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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.
Trial registration: EudraCT: 2005-004406-93.

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

after oral administration, it was the aim of this first prospective study to investigate the feasibility of intraoperative identification of PSM during open retropubic or endoscopic extraperitoneal RP.

2. Patients and methods

2.1. Patients

A total of 40 patients with histologically proven carcinoma of the prostate were enrolled in the study after having provided written informed consent. The study was approved by the local ethical committees of the four participating centres and by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]). Patients were informed about potential side-effects (eg, transient rises in serum aspartase, aminotransferases, skin photosensitivity, nausea, and vomiting). Because one patient dropped out after withdrawing consent immediately before the beginning of the operation, 39 patients (Gleason score 6–10, prostate-specific antigen [PSA] level 2.3–120 ng/ml) underwent RP. Each of the four centres enrolled 10 patients. Twenty-four patients underwent endoscopic extraperitoneal RP and 15 patients received open retroperitoneal RP. Table 1 shows the clinical data for all patients and groups.

2.2. Administration of 5-aminolevulinic acid

A solution of 20 mg/kg of body weight but not >1.5 g/person of 5-ALA was given orally 3 h prior to the beginning of the operation, as described previously [17].

Table 1 – Clinical data and final histopathologic results on laparoscopic and open radical prostatectomies for each centre

Centre	Patient No.	Technique	PSA	Tumour stage	Gleason	Margin
1	1	L	7.07	pT2c	3 + 4 = 7	–
1	2	L	3.30	pT2c	4 + 4 = 8	–
1	3	L	19.82	–	–	–
1	4	L	4.68	pt2c	3 + 4 = 7	–
1	5	L	2.30	pT3a	4 + 3 = 7	R1
1	6	L	7.10	pT3a	4 + 4 = 8	–
1	7	L	17.00	pT3a	4 + 4 = 8	–
1	8	L	18.60	pT3a	4 + 4 = 8	R1
1	9	L	11.19	pT2a	4 + 3 = 7	–
1	10	L	26.0	pT2a	3 + 4 = 7	–
2	1	L	14	pT3a	3 + 4 = 7	–
2	2	L	10.4	pT3b	3 + 4 = 7	R1
2	3	L	10	pT2c	3 + 4 = 7	–
2	4	L	14.9	pT3b	3 + 4 = 7	–
2	5	L	11.4	pT3b	4 + 3 = 7	–
2	6	L	6.8	pT2c	3 + 4 = 7	–
2	7	L	11	pT3a	3 + 4 = 7	R1
2	8	L	8.03	pT2b	4 + 3 = 7	R1
2	9	L	8.48	pT3b	4 + 3 = 7	R1
2	10	L	8.02	pT2c	3 + 5 = 8	–
3	1	O	6.64	pT2c	3 + 4 = 7	–
3	2	O	8.01	pT2c	3 + 3 = 6	–
3	3	O	6.16	pT3b	3 + 4 = 7	R1
3	4	O	8.3	pT2c	3 + 4 = 7	–
3	5	O	8.57	pT3b	4 + 3 = 7	–
3	6	O	15.25	pT2c	3 + 2 = 5	–
3	7	O	49.61	pT3a	4 + 3 = 7	–
3	8	O	6.7	pT3a	3 + 4 = 7	–
3	9	O	5.59	pT2c	3 + 4 = 7	–
3	10	O	15.2	pT2c	3 + 4 = 7	–
4	1	O	42.5	pT3a	3 + 4 = 7	R1
4	2	O	6.8	pT2c	4 + 4 = 8	–
4	3	O	5.41	pT3b	5 + 5 = 10	R1
4	4	O	63.39	pT3b	4 + 5 = 9	R1
4	5	O	120	pT3b	4 + 5 = 9	R1
4	6	L	25.6	pT3b	5 + 5 = 10	R1
4	7	L	49.4	pT3a	3 + 4 = 7	R1
4	8	L	–	–	–	–
4	9	L	14.1	pT3a	4 + 3 = 7	–
4	10	L	4.97	pT3b	3 + 4 = 7	–

L = laparoscopic radical prostatectomy; O = open radical prostatectomy; PSA = prostate-specific antigen.

