Dosimetry in Photodynamic Therapy of the Pancreas

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Introduction

The purpose of this project is to create a dosimeter for use with pancreatic cancer treatments using photodynamic therapy (PDT). One initial study with PDT treatment of pancreatic cancer done without pretreatment dosimetry had promising results. [1] Other related dosimetry studies, suggest that pretreatment dosimetry can reduce variation seen in individual subjects that receive PDT treatments. The overall purpose of this project is to combine dosimetry measurements and modeling studies into an optimal design for PDT treatment of pancreatic cancer.

Photodynamic therapy is comprised of two parts; a photosensitive drug is administered to the patient, typically though intravenous injection, and then the drug is activated with a dose of light at a specific wavelength. This dose of light is absorbed by the sensitizer molecules, bringing the molecules into an excited singlet state which rapidly decays into an excited triplet state. While in the excited triplet state, the photosensitizers are collisionally quenched by ground state (triplet-state) molecular oxygen, producing an energy transfer to yield singlet oxygen species. Through both singlet oxygen and through radical product formation, the treatment causes widespread cellular apoptosis and necrosis in the treated tissue. The treatment kills tumor cells both directly and indirectly through damage to the vasculature around the tumor parenchyma, leading to hypoxia and subsequent cell necrosis. [2] There can additionally be a widespread immunological reaction as well, which is thought to produce further tumor suppression effects, yet quantification of this effect in terms of dosimetry parameters has remained elusive. However, several studies have shown a direct relationship between the drug dose and light dose applied to the tissue, yielding a linear production of singlet oxygen in the target tissue, and this is likely the most quantitative way to plan PDT treatment at the current time.

In a previous Phase I study with 16 patients [1], photodynamic therapy (PDT) using 0.15mg/kg meso-tetrahydroxyphenol chlorine administered intravenously produced significant necrosis in pancreatic tumors. The patients in the study all had large cancers, and responded well to the treatment with good median survival times (9.5 months compared to an average of 6-10 months for other treatments). The recovery time for the procedure was about 10 days. There was no morbidity associated with the treatment, although there some side effects in some of the patients associated with the treatment and the patient’s response to the treatment varied. Light doses were calculated based on the amount of drug administered intravenously and previous animal studies with the same drug. [1]

A recent pre-clinical study indicated that the variation in response to PDT could be reduced by using pretreatment dosimetry. The study found that photosensitive drug concentrations varied greatly within the test groups, even when mice with identical tumors and identical injected doses were used. [4] In addition to the drug concentrations varying, it is known that in solid tumors that the optical properties of the tissue may vary as well, [5] and that compensation for these variations is important. Literature estimates
of tissue optical properties are given as a range, due to the variation in samples and variation in results by different experimenters. Blood has very specific optical properties that differ from the optical properties of other tissues, so differences in blood volume would lead to different optical properties. In this study, the blood concentration and tissue optical property heterogeneity effects of pancreatic tissue are examined computationally, and the dosimetry planning scheme is worked out.

Methods

Dosimetry for PDT of the pancreas is a two step process. First, the optical properties of the organ must be determined, as it is well known that they vary from subject to subject. Secondly, the photosensitizer concentration in the pancreas must be determined. It may be necessary to calculate the concentration at each treatment point, as the photosensitizer concentrations may not be homogenous throughout the pancreas.

There are two methods for determining the optical properties of the pancreas that are currently being considered. The first method is to use contrast CT scans to generate blood flow and concentration data. The optical properties would then be estimated based on those parameters, as the blood and many tissues have well known optical properties. Finite element modeling of the light distribution can be achieved with input geometry data from the preoperative CT scans of each subject. Additionally, since each subject gets a pre and post contrast CT scan, it is feasible to use contrast uptake as a surrogate measure of blood volume. Finite element meshes have been created using this organ-specific information, and large blood vessels around the pancreas are also tagged. Modeling light distribution with and without these known high absorption regions will be studied to see which cases of PDT treatment would be most affected, in terms of light distribution to the desired target of the pancreas regions.

The second method for light dosimetry modeling compensation would be the more direct approach to measure radiance in the tissue either with full spectroscopy and/or over a variety of distances. Optical properties would then be calculated based upon an iterative solution to the homogeneous diffusion equation, in the geometry used for sources and detectors. This approach has been tried by several investigators, and it is as yet unclear if the compensation for tissue properties is sufficient or if the compensation must be dynamic during treatment. Both methods will be evaluated for potential use in pancreas PDT.

Light will be delivered to the pancreas and the subsequent photosensitizer fluorescence will be measured using bundled fibers in a flexible catheter. Finite Element Modeling will be used to calculate the photosensitizer concentration based on the measurements and calculated tissue properties. Light doses for the PDT will then be generated based on the calculated photosensitizer concentrations.

Plan for future work

Finite Element Modeling will be used to quantify the importance of correctly determining the optical properties before attempting to determine the concentration of photosensitizer in the tissue. If the optical properties significantly affect the measurement, then these models will be used to determine the most effective method for determining optical properties in the treatment area. Once the optimal method has been determined, a prototype will be constructed and tested using tissue phantoms. If the
results are promising, tests will be run on tumor models implanted in mice to determine the efficacy of the dosimeter. If those results are promising, then the dosimeter will be used in a new clinical study of PDT treatment of pancreatic cancer which is in the initial planning stages of a phase 1 trial.

References


