Local Integration of Commercially Available Intra-operative MR-scanner and Neurosurgical Guidance for Metalloporphyrin-Guided Tumor Resection and Photodynamic Therapy

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Abstract. We have locally integrated a commercial intra-operative MR-scanner and neurosurgical guidance system in order to conduct a clinical trial testing for improvement in glioma resection following administration of either of two metalloporphyrin drugs, Xcytrin™ or Lutrin™ (Pharmacyclics Inc., Sunnyvale, CA). Like other porphyrins, these two drugs have been shown to bind preferentially to tumor. The metal in Xcytrin is gadolinium. It should enhance intra-operative MR-scans taken during tumor resection. This would overcome problems of non-specific MR-enhancement caused by intra-operative contrast leakage from the vascular compartment. Both drugs provide fluorescence contrast in the presence of 450 nm wavelength light. Intra-operative fluorescence contrast should facilitate Lutrin photodynamic therapy administration to otherwise invisible glioma residual in the walls of the resection cavity. The metal in Lutrin is Lutetium. When illuminated with 732nm wavelength light, Lutrin causes tumor death via release of singlet oxygen (i.e., photodynamic therapy).

1 Introduction

Commercially available intra-operative neurosurgical guidance systems provide for initial tool positioning and craniotomy site placement based on a pre-operative 3D MR or 3D CT image. Currently, neurosurgical image guidance is based primarily on pre-operative images used to optimize craniotomy position and the trajectory used to reach the lesion. Most of the currently available systems use frameless CT and/or

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MR-visible fiducial markers that are located pre-operatively in the operative suite with a 3D localizer in order to register the pre-operative image to the patient. Once registered, the image may be used to choose a craniotomy (skull opening) site near the lesion and initial surgical tool orientation. Subsequent to surgical entry, the occurrence of "brain shift," surgically-induced swelling, and drop in CSF pressure conspire to reduce the utility of pre-operative images.

Intra-operative MR offers the possibility of image update without interrupting the surgical procedure to take the patient to the Radiology Department. Indeed, intra-operative neurosurgical MR devices are most useful if they do not require interruption of anesthesia. Intra-operative MR-guided neurosurgical procedures began in 1994 with the installation of the GE Medical Systems Signa SP™ "double doughnut," a mid-level field (0.5 Tesla) magnet, at Brigham and Womens Hospital in Boston [7]. Because of the groundbreaking nature of this group's activities, it has developed in-house guidance software, 3D Slicer. The 3D Slicer is available for distribution, but to our knowledge is not FDA-approved.

High field (1-2 Tesla) intra-operative MR-scanners have also been utilized [22], [9]. Intra-operative use of these devices require that all surgical instruments be MRI compatible. The Siemens Open Viva™, a 0.2 Tesla low field magnet, has been installed and utilized for neurosurgical applications at our site, University of California Medical Center, Los Angeles, and the University Hospitals in Heidelberg and Erlangen, Germany. This device provides excellent images for stereotactic guidance [13] and quantitation [26]. Indeed, Wirtz *et al.* [26] have found that when this device has been available, brain "tumor removal and [post-operative] survival times were increased significantly." Specifically, they find that intra-operative image updates can compensate for brain shift, and furthermore, unintended residual brain tumor was reduced from 70%, historically, to 30.5% in 242 cases utilizing intra-operative MR-assisted resection.

Wirtz *et al.*'s [26] findings of improved brain tumor resection efficacy associated with intra-operative MR guidance were tempered when they confirmed an observation made by other groups [12], [1], [6]: in all 66 operations with enhancing lesions, and 20 of 29 with non-enhancing lesions, varying levels of intra-operative enhancement was "induced by the surgical procedure itself". That is, intra-operatively administered intravenous contrast media (gadolinium) leaked into tissue spaces (e.g., parenchymal, CSF, or the resection cavity) where it did not appear on pre-operative scans.

The need for tumor-specific guidance and therapies has motivated us to propose clinical trials of two new investigational drugs, both of which are based on the metalloporphyrin substrate referred to as texaphyrin [28], [15]. We hypothesize either drug would improve intra-operative tumor localization, resection, and/or ablation. These localization methods utilize MR-scans or controlled light emissions. The radio frequency and optically shielded intra-operative suite at University Hospitals of Cleveland provides an optimal setting in which to test these new therapies. In order to improve intra-operative tumor localization in this setting, we have integrated an FDA-approved intra-operative MR system, the Siemens (Munich, Germany) OpenViva™, and Medtronic's (Minneapolis, MN, USA) neurosurgical guidance system. It is expected that when used with this equipment both drugs would provide tumor localization options that overcome the difficulty of leakage of vascularly administered gadolinium during intra-operative MR-guided tumor resection or ablation.