2.3. Diagnostic system

The same standard was used in each centre for endoscopic and open RP. For PDD, a suitable laparoscopy optic (Karl-Storz GmbH, Tuttlingen, Germany) was used with a yellow long-pass filter fitted into the eyepiece of the optic to reduce the blue excitation light and enhance the fluorescence colour contrast. The optic was coupled to a fibre-optic light cord with an excitation light source (lambda 380–420 nm, D-Light, Karl-Storz GmbH, Tuttlingen, Germany), which provides blue light (375–420 nm) for fluorescence excitation of PpIX. The optic was also coupled to a PDD-suitable camera, and video and photo documentation was granted by the AIDA DVD system (Karl-Storz GmbH, Tuttlingen, Germany).

2.4. Intraoperative procedure

During endoscopic extraperitoneal RP and open RP, the resection margins were fluoroscopically examined by changing the light source from white light to blue light with a foot switch to avoid bleaching of the photosensitiser. During open retropubic RP, the optic was positioned in front of the resection margins to illuminate the tissue inside the patient after darkening the operating room, as described earlier [16]. PDD-positive areas on the prostate were marked for pathologic examination after extraction of the organ by white ink. PDD-positive areas on extraprostatic tissue were biopsied for pathologic examination. No biopsies were taken from the prostatic specimen. Surgeons were instructed not to alter their standard operative procedure because of information gathered by PDD. After removal of the prostate, the capsule of the prostate as well as the surgical margins were investigated by PDD.

2.5. Pathologic examination

RPs were processed according to the published guidelines [18] using the Stanford protocol. Fluorescence-positive areas were investigated separately for tumour infiltration after inking the margin and standard fixation in formalin. In randomly selected cases, the unfixed samples were investigated for red fluorescence using a standard fluorescence microscope (Fig. 1).

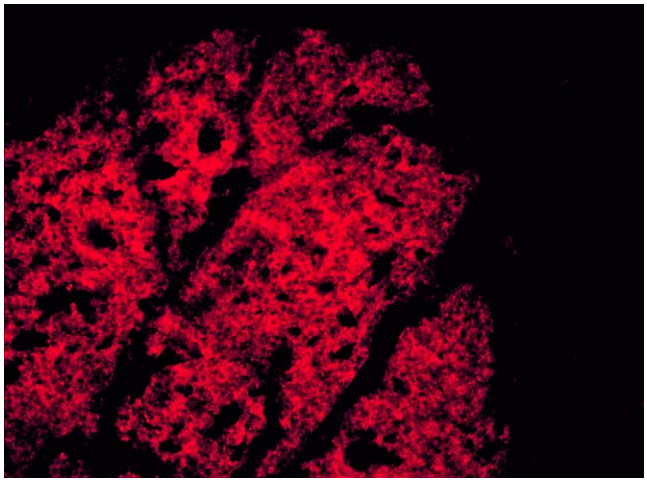

Fig. 1 – Fluorescence microscopy: photo of prostate specimen.

2.6. Statistical analysis

The aim of this descriptive study was the investigation of the feasibility of the method. Therefore, and because of the small patient population, no statistical analysis was performed.

