Photodiagnosis and Photodynamic Therapy 18 (2017) 185–192

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Combination of hand-held probe and microscopy for fluorescence guided surgery in the brain tumor marginal zone☆

Johan C.O. Richter[a,b,*], Neda Haj-Hosseini[a], Martin Hallbeck[c], Karin Wårdell[a]

[a] Department of Biomedical Engineering, Linköping University, Sweden
[b] Department of Neurosurgery Linköping University Hospital, Region Östergötland, Linköping, Sweden
[c] Department of Clinical Pathology and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form
23 December 2016
Accepted 3 January 2017
Available online 20 February 2017

Keywords:
High-grade glioma
Fluorescence guided resection (FGR)
5-Aminolaevulinic acid (5-ALA)
Fluorescence spectroscopy
Protoporphyrin (PpIX)

ABSTRACT

Background: Visualization of the tumor is crucial for differentiating malignant tissue from healthy brain during surgery, especially in the tumor marginal zone. The aim of the study was to introduce a fluorescence spectroscopy-based hand-held probe (HHF-probe) for tumor identification in combination with the fluorescence guided resection surgical microscope (FGR-microscope), and evaluate them in terms of diagnostic performance and practical aspects of fluorescence detection.
Material and Methods: Eighteen operations were performed on 16 patients with suspected high-grade glioma. The HHF-probe and the FGR-microscope were used for detection of protoporphyrin (PpIX) fluorescence induced by 5-aminolevulinic acid (5-ALA) and evaluated against histopathological analysis and visual grading done through the FGR-microscope by the surgeon. A ratio of PpIX fluorescence intensity to the autofluorescence intensity (fluorescence ratio) was used to quantify the spectra detected by the probe.
Results: Fluorescence ratio medians (range 0 – 40) measured by the probe were related to the intensity of the fluorescence in the FGR-microscope, categorized as "none" (0.3, n = 131), "weak" (1.6, n = 34) and "strong" (5.4, n = 28). Of 131 "none" points in the FGR-microscope, 88 (67%) exhibited fluorescence with the HHF-probe. For the tumor marginal zone, the area under the receiver operator characteristics (ROC) curve was 0.49 for the FGR-microscope and 0.65 for the HHF-probe.
Conclusions: The probe was integrated in the established routine of tumor resection using the FGR-microscope. The HHF-probe was superior to the FGR-microscope in sensitivity; it detected tumor remnants after debulking under the FGR-microscope. The combination of the HHF-probe and the FGR-microscope was beneficial especially in the tumor marginal zone.
© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The basic treatment concept for high-grade gliomas proposes cytoreductive surgery in order to enable optimized oncological treatment [1]. A higher extent of resection, over 78 % and even stepwise improvements from 95 % to 98 % and to 100 %, have been associated with a higher survival advantage [2]. The introduction of the FGR-microscopy technique into neurosurgery, based on the pioneering work of Stummer and his team [3,4], has been of substantial benefit to patients with malignant gliomas. The technique has become an integrated routine of the standard operation settings in many European neurosurgical centers [5–7]. The visual discrimination of tumor tissue with fluorescence from healthy brain tissue without fluorescence allows for more extensive resection of the tumors [5] even beyond the MRI contrast enhancement [4,8]. The technique has therefore increased precision in the surgical treatment of these tumors and improved preconditions for the oncologic therapies, thus contributed to prolonged progression free survival [3,9] as well as to prolonged overall survival [5,9].

Generally, the intention of surgical treatment of malignant gliomas within the cytoreductive concept is the so-called gross total resection (GTR), defined by the absence of contrast media enhancing tumor tissue on the postoperative magnetic resonance images [10,11]. However, the problem remains that primary brain tumors have no membranous limitation distinguishing them from healthy

☆ Portions of this paper has been presented in the Scandinavian Neurosurgical Meeting, Reykjavik, Iceland 2013 and Lund, Sweden 2015 and World Congress on Medical Physics and Biomed. Eng., Toronto, 2015.

* Corresponding author at: Department of Neurosurgery Linköping University Hospital, SE-581 85 Linköping, Sweden.
E-mail address: johan.richter@regionostergotland.se (J.C.O. Richter).

http://dx.doi.org/10.1016/j.pdpdt.2017.01.188
1572-1000/© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

brain tissue. The surgical challenge is to delineate the malignant tissue and to preserve functional brain which is mainly achieved by visual means. In addition to the FGR-microscope, the 5-ALA induced PpIX in the tumor can be visualized by other fluorescence measurement techniques e.g. by means of fiber-optic based spectroscopy [12,13]. 5-ALA naturally exists in the heme biosynthesis cycle where its transformation to PpIX in the cells and binding of PpIX to iron produces heme. The externally applied 5-ALA reaches the tumor cells through the disrupted blood brain barrier and accumulates in the mitochondria as PpIX due to the altered enzyme levels in the tumor cells [14–18] and additional factors including pH and temperature [16]. PpIX is a known fluorophore with an emission spectrum in a wavelength range of 600–750 nm and an absorption spectrum in a wavelength range of 250–650 nm. As the maximum absorption of PpIX occurs at approximately 400 nm, it is preferred to use blue light for the excitation of PpIX for diagnostic purposes whereas the excitation light at approximately 635 nm is commonly used for therapy purposes [19] and longer wavelengths for multiphoton excitation [20].

