New insights into photodynamic therapy of the head and neck
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MR and CT based treatment planning for mTHPC mediated interstitial photodynamic therapy of head and neck cancer: description of the method


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ABSTRACT

BACKGROUND AND OBJECTIVE

Interstitial photodynamic therapy is a potentially important tool in the management of voluminous or deep-seated recurrent head and neck cancers.

STUDY DESIGN/METHOD

The described treatment algorithm in this manuscript consists of the treatment simulation, implantation of light sources, verification, modification of the treatment plan if necessary and illumination. The tumor is delineated on imaging sections (CT, MRI, and/or PET/CT) and the treatment is simulated by virtually introducing light sources to the tumor volume on specially modified brachytherapy software. This enables us to determine if the treatment is technically feasible, and information about approximate number and location of light sources necessary. Following implantation of catheters in which the light sources will be introduced, CT or MR scan is performed to verify the actual location of the implanted catheters. The verification-CT is imported to the software and co-registered with pre-treatment images to observe the deviations from the simulation. The simulation is run again with the actual position of the light sources to determine if any additional light sources are necessary and adaptation of the source length in order to cover the tumor volume (modification). Thereafter the tumor is illuminated.

RESULTS

This method has the potential to help with identifying iPDT feasible patients by simulating before the actual treatment. The suboptimal placement of light sources can be identified and corrected. By saving the simulations all of the treatment procedure is well documented, which is essential for evaluation of such new techniques.

CONCLUSION

The proposed technique can help standardize and document iPDT.
1. INTRODUCTION

Meta-tetrahydroxyphenylchlorin (mTHPC) mediated PDT has been shown to be effective in the treatment of recurrent head and neck tumors [1,2] and is approved by the European Medicine Agency (EMA) for this indication. Clinical benefit is only achieved in tumours that can be completely illuminated [1]. One of the main limitations of PDT for larger tumours is the penetration of light in tissues. mTHPC has an activation wavelength of 652 nm which penetrates effectively in tissue, resulting in a treatment depth of 8-10 mm in most tissues (depending on the optical properties of the tissues) [3]. Interstitial Photodynamic Therapy (iPDT), which is a method whereby the light source is percutaneously implanted in the tumour, can potentially overcome this restraint. Multiple fibres can be inserted directly into the tumour 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. This approach is being developed in a number of centres on various tumor sites, especially prostate, skin and head and neck tumors [4-11]. There are studies showing promising results with ultrasound guided interstitial photodynamic therapy of head and neck tumours [8-10]. We have recently published our experience with iPDT based on a simple planning approach [11].

Our initial iPDT protocol comprised of the manual insertion of hollow transparent brachy-therapy catheters through the tumour mass with 10-15 mm distance to each other. The insertion sites of the catheters were determined/established by the physician performing the procedure. Catheter placement was checked by palpation and visual inspection. Recently a non-isocentric C-arm was used to obtain 2D X-ray images, which provided some, however inaccurate information about the length of the catheters and position. This initial inaccurate approach showed promising results. We are convinced that accurately planning and executing the procedure can optimize results, thereby providing better light coverage of the tumor volume and avoiding risk structures. The aim was therefore to develop a methodology for pre-treatment simulation, on-site verification and simulation modification for iPDT.

We have developed a pre-treatment planning algorithm that enables standard light delivery to a predefined gross tumour volume (GTV) while avoiding risk structures. A simple simulation algorithm was developed to determine optimal treatment scheme to yield the best coverage of the tumour volume while at the same time minimum coverage of the risk volume.

The resulting treatment simulation consists of the optimum source positions, the required number and lengths of the sources. A brachy-therapy imaging based simulation technique is
therefore adapted for iPDT purposes, which allows for pre-treatment simulation, verification of the implanted sources and possible modification of the simulated plan.

By employing these steps iPDT can be better standardized and documented. The current manuscript details the methods used to achieve this goal. For practical purposes we describe the technique used for a recurrent squamous cell carcinoma of the base of tongue.

2. METHOD

The described method involves several steps represented in the flow chart in Figure 1. The first step is the selection of a suitable patient. Patient selection was described in detail in our previous publication (11).