3. Results

3.1. Clinical and histopathologic results

Thirty-nine of the 40 enrolled patients underwent RP and PDD after oral application of 5-ALA. One patient dropped out of the study after withdrawing informed consent. Twenty-four patients were operated on by endoscopic technique, while 15 patients underwent open retropubic access. Mean and median preoperative PSA for the open, laparoscopic, and both groups was 24.57 ng/ml (median: 8.3; range: 5.42–120 ng/ml), 13.09 ng/ml (median: 10.7 ng/ml; range: 3.3–49.4 ng/ml), and 17.49 ng/ml (median: 10 ng/ml; range: 3.3–120 ng/ml), respectively. Postoperative histopathologic evaluation revealed a pT2 tumour in 16 (42%) and a pT3 tumour in 22 (58%) patients (Table 1). In one prostatic specimen, a tumour was not found in the final histopathologic examination (centre 1). Thirteen of the 39 patients had PSM (eight endoscopic and five open). Overall, there was no difference in the open or laparoscopic group for a PSM (33% in both groups). In the open group, three initially positive surgical margins (Table 2, centre 3) detected by intraoperative frozen sections have been corrected in the same operation by secondary resection of the NVB. This resulted in histologically negative margins in the final histopathologic findings. Thus, without frozen sections, there would have been three more positive margins, which would reduce the number of negative margins to 47% in the open group and to 59% for both groups.

3.2. Photodynamic diagnostic

In 28 patients, no positive fluorescent signal was detected. Of those, 22 patients were right PDD negative, and 6 patients were classified falsely negative. The majority of the false-negative cases were in the open group rather than the laparoscopic group (four vs two). This revealed in a false negative rate of 50% for the open group and 25% for the laparoscopic group.

Table 2 – Results of photodynamic diagnosis during radical prostatectomy with surgical margin status

Centre	Patient No.	Technique	FL	Location	SM	FS	Location	Interpretation
1	1	E	–	–	–	–	–	rn
1	2	E	–	–	–	–	–	rn
1	3	E	–	–	–	–	–	rn
1	4	E	–	–	–	–	–	rn
1	5	E	+	BN	+	–	BN	rp
1	6	E	–	–	–	–	–	rn
1	7	E	–	–	–	–	–	rn
1	8	E	+	AP/Lat	+	–	AP/Lat	rp
1	9	E	–	–	–	–	–	rn
1	10	E	+	Ventral	–	–	–	fp
2	1	E	–	–	–	–	–	rn
2	2	E	+	BN, Lat	+	–	BN	rp, fp
2	3	E	–	–	–	–	–	rn
2	4	E	–	–	–	–	–	rn
2	5	E	–	–	–	–	–	rn
2	6	E	–	–	–	–	–	rn
2	7	E	+	Apex	+	–	Apex	rp
2	8	E	+	Apex	+	–	Apex	rp
2	9	E	–	–	+	–	BN	fn
2	10	E	–	–	–	–	–	rn
3	1	O	–	–	–	–	–	rn
3	2	O	–	–	–	–	–	rn
3	3	O	+	Ventral	+	+*	NVB	rp/fn
3	4	O	–	–	–	–	–	rn
3	5	O	–	–	–	+*	NVB	fn
3	6	O	–	–	–	–	–	rn
3	7	O	–	–	–	+*	NVB	fn
3	8	O	–	–	–	+*	NVB	fn
3	9	O	–	–	–	–	–	rn
3	10	O	–	–	–	–	–	rn
4	1	O	+	Apex	+	–	Apex	rp
4	2	O	–	–	–	–	–	rn
4	3	O	–	–	+	–	Apex	fn
4	4	O	+	BN	+	–	BN	rp
4	5	O	+	Apex	+	–	Apex	rp
4	6	E	+	Apex	+	–	Apex	rp
4	7	E	–	–	+	–	Lateral	fn
4	8	Dropout	–	–	–	–	–	–
4	9	E	–	–	–	–	–	rn
4	10	E	–	–	–	–	–	rn

AP = anterior-posterior; BN = bladder neck; E = endoscopic radical prostatectomy; FL = fluorescence; fn = false negative; fp = false positive; FS = frozen section; Lat = lateral; NVB = neurovascular bundle; O = open radical prostatectomy; rn = right negative; rp = right positive; SM = surgical margin.

* Centre 3 performed intraoperative frozen sections: In four cases, the NVB has been secondarily resected because of a positive margin in the frozen section.

