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Original Research

Image-guided interstitial photodynamic therapy for squamous cell carcinomas: Preclinical investigation

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ABSTRACT

Objective: Photodynamic therapy (PDT) is a clinically approved minimally invasive treatment for cancer. In this preclinical study, using an imaging-guided approach, we examined the potential utility of PDT in the management of bulky squamous cell carcinomas (SCCs).
Methods: To mimic bulky oropharyngeal cancers seen in the clinical setting, intramuscular SCCs were established in female C3H mice. Animals were injected with the photosensitizer, 2-[hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH; 0.4 μmol/kg, i.v.) and tumors were illuminated 24 h post injection with 665 nm light. PDT as a single treatment modality was administered by surface illumination or by interstitial placement of fibers (iPDT). Magnetic resonance imaging was used to guide treatment and assess tumor response to PDT along with correlative histopathologic assessment.
Results: Interstitial HPPH-PDT resulted in a marked change on T2 maps 24 h post treatment compared to untreated controls or transcutaneous illumination. Corresponding apparent diffusion coefficient maps also showed hyperintense areas in tumors following iPDT suggestive of effective photodynamic cell kill. Histologic sections (H&E) confirmed presence of extensive tumor necrosis following iPDT.
Conclusions: These results highlight the potential utility of PDT in the treatment of bulky oropharyngeal cancers. The findings of our study also demonstrate the utility of MRI as a non-invasive tool for mapping of early tissue response to PDT.

1. Introduction

Squamous cell carcinomas (SCCs) of the tonsils and tongue base (oropharynx) are locally and regionally aggressive tumors that result in debilitating changes in appearance, speech, deglutition and respiratory function in patients [1]. Standard treatment approaches such as surgery and chemoradiation often result in prolonged and severe morbidities including xerostomia, trismus, dysphagia, loss of dentition and mandibular osteoradionecrosis [2–4]. Clearly, there is a need to investigate novel strategies that can be effective in treating the disease without associated long-term toxicities and treatment-related complications.

Photodynamic therapy (PDT) is a clinically approved treatment for cancer that involves localized activation of a drug (photosensitizer) using light of a specific wavelength (Fig. 1A) which in turn results in cell kill and vascular damage within the tumor [5]. Clinically, PDT offers a minimally invasive alternative to traditional anticancer therapies (chemotherapy, radiation) without risk of permanent, systemic sequelae in patients [6]. Additionally, PDT may be repeated when necessary without risk of additional toxicities and is often associated with favorable cosmetic and functional outcomes [6–8]. The potential of PDT against head and neck cancers has been active area of investigation [9–12]. Retrospective analysis of outcomes in 170 patients with early stage oral cavity and oropharyngeal cancers have revealed overall response rates and complete response rates of 90% and 70% respectively [11]. We have recently demonstrated the safety of PDT against premalignant and early malignant lesions of the oral cavity and larynx with encouraging results on treatment efficacy [12].

The most common approach to PDT involves surface illumination of tumors (Fig. 1B) following intravenous administration or topical application of a photosensitizer. This transcutaneous approach for tumor illumination is often effective in treating early