Figure 1. Flowchart of the algorithm of imaging based iPDT procedure
All the figures used in this manuscript are from the same patient for demonstration purposes. The patient is a 55 year old Caucasian male with inoperable recurrent base of tongue squamous cell cancer. The patient was first diagnosed with a T4N2M0 oropharynx squamous cell cancer in 2003. The treatment consisted of concurrent chemoradiation (60 Grey, 3 cures of cisplatin). There was complete response. In 2010 the patient had osteoradionecrosis of the mandible. He received conservative management with regular debridement and hyperbaric oxygen therapy without success. In 2010 a segment of the mandible was removed and reconstructed with a free composite fibula flap. The flap reconstruction failed after 5 weeks and replaced by a pectoralis major myocutaneous flap. In September 2011 patient presented with a large base of tongue tumor. A pan-endoscopy was performed with biopsies, which showed squamous cell cancer. The tumor was evaluated with MRI, and PET-CT. The tumor consisted of a 7 cm mass located at the entire base of tongue without regional or distant metastasis. The patient consented to iPDT as an experimental procedure.

Once the patient is considered to be a candidate the treatment simulation takes place, followed by photosensitizer injection, implantation of catheters, verification, modification of the treatment plan if necessary and illumination.

2.1. IMAGE BASED IPDT TREATMENT PLANNING AND SIMULATION

Two weeks prior to iPDT the tumour and risk structures are assessed from MRI, CT and/or PET-CT. The image sets are imported in the simulation planning software (Oncentra Masterplan 4.1, Nucletron, Veenendaal, The Netherlands), and the tumour border including a 5mm margin (gross tumor volume (GTV)) is marked on the axial and sagittal planes slices of 1mm intervals. Critical structures such as major blood vessels and nerves are marked during this procedure to evaluate the light dose these structures will receive. Depending on the location and accessibility of the tumor the light sources can be inserted in various orientations such as anterior-posterior, trans-oral, caudo-cranial or lateral. For the demonstrated case, the simulated positions of the linear sources were in a caudo-cranial direction with planned vertical insertions via the sub mental skin to the base of tongue in a straight and parallel geometry. The virtual placement of the light sources enables us to evaluate if the implantation is technically feasible. The linear light sources can be simulated by an array of adjacent isotropic point sources at a 1mm interval. The decrease of the fluence rate of light (\( \lambda = 652\text{nm} \)) with depth implemented in the software for the simulations was determined in-vivo. From our clinical iPDT experience we have empirically determined that iPDT using the photosensitizer mTHPC at standard dosimetric parameters \( P_{\text{out}} = 100\text{mWcm}^{-1} \), \( 30\text{Jcm}^{-1} \) induces a radius of necrosis around a linear source ranging from 8 up to 10mm. This observation is confirmed by the literature [3]. At given source positions it is possible...
to estimate the distribution of tissue necrosis using this radius. The presented approach assumes a standard radius of iPDT-induced necrosis around a single linear source, and does not take into account the influence of adjacent sources nor patient specific parameters such as light scattering and absorption.

The iso-dose i.e. expected induced necrosis line for a single source is placed at a radial distance of <8mm from the longitudinal centre of the source. The cumulative iso-dose line as a result of multiple sources is then calculated in 3D for all catheters. The pre-treatment simulation allows for the determination of the minimal amount of sources required, approximate insertion location and angle, and the length of the linear sources. Seventeen catheters were virtually planned to be implanted in the demonstrated case (Figure 2). Figure 3 (left) is a 3D reconstruction of the simulation.

Figure 2. On the left a sagittal view of a MR image of a Bilateral T4 N0 M0 Squamous Cell Carcinoma at the Base of Tongue including the simulated treatment planning of the linear source/catheter implant within the GTV. The straight lines are the linear light sources/catheters. The solid line the corresponding expected necrosis line and the dotted line represents the GTV (~5mm margin). On the right the corresponding axial view. Below the MR images are the dots that represent the active length (mm) and longitudinal shift of the linear sources.
The treatment simulation is transferred to the clinicians who will implant the catheters. Due to the fact that this is a manual procedure without any real time 3D imaging feedback, it is expected that the resulting locations of the implanted catheters will deviate from the ideally planned location. In addition, the sources are not expected to be perfectly straight and parallel to each other and may bend due to differences in tissue density and deformation.

2.2. PHOTOSENSITIZER INJECTION

Four days before the illumination mTHPC (Foscan®) is administered intravenously at a dose of 0.15mg/kg with a slow injection rate of over 6 minutes. After injection, the patient is immediately light sensitive.