The first two years of the proposed clinical trial would use the MR-visible porphyrin-based drug, Xcytrin™ (Pharmacyclics Inc., Sunnyvale, CA). It is a porphyrin bound to gadolinium, and has been shown to preferentially bind (specificity) to tumor. Indeed, Phase I clinical trials have already determined details of the toxicity and specificity of this drug [18]. Since Xcytrin is administered pre-operatively, and is expected to provide durable enhancement intra-operatively, it obviates the need for additional intravenous contrast administration. It should prove useful for intra-operative localization of residual tumor and eliminate the occurrence of enhancement induced by surgical disruption of the blood-brain barrier. It is our expectation that resection efficacy will improve if this phenomenon is curtailed. Moreover, it is possible that Xcytrin may provide more contrast enhancement of tumor than is seen following standard vascular gadolinium administration.

The third year of the proposed clinical trial would use a lutetium-bound porphyrin, Lutrin™ (Pharmacyclics Inc., Sunnyvale, CA), for fluorescence-guided localization of tumor. This drug has also been shown to bind specifically to tumor. However, the proposed phase I trial of this drug is necessary [17]. Therefore, we propose to test the specificity of this drug for brain tumor and its sensitivity to photoactivating wavelengths of light (i.e., photodynamic therapy) on resection samples following removal from on study patients. If these tests demonstrate high specificity and sensitivity, a subsequent clinical trial would be proposed to test Lutrin-mediated photodynamic therapy for brain tumors (see Section 6).

2 Metalloporpyrins for Tumor Therapy

The use of metalloporphyrin drugs to locate and ablate cancer cells has been made possible by the work of many photochemists, surgeons, and basic scientists who have pursued the one hundred year old observation that porphyrin molecules bind with high specificity to tumor. There is general speculation on the biochemical mechanism causing tumor's highly selective uptake of porphyrins, but the specific mechanism is unknown. Shibata *et al.* [20] present evidence that porphyrin uptake by glioma cells is greatest during the mitotic portion of the cell life cycle. Discussion of basic porphyrin structure, including metalloporphyrins such as Xcytrin, and the use of porphyrins for photodynamic therapy is presented in Section 6.

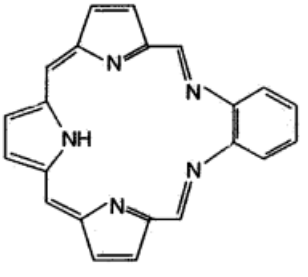

Fig. 1. Texaphyrin.

Porphyrins are intermediate molecules that serve as ligands capable of binding heme, which functions in red blood cells in the mechanism of oxygen distribution. Later, the heme group is recycled in the liver when the red blood cells become too worn. When blood transfusion is used to overcome hemoglobin synthesis deficiency the result is accumulation of non-excretable iron in the liver. The same effect is to be expected with metalloporphyhrins as they are broken down and the associated metal is deposited in fatty organ tissue, rather than excreted. The metal deposited in the case of Xcytrin is gadolinium, and in the case of Lutrin it is lutetium. While the risk of side effects from metal deposition is small with

small doses, it would be desirable to determine the minimum Xcytrin or Lutrin dose necessary for MR tumor contrast, photodynamic therapy, and/or fluorescence tumor contrast.

Metalloporphyrins are more hydrophilic than hematoporphyrins (see Section 6). Thus, they move efficiently into plasma and subsequently to tumor. They also wash quickly from the circulation, thus quickly reducing skin and eye photodynamic sensitivity. Prior to 1988, none of the previously created expanded porphyrin systems formed stable complexes with large metal cations, a level of non-lability not equaled in any lanthanide(III) porphyrin complexes [19]. Sessler *et al*. [19] first demonstrated the binding of "Texas-sized" (texaphyrin) porphyrins to lanthanide metal ions, showing that the central binding cavity is expanded 20% over metal-free porphyrins from 4 Nitrogen atoms in hematoporphyrin (i.e., naturally occurring porphyrin) to 5 in texaphyrin (Figure 1). The additional equatorial binding region allows for free interaction of the axial poles of the metal with other molecules. This is important for lanthanide (III) metals such as gadolinium(III) and lutetium(III) which remain free to bind with readily disassociated ligands such as chloride, acetate, and nitrate found at the target cell surface. In distinction to other metalloporphyrins, texaphyrin complexes are more difficult to oxidize and easier to reduce. It is suspected that this enhances their specificity for tumor.

