after iPDT). One of these patients was salvaged with total laryngectomy and total glossectomy. This patient has died because of metastatic disease 24 months after iPDT. The remaining patients received best palliative care.

Nine tumours had partial response with reduction of tumour diameters. It was noted that the non-responding parts were at the borders of the tumour treated. Four of the patients received weekly methotrexate as palliative chemotherapy. The others received best palliative care.

Figure 5. Six-month control MRI images shows complete disappearance of tumor tissue located close to midline of the base of tongue, leaving a tissue defect behind. The illustrated patient refused surgical options and opted for iPDT. There was a complete response that is sustained for 46 months and he is still free of disease.
3.3. TIME TO PROGRESSION

The presence of extensive necrosis gave the radiologic impression of progression at 3 month post-treatment. However this apparent progression reversed to regression at 6 month post-treatment with 9 patients showing complete response. From these 9 patients 4 had durable tumour response. Five patients had recurrences with a range of 8-15 months, and median 9 months.

3.4. OVERALL SURVIVAL

The overall survival was analysed with Kaplan-Meier method. The mean overall survival was 25.5 months (95%CI: 13-37 months) and the median overall survival was 12 months (95%CI: 6-17 months). Four patients had long term sustained complete response and are still alive after 42-80 months (Figure 6).

Figure 6. Overall survival of the study group showing sustainable complete response in four patients. The mean survival period is 25.5 months (95%CI: 13-37 months) and the median survival period is 15 months (95%CI: 9-21 months).
3.5. COMPLICATIONS AND SAFETY

The median admission time after the iPDT treatment was 11 days (range 7 – 16 days). All patients experienced oedema of the tongue and lower half of the face justifying the need for tracheotomy. The catheter insertion sites healed spontaneously. Post-PDT pain was managed by transdermal and enteral opioids. The duration of the admission was limited by pain management. There were no short term complications or fatality. One patient was lost due to pneumonia 2 months after the procedure.

Six of the patients developed necrosis of the tumour and of the submental skin creating through and through defects. Three of these patients had complete response after iPDT. Therefore the defects were surgically closed with a pectoralis major myocutaneous flap (PMMF). One of these patients is still alive, while two were lost due to distant metastasis. The pharyngocutaneous fistulas of the remaining three patients, with partial responses to iPDT, were managed by wound care and tube feeding.

Two patients developed cutaneous metastasis at catheter introduction sites (2-4 months after iPDT). Both of the patients received weekly methotrexate as palliative chemotherapy.

One patient had major bleeding 8 weeks after the iPDT, requiring hospitalization. The patient had intra-arterial embolization of the bleeding artery. Seven patients had reported episodes of minor bleeding accompanied with detachment of necrotic tissues from the treated area, requiring no interventions. Table 2 summarizes the complications observed linked to individual patients.
## Table 2. Response to iPDT, functional results and complications.