2.3. IMPLANTATION

Before percutaneous insertion of the light sources, the skin is disinfected with alcohol. Hollow brachytherapy needles (ProGuide needle 6F, sharp, 200 mm, Nucletron, Netherlands) are inserted via the submental skin, all the way through to the surface of the base of tongue. A guide-wire is introduced through the needle from the skin side and retrieved from the oral cavity. Transparent flexible brachytherapy catheters (Flexible Implant Tube, 6F, Single leader, 50cm, Nucletron, Netherlands) are attached to the guide-wire and pulled through the hollow needles from the oropharynx to the skin. The insertion needles are removed leaving the sealed translucent catheter in position. For identification and fixation purposes, each catheter is provided with a single or double color-coded radio opaque button on the
Treatment planning interstitial PDT

skin side (figure 4). A total of 17 catheters were implanted in the demonstrated case. The total insertion time was approximately 150 minutes.

Figure 4. a) A brachy loop-catheter modified for iPDT. 1) The white radio-opaque button connected to the distal end of the catheter (Located at the base of tongue). 2) The linear source, 3) the light shielding metal tube with distance markings, 4) the colored buttons placed after implant at the proximal (submental) side. This approach enables for a variable source length and location. b) Implanted catheters can be seen from the submental side.

2.4. VERIFICATION AND MODIFICATION

Following insertion a CT scan is obtained to verify the positions of the catheters placed. This could be done either intra-operatively if a CT scan is available in the operating rooms or the patient can be weaned from general anesthesia and brought to the CT-suite. The implanted catheters can be easily identified by their air containing hollow lumens. The CT/MR scans are imported to the simulation software. The software can either identify and reconstructed the catheters automatically or manually. In the demonstrated case the catheters were drawn in
manually into the CT data set. The next step is to verify the location of the catheters within the region of interest and compare with the original simulation. The tumor boundaries cannot always be indentified on a CT scan. We therefore perform image fusion of the post-implant CT image set with the MRI and/or PET/CT data that were gathered before. Image fusion is established by assigning landmarks coordinates to anatomical structures that are recognizable in both image sets i.e. spinal cord, hyoid, soft palate, etc. The diffusing length of each linear diffuser and longitudinal positions is modified to the actual position and the dose plan recalculated based on the fused CT/MR image data set (Figure 5).

**Figure 5.** On the left a sagittal view of a CT verification image of the treatment planning after the actual catheter implant within the GTV. The curved lines are the actual implanted linear light sources. The solid line the corresponding necrosis iso-dose line and the dotted line represents the tumor volume. The tumor volume is merged from the MR image taken prior to implant. On the right the corresponding axial view can be seen. Below the images are the dots that represent the modified active length (mm) and longitudinal shift of the linear sources.

For this particular case there was no need for major modification (e.g. additional source implant in case of insufficient coverage or removal in case of possible risk structure damage) of the treatment simulation thus the entire GTV was fully covered with a sufficient fluence. However some minor adjustments were made regarding the lengths of the linear light sources.
2.5. ILLUMINATION

If the verification-CT was not performed under general anesthesia the patient is brought under general anesthesia for a second time for the illumination procedure. After confirmation simulation, linear diffusers (Cylindrical diffuser CD 405-50C, Ceram Optec, Bonn, Germany) are connected to a four-channel 652nm wavelength diode laser (Ceralas PDT, Biolitec, Bonn, Germany), as the light source. The 50mm diffusing linear sources are calibrated with respect to their total output in the integrated calibration unit.

Mucosal surfaces and skin not intended to receive light are shielded from scattered light with wet green cloth. Before the linear light sources are inserted into the catheters they are provided with thin metal shielding tubes. Shifting the shielding over the emitting part of the source enables for any desired diffuser length according to the modified plan (Figure 4). A major advantage of this approach is that the diffusers only have to be calibrated once. Each catheter along with the shielding tube was then filled with the corresponding sources, after which light was delivered at 100mW cm\(^{-1}\) for 300 seconds (30 Jcm\(^{-1}\)). Since the vascular supply of the tongue is provided via the lingual arteries entering the tongue from posterior, the illumination was performed from anterior to posterior not to potentially compromise the blood circulation due to vascular shutdown. In another tumor location this sequence can be different. The entire illumination procedure consisted of 4 sequential sessions i.e. 3 times simultaneous 5 linear sources and one time 2 sources (17 in total). After the illumination the catheters are removed at the OR. The patient is then transferred to the ward.