3 Intra-operative MR Xcytrin-Based MR Guidance

Why MR and why Xcytrin? The primary advantage of MR over CT is that it usually provides better definition of internal inhomogeneous soft tissue structures like the brain. This is due to the spatial distribution of the MR signal, which is partly determined by the nuclear density of the object imaged. It is also a function of parameters such as the relaxation times T1 and T2 and of fluid flow at each point. MR imaging of the brain primarily measures the distribution and properties of hydrogen, the most abundant element in tissues of living systems. While there can be artifacts from ferrous objects, MR radio frequency electromagnetic radiation penetrates boney material like the skull, enabling the brain to be imaged without significant attenuation. Unlike CT, through instrument design and operator control, the influence of all of these parameters on the MR image may be emphasized to give discrimination between tissues with similar electron density. Relevant examples include, first, the strong discrimination seen between gray and white matter on the basis of their significantly different T1 values, and, second, the good contrast commonly obtained between tumor, edema, cerebrospinal fluid, gray matter, and white matter in T2 weighted images.

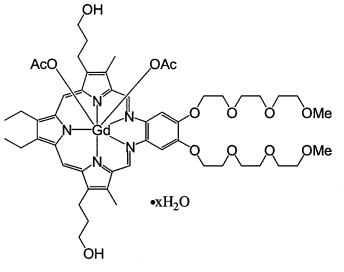

Fig. 2. Xcytrin™ is also referred to as Gadolinium(III)-Texaphyrin.

Damadian [4] found that values of proton relaxation times, T1 and T2, in neoplastic tissue are significantly larger than those in normal brain tissue. Differential proton relaxation times thus potentially provide a valuable neurosurgical pathologic discriminator. However, the shift to MR imaging of brain tumors from CT occurred relatively slowly. It first required demonstration of sufficient MR spatial fidelity [5]. It is generally thought that CT underestimates brain tumor volume, but studies where both CT and MR were available for the same patient at the same time have shown that both modalities have the possibility of detecting a larger volume [23]. Perfusion of the tumor is the basis for gadolinium enhancement, which roughly corresponds to tumor cell proliferation [24]. Therefore, and unfortunately, not all tumors provide good contrast with surrounding tissue following gadolinium administration. It enters the microvasculature of the tumor where the blood brain barrier has been broken, but has no unique specificity for tumor tissue.

Xcytrin™ (Figure 2), referred to as PCI 0120 (Pharmacyclics Inc., Sunnyvale, CA), is a complex of texaphyrin and a trivalent gadolinium. The latter paramagnetic molecule results in Xcytrin's high MR visibility. Selective uptake of Xcytrin by tumor has been associated with long-lasting MR enhancement. This was first observed *in vitro* in isolated tumor cells, murine mammary carcinoma, injected in rat and rabbit thigh and liver, respectively [29]. In clinical trials of radiation therapy sensitization effects, MR enhancement of brain tumor has been reported up to 8 weeks following Xcytrin administration [25]. Deposition of trace amounts of the metallic gadolinium Xcytrin core are also observed in healthy tissues (e.g., kidney, liver, gastrointestinal tract), therefore Xcytrin is not appropriate as a general diagnostic contrast agent. However, if significant therapeutic benefit is expected, such as enhanced glioma resection or radiation therapy sensitization, Xcytrin administration is justified.

4 Intra-operative MR Benefits from Xcytrin-Based Guidance

Commercially available neurosurgical navigation systems help plan and guide surgery based on a pre-operative 3D MR image. Primarily, these systems use so called "frameless" fiducial imaging markers, which are usually MR-visible objects affixed to the patient's scalp. Software is used to match the pre-operative volume MR image to the patient on the operating room table by superimposing the scalp-bound fiducial imaging markers seen in the image to their location seen in a coordinate system established in the operating room. The "operating room" location of the markers is obtained by 3D localizer once the patient's head position is fixed for surgery. Surgical entry location and tool trajectory may then be planned and tracked in software on the guidance computer. This procedure assumes that the pre-operative image on the computer is true to the patient's anatomy on the operating room table. Since this condition is known to be violated once the procedure begins, the use of conventional neurosurgical guidance systems is often limited to procedure initiation.