In total, 11 (28%) patients showed a positive fluorescent signal. Of those, 9 (69%) were right positive. Distribution for intraoperatively correctly detected PDD-positive surgical margins were six in the endoscopic group and four in the open group. One of these patients (endoscopic) showed an additional false-positive spot (Table 2, centre 2, patient 2).

Nine of the 13 PSM were recognised by PDD at the correct site. Three PSM (two endoscopic and one open) were overlooked, because one of them (open) was PDD positive ventrally, while the histologically positive site was also at the nerve bundle, where no fluorescent signal has been detected (Table 2, centre 3, patient 3).

There were more false-negative cases in the open group (two vs five) 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 for the open group specificity was higher (88.2% vs 100%).

Table 3 – Fluorescence results: photodynamic diagnosis compared with histopathologic evaluation

	Overall $n = 39$	Laparoscopic $n = 24$	Open $n = 15$
Fluorescence	11 (28%)	7 (25%)	4 (27%)
No fluorescence	28 (72%)	–	–
PSM	13 (33%)	8 (33%)	5 (33%) 8 (53%)*
False positive	2 (7%)	2 (13%)	–
False negative	7 (54%)	2 (25%)	5 (63%)
Right positive	9 (69%)	6 (75%)	3 (38%)
Right negative	22 (96%)	15 (93%)	7 (100%)
Sensitivity, %	56	75	38
Specificity, %	92	88	100

NVB = neurovascular bundle; PSM = positive surgical margins.
* Without frozen section and intraoperative secondary resection of the NVB.

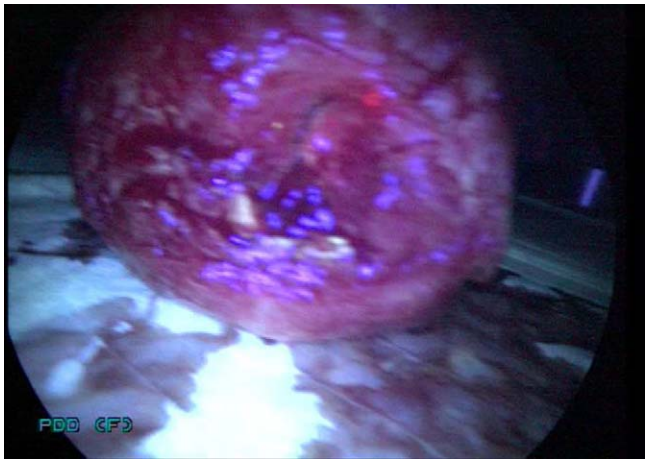

Fig. 2 – Resected prostate under photodynamic diagnosis.

All results are shown in Table 3. Fig. 2 shows a typical PDD-positive spot on the apex.

4. Discussion

Although PCa is increasingly diagnosed at an early stage, a substantial percentage of patients suffer from PSM, especially in an unexpected ECE situation. Patients with negative surgical margins (NSM) have a more favourable prognosis than patients with PSM [19]. A substantial number of patients with PSM develop BCR within 5 yr after curative treatment [20,21]. However, the closeness of the functional tissue, which is (1) the NVB and (2) the rabhdosphincter surrounding the urethra, makes this procedure filigree. The knowledge about tumour stage is the most important factor. Intraoperative identification of extraprostatic tumour or PSM during RP is difficult. An intraoperative finding of a palpable tumour might be a contraindication for an ipsilateral nerve-sparing procedure [22]. Nevertheless, these findings are somewhat subjective and can also be a result of a benign lesion. A secure imaging modality visualising cancerous tissue in situ would be most helpful for deciding whether the NVB's or the sphincter can be preserved. Noninvasive tissue-differentiation systems [23] might be available someday, but these techniques are still under development and their value and practicability have to be determined. The best way for a surgeon would be direct visualisation, allowing the surgeon to rely on his or her eyes. The use of endogenous fluorophores such as 5-ALA–induced PpIX might be promising in achieving this goal. Several randomised, prospective trials of superficial BCa have demonstrated that the additional colour contrast provided by PDD can significantly reduce the residual tumour rates [24]. It was the aim of this study to investigate the feasibility of identification of PSM during open retropubic or endoscopic extraperitoneal RP.