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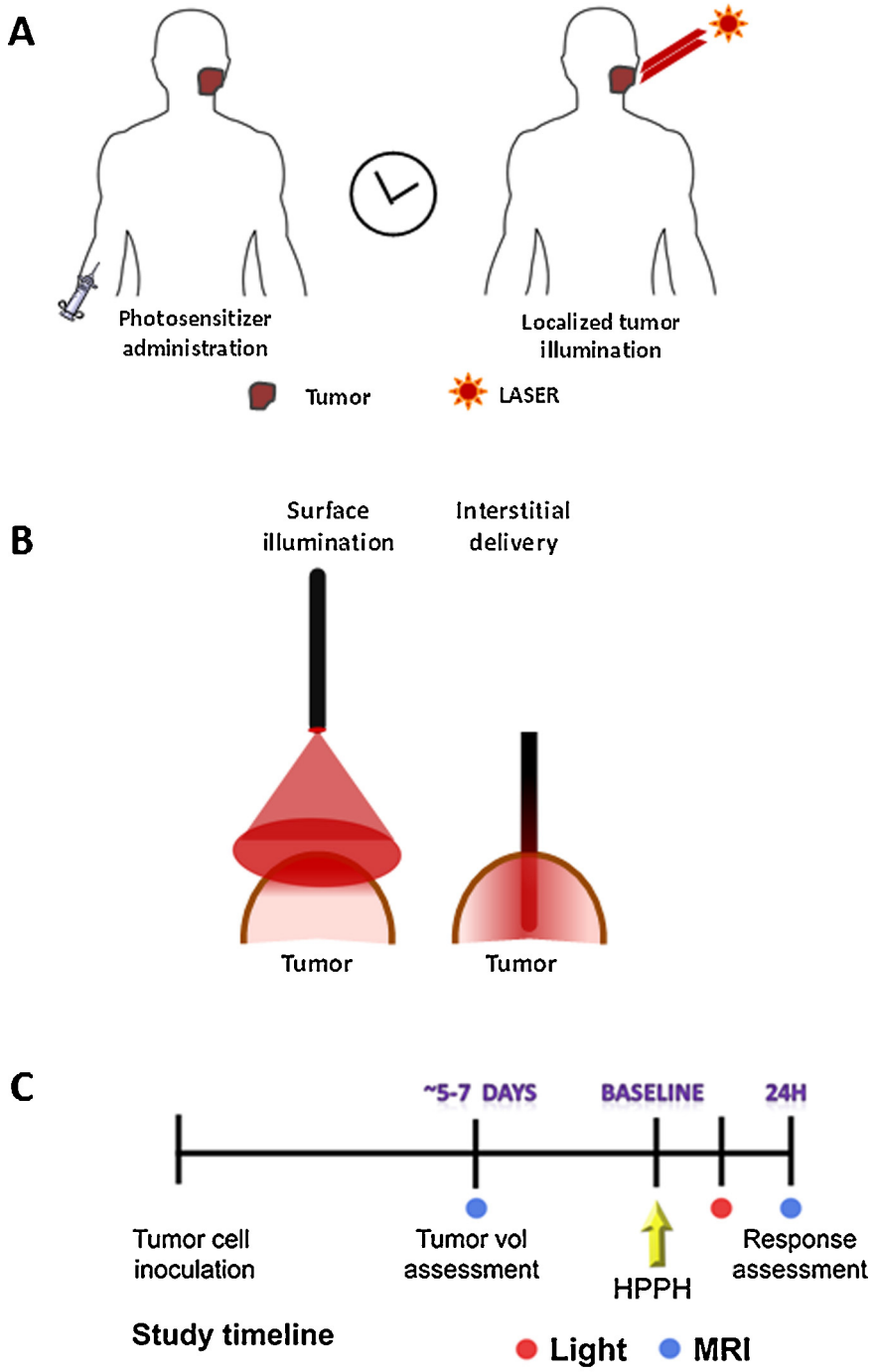

Fig. 1. (A) Basic methodology of PDT: PDT involves localized activation of a systemically administered photosensitizer by light of a specific wavelength from a laser light source. (B) Light delivery in PDT is typically performed by surface illumination of tumors using optical fibers or by interstitial delivery that involves placement of optical fibers into the tumor interstitium. (C) Schematic of experimental study design. Following inoculation of SCCVII tumor cells, animals underwent MRI examinations 5–7 days post injection to visualize tumor growth. Upon successful establishment of tumor growth (days 8–10), animals were randomized into control or PDT treatment arms. MRI and histologic response assessment was performed 24 h post PDT.

stage lesions of the head and neck that are limited in depth. However, this manner of light delivery may only result in limited photoactivation within thicker (bulkier) solid tumors similar to those seen in the tongue base and the oropharynx. To address this issue, preclinical and clinical studies have investigated the potential of interstitial PDT (iPDT), in which light is delivered through optical fibers inserted into the solid tumor mass (Fig. 1B) with encouraging results [13–15].

The overall objective of the present study was to characterize the response of SCCs to iPDT. To mimic bulky oropharyngeal cancers observed in the clinical setting, intramuscular tumors were established in mice. Magnetic resonance imaging (MRI) was utilized to guide placement of the fiber for iPDT. Multiparametric MR mapping (T2-weighted and diffusion weighted imaging) along with correlative histopathology was performed to compare the photodynamic tissue damage following surface illumination or interstitial