A significant change in spatial relationships occurs following surgical entry. It is referred to as "brain shift." It results from: cerebral edema, release of cerebrospinal fluid (CSF), tissue removal, and gravitationally induced sagging. These factors conspire to reduce the utility of pre-operative images once the procedure has begun [14].

Intra-operative update of the pre-operative MR guidance image can indicate the serial change in lesion and critical brain structure location during surgery. However, as noted in the introduction the value of these images diminished by leakage of intra-operatively administered contrast media can leak from the vascular compartment into other tissue spaces. It is our expectation that resection efficacy will improve if this phenomenon is curtailed. Moreover, it is possible that tumors that do not enhance following vascular gadolinium administration will do so following an Xcytrin regimen. If cases where that occurred we would expect a significant increase in resection efficacy and therapeutic benefit.

5 Intra-operative Metalloporphyrin-Based Fluorescence Guidance

Like other porphyrins, both Xcytrin and Lutrin are excited to fluorescence when exposed to light emissions in the 450-480 nm range. High specificity for fluorescent biolocalization of tumor using both drugs has been shown in mice [27], [Woodburn, unpublished data].

The fluorescence of several other photosensitizing porphyrin drugs have been studied in the C6 and 9L mouse and rat glioma models following administration of 3 non-texaphyrin porphyrin drugs: HpD [3], Photofrin [3], [11], ALA [11], and Boronated Protoporphyrin [2]. Stummer *et al.* [21] found human glioma resection aided by the presence of a fluorescing porphyrin drug, ALA, where "for seven of nine patients, visible porphyrin fluorescence led to further resection of the tumor". The usefulness of Xcytrin and Lutrin for fluorescence contrast localization depends on the specificity of these two drugs for glioma; a determination that is a major goal of the proposed clinical trial.

The hardware necessary to detect residual glioma via fluorescent contrast has been tested in a clinical trial of another porphyrin, Photofrin, at the University of Toronto. The image in Figure 3 was taken after the neurosurgeon had stated that he had completed the brain tumor resection based on information available to him from white light visual inspection of the resection cavity through the operative microscope. Operative white light was then turned off to capture this image through a novel long working distance camera which applies fluorescence excitation light of 450-480 nm wavelength. After capture of the fluorescent light photograph, the operative room white lights are then restored. The fluorescent portion of the image (lighter color in Figure 3) is then overlain on the white light image the surgeon sees in a stereotactic operative microscope. This provides resection guidance for otherwise invisible residual tumor and the surgery continues. It should be noted that because Photofrin has a very low extinction coefficient in the white light used by the surgeon, no light shielding is needed against the 600-650nm range of the Q band that would photoactivate Photofrin and cause tissue necrosis. Thus, it is possible to bring about Photofrin fluorescence without causing inadvertent photodynamic therapy.

We propose to verify the same scenario (i.e., intra-operative fluorescent localization without photoactivation) for Lutrin. This is not necessary for Xcytrin as it cannot photoactivate. If Xcytrin were utilized, we expect resection completion would be additionally sped by detection of larger pieces of residual tumor, including their entire depth, on intra-operative MR images taken after the surgeon had lost all white

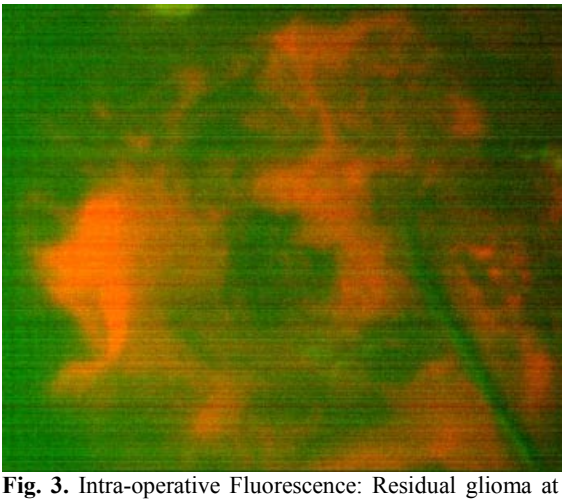

Fig. 3. Intra-operative Fluorescence: Residual glioma at the innermost margin of the resection cavity. This tumor was visualized following 5mg/kg Photofrin intravenous injection and excitation to fluoresce. After the fluorescent picture is taken, the fluorescent portion (lighter color) of this image is superimposed over white light view on screen in the operating room microscope.

light visual cues for tumor location in the operative microscope. The use of intra-operative MR-scanning Lutrin or Xcytrin to locate residual tumor would allow the surgeon to complete the resection going back and forth between updated intra-operative MR-scan, white light (for resection), and fluorescent light (to survey for residual tumor). The use of fluorescent contrast for tumor localization could occur as often as desired as long as photo-bleaching of the metalloporphyrin does not occur.

