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Platinum Priority – Prostate Cancer

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Photodynamic Diagnosis Using 5-Aminolevulinic Acid for the Detection of Positive Surgical Margins during Radical Prostatectomy in Patients with Carcinoma of the Prostate: A Multicentre, Prospective, Phase 2 Trial of a Diagnostic Procedure

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Abstract

Background: Surgical margin status after radical prostatectomy (RP) is a significant risk factor for tumour recurrence. It is an intriguing concept to find a fluorescence marker for photodynamic diagnosis (PDD) to make tumour margins visible during surgery.
Objective: To investigate the feasibility of identification of positive surgical margins (PSM) during open retropubic or endoscopic extraperitoneal RP by 5-aminolevulinic acid (5-ALA)–induced protoporphyrin IX (PpIX) to enhance surgical radicality.

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5-ALAFluorescence
PDD
Photodynamic diagnosis
Prostate cancer
Protoporphyrin IX
Radical prostatectomy
Surgical margin

Design, setting, and participants: Thirty-nine patients (Gleason score 6–10, prostate-specific antigen [PSA] 2.3–120 ng/ml) received 20 mg/kg of body weight of 5-ALA orally and underwent RP (24 endoscopic extraperitoneal, 15 open retropubic).
Measurements: A PDD-suitable laparoscopy optic (Karl-Storz GmbH, Tuttlingen, Germany) with a yellow long-pass filter was coupled to a fibre-optic light cord with an excitation light source (380–420 nm, D-Light, Karl-Storz GmbH, Tuttlingen, Germany) for fluorescence excitation of PpIX and to a PDD-suitable camera for video and photo documentation by the AIDA DVD system (Karl-Storz GmbH, Tuttlingen, Germany).
Results and limitations: There were more false-negative cases in the open group (four vs two) than in the endoscopic group but more false-positive cases in the endoscopic group (two vs none) than in the open group. The overall sensitivity and specificity were 56% and 91.6%, respectively. The sensitivity of the endoscopic cases was much higher (75% vs 38%) than for the open cases, while the specificity was higher for the open group (88.2% vs 100%).
Conclusions: PDD with 5-ALA–induced PpIX during RP might be a feasible and effective method for reducing the rate of PSM. The technique seems to be more practicable during endoscopic RP rather than open RP. Further clinical studies with higher patient volumes and further development of the technique seem justified.
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1. Introduction

Radical prostatectomy (RP) is a standard therapy for localised prostate cancer (PCa). The goal of this procedure is to achieve the ideal trifecta [1]: cancer control, continence, and potency. Postoperative results rely on surgical skill [2]. An ideal procedure would include eradication of all cancerous tissue and preservation of as much functional tissue as possible. In selected cases, a nerve-sparing operation may be performed to preserve potency. The cancer extension (eg, infiltration of the neurovascular bundle [NVB]) can be estimated by nomograms [3,4]. Nevertheless, these tools only estimate the general risk of extracapsular extension (ECE) [3]. Thus, we cannot predict with certainty an ECE situation in the individual patient.

A positive surgical margin (PSM) is associated with biochemical recurrence (BCR) [5] and is reported in 11–38% of patients undergoing RP. The only available tool for determining complete tumour resection during surgery is the examination of frozen section [6]. The drawback of this procedure is that it is time and cost consuming. In addition, it is not available in every institution, and there is a certain risk of false-negative results [6]. It is therefore an intriguing concept to make the tumour visible during surgery to reduce the risk of positive surgical margins. Fluorescence markers might be in favour to illuminate cancerous tissue. In bladder cancer (BCa), several investigators have used photodynamic agents, such as protoporphyrin IX (PpIX) induced by intravesical administration of 5-aminolevulinic acid (5-ALA), to distinguish between malignant and benign tissue [7–10]. Among others, 5-ALA–induced, PpIX–guided surgery after oral administration has been investigated in organ-sparing resection of kidney tumours [11] and is routinely performed in some centres for neurosurgery of malignant gliomas [12–14], where the exact definition of tumour margins is of the utmost importance.

5-ALA is a precursor in the heme biosynthesis pathway and is metabolised to fluorescent PpIX before being converted to photoinactive heme. PpIX, which accumulates temporarily in tumour tissue after the exogenous application of 5-ALA, is the endogenous photosensitiser needed for photodynamic diagnosis (PDD) [15]. The selective accumulation of PpIX in malignant tissue provides an intense colour contrast between the red fluorescing of malignant lesions and the nonfluorescing normal tissue when blue light at a wavelength around 400 nm is used.

Based on the first clinical experiences by Zaak et al [16], who were able to show a very selective enhancement of 5-ALA–induced PpIX in human PCa

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