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Age</th>
<th>Gender</th>
<th>Maximum tumor radius (cm)</th>
<th>Tumor response†</th>
<th>Overall survival (months)</th>
<th>Time to closure of tracheotomy</th>
<th>Duration of tube feeding</th>
<th>Complications related to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>male</td>
<td>2</td>
<td>CR</td>
<td>80</td>
<td>4 months (1 month after PMMF)</td>
<td>gastrostomy in situ</td>
<td>PCF (PMMF reconstruction)</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>female</td>
<td>CR</td>
<td>24</td>
<td>10 days</td>
<td>10 months</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>male</td>
<td>CR</td>
<td>24</td>
<td>7 days</td>
<td>1 month</td>
<td>gastrostomy in situ</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>female</td>
<td>3.5</td>
<td>NE</td>
<td>2</td>
<td>Not closed</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>female</td>
<td>CR</td>
<td>11</td>
<td>tracheostoma before PDT</td>
<td>2 weeks</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>male</td>
<td>1.5</td>
<td>CR</td>
<td>66</td>
<td>10 days</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>male</td>
<td>1.2</td>
<td>CR</td>
<td>46</td>
<td>3 months</td>
<td>gastrostomy in situ</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>male</td>
<td>4.3</td>
<td>CR</td>
<td>42</td>
<td>7 days</td>
<td>gastrostomy in situ</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>female</td>
<td>1.6</td>
<td>NE</td>
<td>4</td>
<td>Not closed</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>male</td>
<td>2.5</td>
<td>CR</td>
<td>16</td>
<td>6 months</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>male</td>
<td>1.3</td>
<td>PR</td>
<td>17</td>
<td>7 days</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>female</td>
<td>2.9</td>
<td>PD</td>
<td>15</td>
<td>tracheostoma before PDT</td>
<td>gastrostomy in situ</td>
<td>cutaneous metastasis</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>female</td>
<td>4.5</td>
<td>PR</td>
<td>12</td>
<td>tracheostoma before PDT</td>
<td>gastrostomy in situ</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>male</td>
<td>2.1</td>
<td>PR</td>
<td>11</td>
<td>Not closed</td>
<td>gastrostomy in situ</td>
<td>cutaneous metastasis</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>male</td>
<td>6</td>
<td>CR</td>
<td>15</td>
<td>Not closed</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
<tr>
<td>16</td>
<td>71</td>
<td>male</td>
<td>3</td>
<td>PR</td>
<td>10</td>
<td>tracheostoma before PDT</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
<tr>
<td>17</td>
<td>58</td>
<td>male</td>
<td>3</td>
<td>PR</td>
<td>6</td>
<td>Not closed</td>
<td>gastrostomy in situ</td>
<td>none</td>
</tr>
<tr>
<td>18</td>
<td>63</td>
<td>male</td>
<td>3.5</td>
<td>PR</td>
<td>7</td>
<td>1 month</td>
<td>gastrostomy in situ</td>
<td>no</td>
</tr>
<tr>
<td>19</td>
<td>66</td>
<td>female</td>
<td>4.9</td>
<td>PR</td>
<td>9</td>
<td>Not closed</td>
<td>gastrostomy in situ</td>
<td>bleeding</td>
</tr>
<tr>
<td>20</td>
<td>61</td>
<td>male</td>
<td>4.2</td>
<td>PR</td>
<td>9</td>
<td>2 months</td>
<td>gastrostomy in situ</td>
<td>PCF</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete response; PMMF, pectoralis major myocutaneous flap; PCF, pharyngocutaneous fistula; PDT, photodynamic therapy; NE, not evaluable; PR, partial response; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

* Patient numbers correspond to the patient numbers in Table 1.

† Based on comparison of pre-PDT and 6-month post-PDT MRI images according to RECIST1.1 criteria.
3.6. AIRWAY MANAGEMENT

Five patients had total laryngectomy with permanent tracheostoma before iPDT. The remaining patients received tracheotomy right before the iPDT procedure. Eight patients could not be decannulated and remained tracheotomised until the time of death. Four patients could be decannulated in the early post-operative period of 7 -10 days. Three patients were decannulated at later period (4-10 months) (Table 2).

3.7. TUBE FEEDING

Six patients were already gastrostomy tube feeding dependent before iPDT. The remaining patients were initially fed through a nasogastric tube after iPDT. Four patients successfully restarted sufficient oral intake in the early post-operative period of 2-12 weeks. In addition to the six patients who had pre-PDT gastrostomy catheters, 10 patients also had gastrostomy catheters placed. Two additional patients started sufficient oral intake at 10 and 12 months after iPDT. Fourteen patients remained tube feeding dependent until the time of death. Three of the patients who had long term survival has sufficient oral intake. One patient who is still free of disease after 46 months is tube-feeding dependent (table 2).

4. DISCUSSION

Patients with metastatic or recurrent head and neck carcinomas, have a median survival of about 4 months if untreated [21]. There are no reliable data about survival of patients with recurrent non-metastatic SCC of the tongue base. Therefore it is not feasible to comment about any survival benefit achieved by iPDT of these tumours. The technique described in this manuscript can be applied to a limited number of patients. Patients with distant metastasis or neck node recurrences that invade into vital structures cannot benefit from this technique. The rarity of the indication to perform iPDT suggests that a few centers should specialize and perfect their techniques to perform this procedure.