As with photodynamic therapy (see Section 6), dosimetry is essential for use of fluorescent activity. At a measurable point the photosensitizer will become "bleached" and fluorescence ceases (i.e., it converts to its inactive form). Fluorescence properties would be a function of the sum photo-activation (fluorescence) and the light intensity used throughout the operative procedure. Stummer *et al.* [21] found that when using ALA5 as a tumor marker: "Under operating light conditions, fluorescence decayed to 36% in 25 minutes for violet-blue light and in 87 minutes for white light." Photobleaching rates must known *a priori*; they are clearly a function of the photosensitizer used.

6 Intra-operative MR-Guided Photodynamic Therapy

Lutrin (Figure 4), referred to as PCI (Pharmacyclics Inc., Sunnyvale, CA) 0123, has been designed to overcome a number of the limitations of other second-generation photodynamic therapy photosensitization agents. It is a tripyrrolic pentadentate aromatic complex. Its lowest activation wavelength, λ=730nm (range 730-770), allows deep tissue penetration [19]. The administration of PDT activation light delivery and dosimetric accuracy should benefit from intra-operative MR guidance and light shielding of the intra-operative MR suite at University Hospitals of Cleveland. Intra-operative fluorescence of Lutrin should also assist in verifying the location of regions targeted for Photodynamic therapy. It is noteworthy that photons and the optical tools for Lutrin-mediated fluorescent localization and/or photodynamic therapy of brain tumors are inherently MR compatible.

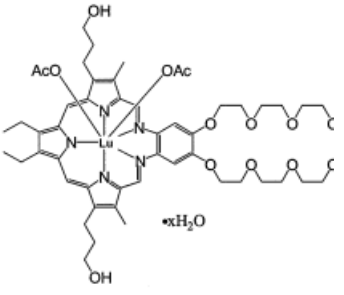

Fig. 4. Lutrin^{TM} is also referred to as Lutetium(III)-Texaphyrin.

Lutrin's high water solubility and aqueous formulation allow it to clear quickly from plasma and other tissues where irreversible toxicity may be a concern and inadvertent photodynamic therapy sensitization is not desired [27]. When irradiated at 732nm Lutrin has a high singlet oxygen ($^1O_2$) yield of >20%, depending on availability of ground state oxygen ($^3O_2$) in local tissues [19], [8].

Selectivity of Lutrin uptake has been demonstrated in two mouse tumor model studies, murine mammary carcinoma [29] and murine melanoma [27]. An expected corollary to the presence of the blood-brain-barrier [16], is a finding of the latter study that lowest levels of Lutrin uptake were in normal brain tissues (i.e., where brain tumor had not broken down the blood-brain-barrier). Lutrin has been found more sensitive to photodynamic therapy illumination than Photofrin in a mouse mammary adenocarcinoma [10]. The proposed study would assay specificity of Xcytrin or Lutrin uptake in normal brain versus brain tumor (glioma).

There are at least two stages of patient care at which there is significant risk for inadvertent and unintended photosensitization to occur. The first is the pre-operative period, between drug administration and surgery. If the drug has high specificity and clears the blood stream reasonably quickly there should be little risk at this stage. The second period where patients are at risk for photoactivation of non-tumor tissue is during surgical treatment and immediately thereafter. It appears for photodynamic therapy of brain tumors there may be two causes of non-specific drug uptake. First, drug may associate with normal tissues because of a natural affinity. Second, drug may spread to the region of normal tissues due to edema associated with surgery [21]. Edema may be controlled by utilizing optimal lag time and appropriate and accurate illumination dosimetry and distribution.

7 Conclusions

Intra-operative MR scanning has been demonstrated to improve glioma and other brain tumor resection efficacy. Metalloporphyrins offer three new opportunities to improve brain tumor resection efficacy when used in conjunction with intra-operative MR. First, an MR-visible contrast agent that binds specifically to tumor, such as Xcytrin, should be able to overcome the non-specific contrast resulting from leakage of vascularly administered gadolinium leakage during intra-operative procedures. Second, Xcytrin or Lutrin fluorescence should provide fluorescent guidance to residual tumor that is not visible under white light. Finally, in future, we expect that Lutrin-mediated fluorescence will insure maximum tumor resection and photodynamic therapy ablation of unresectable residual.

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