3. DISCUSSION

The photodynamic therapy procedure is a complex interaction of three variables: light, oxygen and photosensitizer. There are several factors that have influence on these variables such as microvascular saturation, blood circulation, optical properties of the tumor, and the distribution of the photosensitizer [12]. What actually takes place in the tissues during PDT is very difficult to reveal, and therefore ensuring adequate and uniform treatment is a challenge.

A reasonable start in attempting the task of optimization is to standardize the way light is delivered to the tumor. From earlier experience we have postulated that 652 nm wavelength light diffuses around 8-10 mm in the tissues. Therefore we perform our simulation with light sources placed at a maximal inter source distance of 14 mm. The software assumes an mTHPC iPDT induced 8mm necrosis radius around a single linear diffuser. The current approach does not account for, nor assesses information on any patient specific optical parameters such as inter-patient variations in light transport or variations in optical properties i.e. scattering and
absorption during PDT. PDT causes vascular shutdown leading to changes in the quantity of haemoglobin, which has very similar absorption wavelength as the treatment light. Due to the inhomogeneous distribution and dynamic nature of tissue optical parameters, optimal light delivery schemes and planning remains a major challenge. Therefore the simulated light distribution does not necessarily represent the actual light distribution. We are currently investigating the role of these parameters on the light distribution during PDT by means of \textit{in-vivo} fluence rate measurements within the region of interest.

The imaging method of choice to use in simulation is MRI. With MRI the extent and borders of the tumor can usually be identified. CT can be used as well, but in our experience especially in the oral cavity/pharynx region MRI provides better soft tissue detail. We should not forget that many of these patients have received conventional treatments to the area of interest before. Especially patients who have received surgical intervention may have metal plates and screws and sometimes underwent reconstruction with free tissue transfers from different parts of the body. Therefore the anatomy of the area is complicated leading to insufficient analysis of the tumor extensions. In such cases PET-CT is very helpful identifying the metabolically active tumor. Marking the GTV on the MRI images, while consulting the PET-CT images, seems to be the most accurate method to identify the extent of the tumor.

The simulation provides information about minimal number of sources necessary and the location of possible risk structures and the accessibility of the region the target volume; e.g. the mandible may block a particular needle trajectory. The insertion technique and trajectory angles of the catheters can be determined before the actual procedure, which saves considerable operation room time and makes planning easier as the operation time and amount of acquired sources can be approximated in advance. The simulation is essential in the decision-making process e.g. the simulation can predict when it is technically not possible to cover the whole treatment volume. In such case the patient should not be treated with iPDT.

Once the patient is under general anaesthesia the soft tissues deform because of the lack of muscle tone. So the actual treatment volume does not exactly match the simulated treatment volume. As the catheters are being implanted the tissues deform further by the traction forces. Therefore the pre-treatment simulation cannot be executed in a manner that is completely identical and thus treatment, based on simulation only, is not reliable. Consequently the location of the implanted catheters should be verified with imaging. The verification CT/MR scan allows assessing the actual locations of the catheters. Therefore the simulation performed with the actual catheters is more relevant than the pre-treatment simulation. The former allows us to identify any potentially dark areas. These dark areas can be covered by placing additional catheters. Placement of the catheters too near to
each other does not seem to cause more damage than standard illumination. However too many catheters within close range off each other may alter the vasculature and thus the oxygenation, aiming at a inter catheter distance of ~14 mm is preferable. The simulation also helps the physician to protect the overlying skin which might potentially decrease the risk of oro-cutaneous fistulas reported in our earlier publications [11].

The main advantage of the treatment algorithm, described in this manuscript, is documentation of the location of the implanted light sources. Our previous clinical applications and US-guided applications lack this aspect of accurate documentation [4,8-11]. This documentation coupled with clinical results can help us to analyse failures critically. The failures can be due to geographical miss, insufficient light dose or characteristics of the tumor or the treated location. As experience with the technique described in this manuscript accumulates, patterns of failure can be identified, potentially leading to refinement of the planning and simulation procedure. Standardizing the light delivery method enables uniform treatment cohorts making clinical analysis and comparisons to other treatment methods more feasible and valid. In such a cohort where the variations in treatment method do not play a role, the clinical success of the treatment could be more accurately evaluated.

4. CONCLUSION

The treatment algorithm described in this manuscript has the potential to standardize and document the interstitial PDT technique. The simulation helps to identify the tumors suitable for iPDT before actually treating the patient. Verification and modification procedures can identify the suboptimal placement of light sources and enable the physician to correct. By archiving the simulations all of the treatment, the procedure is well documented, which is essential for evaluation of such new techniques.
5. REFERENCES