5-ALA–induced PpIX after oral application was reported to be selectively concentrated in malignant cells of the prostate [25], and Zaak et al reported the feasibility of a photodynamic therapy approach in an animal model [26]. The safety of 5-ALA after oral application of 20 mg/kg of body weight has been well demonstrated [14,16]. It could also be shown that 5-ALA–induced PpIX accumulates very selectively in human PCa, with the best PDD contrast after an incubation time of 4 hr (ie, 3 h before the beginning of the operation) [16].

The main results of this study show that PDD of PCa during RP is feasible and practicable. The result of sensitivity and specificity are preliminary and will be further evaluated in future studies. In this cohort of patients, it seems to be more favourable for an endoscopic procedure rather than for an open RP. Two-thirds of the PSM in the endoscopic group could have been intraoperatively detected by fluorescent signals. If these positive sites would have been resected, the PSM rate might have been reduced. In addition, in two patients, a false-positive result

would cause unnecessary resection of potentially functional tissue in the endoscopic group. No unnecessary tissue would have been resected in the open group, with no false-positive rate. Four patients would have had an NSM if fluorescenting, and, therefore, malignant tissue would have been intraoperatively resected. Of course, this is hypothetical, because it is unclear whether all cancerous tissue would have been resected under fluorescent guidance in the individual patient. It has to be mentioned that centre 3 also performed intraoperative frozen sections. Four patients showed cancerous tissue in the frozen sections. All were situated at the site of the NVB. The secondary resection of the NVB on the site resulted in NSM in three resected prostates; these were not detected by PDD. The fourth had a ventral positive margin, which was not detected by frozen section but was PDD positive. Nevertheless, it was not the aim of this study to compare frozen sections with the possibility of PDD.

Some drawbacks need to be considered: In this series, the PDD procedure proved more practicable during endoscopy than during the open operation. It is easier and less time-consuming to change from white to blue light by using the foot switch immediately during the operative procedure rather than turning off the lights in the operating room and holding the optic on the resected margins. This allows more continuous PDD control and faster evaluation of the operative field for PDD-positive spots, with less time for bleeding to occur. This might account for the higher rate of false negatives in the open cases versus endoscopic cases, because the presence of heme impairs PDD by PpIX fluorescence dramatically as a result of light absorption on the excitation as well as emitting wavelengths. Evaluation of different photosensitisers that do not overlap with heme might also be a useful approach for the future. Furthermore, there is a substantial training curve, with a tendency of the surgeon to classify less intense areas at the beginning as PDD positive, which might explain the false-positive cases.

A limitation of this study is that selective cases have been enrolled. Furthermore, the number of patients is small, and the ideal conditions for the usage of PDD have not been fully established. In addition, different operative techniques and different surgeons performed the PDD. Further studies should investigate the intensity of fluorescence, taking operation time and the possible bleaching effect of the photosensitiser into consideration. Nevertheless, the feasibility of the technique could be demonstrated. Further studies with a greater number of patients have to be performed.

5. Conclusions

PDD with 5-ALA–induced PpIX during RP might be a feasible and effective method for imaging and reducing the rate of PSM. The technique seems to be more practicable during endoscopic rather than open RP. It might also be of value for training purposes in times of increasing quality standards and high-volume surgery. Further clinical studies with higher patient volumes and further development of the technique seem justified.

Author contributions: Christoph Adam and Georg Salomon (both equally contributed to this manuscript) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Adam, Salomon, Walther, Khoder, Becker, Reich, Blana, Ganzer, Denzinger, Popken, Sroka, Knüchel-Clarke, Köllermann, Sauter, Hartmann, Bertz.
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