The described treatment technique is based on established brachytherapy methods of the base of tongue [5]. The planning and application was modified to accommodate full light coverage of the tumour. The placement of the catheters with relation to each other was dictated by the penetration of the treatment light in the tissues. iPDT of the head and neck with ultrasound guided placement of spinal catheters was described by another group [18-20]. The overall survival and response rates observed in our patient group are similar to earlier published articles describing ultrasound guided interstitial photodynamic therapy of head and neck tumors [18-20].
Interstitial PDT of recurrent tongue cancer

Immediate tissue oedema after iPDT was expected and therefore patency of the airway was guaranteed by a placement of a tracheotomy cannula except for those who already had a tracheostoma before the procedure. For the same reasons the patients were provided with tube feeding. The tissue oedema subsided after 7-10 days. At this point decannulation was attempted and was successful in four patients. The rest of the patients could not tolerate decannulation due to extensive tissue necrosis in the upper airway. Decannulation seems to be dependent on the extent of the necrosis and clinical response. Patients who recovered from the necrotic debris could be decannulated at a later time. Patients who had residual disease endangering the airway were not decannulated.

The therapy proved to be efficacious with all tumours responding with necrosis of different degrees. The tumour necrosis became evident once the oedema subsided after 2 weeks. The tumor response to iPDT seems to be a slow acting process. This was evident by the presence of persistent mass at the 3 month MRI imaging, which could not be distinguished if it still contained viable tumor tissue. The therapy does not seem tumor specific as the margin of tissue illuminated around the tumor also becomes necrotic. In some cases the necrotic margin included submental skin. The skin necrosis was independent of direct tumor extension. The skin could not be protected from treatment light due to the proximity of the tumor. Previous radiation received might make the skin more susceptible to break-down. At the 6 month evaluation MRI images, the necrotic tissue had disappeared leaving significant tissue defects behind. In some cases the tissue defect included the skin creating through and through defects or in other words pharyngocutaneous fistulas (PCF). Management of the tissue defects is dependent on the clinical response. The decision to reconstruct was taken after the 6 month evaluation. If complete tumor response was achieved reconstruction was considered. This approach is justified by the long term disease free survival of four patients in the study.

The high incidence of PCF is a point of concern when palliation is aimed. If long-term disease control can be achieved, it can be argued that the risk of PCF can be tolerated. However if long-term disease control is not achieved presence of PCF can diminish the quality of the already limited remaining lifetime of these patients. In the light of the initial experience presented in this manuscript, for future treatments, we have elected to try to prevent the forming of PCF by limiting the light dose received by the skin and subcutaneous tissues by careful pre-operative planning and simulation. This decision carries the risk of not eliminating the tumor cells located close to the skin.

There were no patients with major bleeding immediately after the procedure. This implies that in short term after iPDT, major blood vessels such as lingual artery -although included in the treatment field- are either immune to the destructive effects or are contained by
the tissue edema and necrosis around them. The recurrences or non-responsive parts of
the tumors treated were mainly at the margins of the tumor, suggesting a “geographical
miss”, or in other terms an area not receiving enough light dose. The way to overcome
this problem is to treat larger volumes of tissue with bigger safety margins. However this
approach is limited by the destructiveness of the treatment resulting in tissue defects.

Accurate light dosimetry has not yet been performed for IPDT in head and neck region and
in many cases the treatment was probably inadequate for one or more of the following
reasons: 1) No dosimetric planning was done prior to treatment. The catheters for placement
of the sources were inserted on the basis of palpation and approximate information on the
location of the tumor. 2) Tumor boundaries and risk structures were not–visible on X-ray
imaging. 3) There was no strategy regarding coverage of the light distribution over the entire
tumor volume and no information on fluences actually delivered.

The initial relative safety and apparent efficacy of iPDT of tongue base is encouraging to
further develop the method to be less destructive to the tissues that are desired to be
protected and more efficiently treating the whole tumor volume. In a recently initiated
study we are developing a 3-step approach: 1) Pre-treatment planning, based on MRI in
which the tumour and risk volume (normal tissue structures) are identified. A planning
algorithm will then estimate the optimal positions, amount and lengths of the linear light
sources. 2) Verification imaging of the source locations after placement. 3) Modification of
the pre-treatment planning based on the actual source locations. In the modification step
we aim to investigate methods to measure the actual light transport within the tumour and
risk volumes. These measurements will facilitate a patient tailored inverse planning strategy
aiming for improved accuracy.

5. CONCLUSION

Interstitial photodynamic therapy (iPDT), which utilizes a completely different mechanism
of action than the conventional methods, can be a curative alternative to palliative care
to patients with non-metastatic recurrent base of tongue tumors who cannot be treated
with surgery or radiation therapy. The current study demonstrates that long-term disease
control is achievable with iPDT. With refinements in planning and monitoring the treatment
technique iPDT may be the treatment of choice after conventional curative techniques are
exhausted.
6. REFERENCES