The conventional FGR-microscope allows for safe resection of the viable tumor bulk, which in the operational field is perceived by the surgeon as “strong” fluorescence, whereas “weak” fluorescence areas represent tissue with an uncertain degree of tumor infiltration. It has been stated that the “weak” areas should not be considered for resection [21]. However, this transitional zone, where stronger signals gradually or irregularly shift into weaker signals, remains poorly defined and dependent on the surgeon’s subjective eyesight. Data published on the relation between 5-ALA induced PpIX fluorescence and the actual degree of infiltration in areas with “weak” fluorescence is limited and retrieved by means of the FGR-microscopy method only [7,22–24]. Moreover, there is no practical procedure that takes into account fluorescence attenuating factors including photobleaching which inevitably occurs due to light exposure from various sources in the operating room (OR), including the FGR-microscope.

At Linköping University Hospital, the FGR-microscope and an in-house HHF-probe have been implemented as stand-alone systems in the clinical practice during tumor resection. The HHF-probe has been used as a hand-held device [12] and in combination with ultrasound based navigation [13]. Fluorescence intensity in the tumor and marginal zone have been measured using a lower 5-ALA dose (5 mg/kg) with the HHF-probe. This lower 5-ALA dose showed comparable diagnostic performance to the conventional dose of 20 mg/kg used for FGR-microscopy [25]. In the present study, integration of the FGR-microscope and the HHF-probe was evaluated in the process of intraoperative tumor tissue identification. Of special interest were the systems’ diagnostic performances in the tumor marginal zone, and the practical aspects of the detection techniques.

2. Material and methods

2.1. Patients

Sixteen patients (7 males and 9 females, median age of 62 years, range 18 – 82 years) with suspected glioblastoma (GBM) were included in the study. Fifteen patients at the Department of Neurosurgery at Linköping University Hospital and one patient at Norrland University Hospital in Umeå. Patients were randomly included from referrals with clinical and radiological signs of suspected high-grade glioma or with a known recurrence, on the basis of standard criteria for surgery in these categories. Most of the surgical procedures (n = 13) were performed by the study surgeon (JR), as he was well acquainted with both the FGR-microscope and the HHF-probe techniques. Postoperative MRI-scans within 72 h were used to verify GTR. Written informed consent was obtained from the patients. The protocol was approved by the local ethical board (Project No.: M139-07, 2012/333-32). In total 18 operations were performed, two of them on recurrent tumors both of which were included in the study for the primary tumor operation as well.

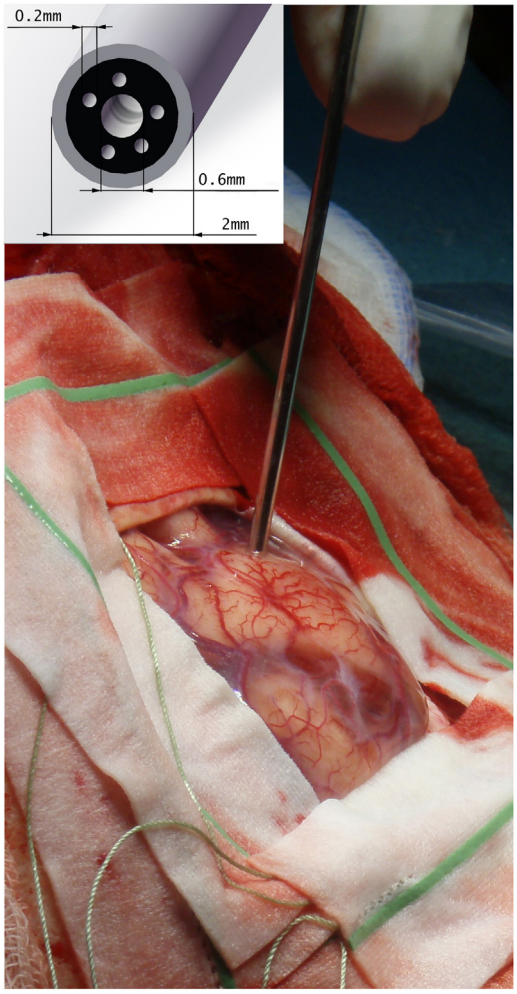

Fig. 1. Placement of the HHF-probe on a measurement site in the brain. The configuration of the fibers in the probe are shown at the top left of the image.

2.2. HHF-probe and FGR-microscope

The FGR-microscope (M720 OH5, Leica GmbH, Germany) was used with the FL400 fluorescence module (blue light). The FGR-microscope’s light source is a 300 W xenon-arc lamp (irradiance of 40 mW/cm^2), the field of view is 125 × 143 mm. The in-house built probe based system [12,26] consisted of an excitation laser (Oxxius, Lannion, France) with a wavelength of 405 nm. A spectrometer (EPP2000, Stellarnet, Tampa, FL) operating in the wavelength range of 240–850 nm with a spectral resolution of 3 nm, measured dynamic range of 3900 (maximum scale of 8190 a.u.) and signal to noise ratio (SNR) of $\leq$ 620 collected the data for further processing and real-time presentation in the OR. The measurement probe (l_{probe} = 12 cm, Ø = 2 mm, l_{cable} > 4 m) had one excitation and several collecting fibers connected to the laser and the spectrometer, respectively. The collecting fibers were placed adjacent to the excitation fiber, center–center distance = 450 μm [12] (Fig. 1). The surface of the probe tip was flat but the outer circumference was rounded to avoid tissue damage. The fluorescence spectroscopy system could be used in a pulsed or in a continuous mode. The

Download English Version:

https://daneshyari.com/en/article/5682375

Download Persian Version:

https://daneshyari.com/article/5682375

Daneshyari.com