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Review – Prostate Cancer

State-of-the-art Intraoperative Imaging Technologies for Prostate Margin Assessment: A Systematic Review

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Abstract

Context: The main challenge in radical prostatectomy is complete excision of malignant tissue, while preserving continence and erectile function. Positive surgical margins (PSMs) occur in up to 38% of cases, are associated with tumour recurrences, and may result in debilitating additional therapies. Despite surgical developments for prostate cancer (PCa), no technology is yet implemented to assess surgical margins of the entire prostatic surface intraoperatively.
Objective: The aim of this systematic review is to provide an overview of novel imaging methods developed for intraoperative margin assessment in PCa surgery, which are compared with standard postoperative histopathology.
Evidence acquisition: A literature search of the last 10 yr was conducted in the Scopus, PubMed, and Embase (Ovid) databases. Eligible articles had to report the PSM rate according to their intraoperative margin assessment technology in comparison with standard histopathology.
Evidence synthesis: The search resulted in 616 original articles, of which 11 were included for full-text review. The main technical developments in PCa margin assessment included optical coherence tomography, photodynamic diagnosis with 5-aminolevulinic acid, spectroscopy, and enhanced microscopy. These techniques are described and their main advantages, limitations, and applications in the clinical setting are discussed.
Conclusions: Several imaging methods are suggested in literature for the detection of positive margins during PCa surgery. Despite promising qualifications of the mentioned technologies, many struggle to find implementation in the clinic. Surgical conditions hampering the signal, long imaging times, and comparison with histopathology are mutual challenges. The next step towards reduction of PSMs in PCa surgery includes evaluation of these technologies in large clinical trials.
Patient summary: In this review, new technologies are reported that can assist the surgeon by detecting insufficient removal of all tumorous tissue during surgery, instead of the standard postoperative histopathological assessment. Currently, it is not clear whether these technologies improve the patient outcome directly; however, the review shows potential future implementations.

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1. Introduction

The main objective of radical prostatectomy (RP) is to ensure complete tumour resection while minimising nerve, bladder, and membranous urethra damage. Successful prostate carcinoma (PCa) surgery is established by both securing good therapeutic outcome and preserving sexual function and continence, the so-called trifecta [1]. However, incomplete tumour resections or positive surgical margins (PSMs), defined as tumour on ink in histopathology, are observed in up to 38% of cases [2–4]. The risk on a PSM is higher with a higher T category and biopsy Gleason score (GS). A PSM correlates with a shorter time to progression and an increased rate of biochemical recurrence (BCR). Subsequently, complementary therapies such as androgen deprivation therapy or radiotherapy might be necessary for these males [5–7]. The presence of a PSM is associated with a high preoperative prostate-specific antigen levels, a high GS, pathological T category, and the surgeon's experience. These parameters only predict the chance of a PSM preoperatively; however, the surgeon is not guided during the surgery to reduce the number of PSMs observed after surgery. The PSM rate is reduced when experienced surgeons perform RP; however, it is still present in up to 17% of the cases [8].

In current practice, the intraoperative frozen section (IFS) technique is available for margin assessment of suspected areas. After resection, the specimen is immediately frozen and stained, and areas of interest are evaluated for the presence of cancer cells. However, being a time-consuming procedure with low sensitivity (42%), clinical use of IFS is controversial [9,10]. Recently, an approach with improved sensitivity, called neurovascular structure-adjacent frozen-section examination (NeuroSAFE), was introduced to enable assessment of neurovascular structures adjacent to the prostate [11,12]. NeuroSAFE enables nerve-sparing surgery in a larger number of patients with 93.5% sensitivity and 98.8% specificity compared with standard histopathology. The study of Schlomm et al [11] showed that patients with NeuroSAFE evaluation had fewer postsurgical histopathologically confirmed PSMs than patients without NeuroSAFE (15.2% vs 21.7%); however, no difference in BCR percentage was found. A disadvantage of this technique is the requirement for standby qualified pathological personnel and the absence of the entire prostate circumference assessment. Although the examination time has a duration of at least 35 min, there is no prolonged surgical time in case of lymph node dissection following prostate removal [13].

There are several conditions that imaging technologies should adhere to, in order to be used for intraoperative assessment in clinical practice. Ideally, margins are evaluated in vivo, which obliges incorporation in minimally invasive surgery tools. Other requirements for margin assessment tools include fast, preferably real-time, examination times (order of minutes) without complicated sample preparation to minimise surgical delay. Next, the entire surface of the prostate specimen (3–5 cm diameter) should be assessed to evaluate the total margin status and distance of tumour cells to the nerves. Furthermore, high detection efficiency, sensitivity for micrometastases, and a tumour to nontumour distinction are mandatory without suffering from changes in tissue due to surgical intervention (ie, coagulation) [5,14,15]. Finally, the technology should be user friendly, and safe for both personnel and patients, and the specimen should be left sufficiently intact to perform standard diagnostic histopathological examination.

The aim of this systematic review is to identify new technologies for intraoperative tumour margin assessment for PCa and, subsequently, to evaluate the performance of these technologies compared with standard postoperative histopathology in detecting PSM status.

2. Evidence acquisition

This review was registered on PROSPERO (registration number CRD42019124616) [16]. The literature search was performed by an information specialist (P.A.B.) in Scopus, PubMed, and Embase (Ovid) databases, according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [17]. Different associations of the following keywords were applied in the abstract and/or title: prostate cancer; prostatectomy; margin; intraoperative; technology; imaging (full search string is provided in the Supplementary material). Studies published between 2008 and 2019 were included. If imaging modalities were not implemented within 10 yr, we presume that technologies were not suitable enough to be implemented in the clinic.

Letters, commentaries, editorials, case reports, reviews, and conference abstracts were excluded, as well as non-English manuscripts. Initially, titles and abstracts were screened by two reviewers independently (J.o.H. and D.M.V.H.) to select publications for full-text review. Disagreement was resolved by consensus or with the help of an independent reviewer (B.J.d.W.v.d.V.).

2.1. Selection of full-text publications

Articles identified based on the search strategy were assessed for relevance and scientific quality. The technologies should compare their findings with standard histopathology. The articles have to focus on surgical margin assessment in PCa with an aim for actual intraoperative application. Studies were excluded if the technology was not applied in a surgical setting, for example, only referred to preoperative margin prediction. Articles should at least include (1) basic description of the intraoperative technology, (2) quantitative or qualitative description of the margin, and (3) comparison of margin status with histopathological examination. Additional publications could be added to this review based on cross-referencing. Two independent reviewers screened full texts for selection (J.o.H. and D.M.V.H.).

2.2. Risk of bias assessment

The included publications were assessed for the risk of bias (RoB) by three reviewers (J.o.H., D.M.V.H., and B.J.d.W.v.d.V.) independently, using the criteria of the Quality Assessment

of Diagnostic Accuracy Studies (QUADAS-2) tool [18]. As proposed by the QUADAS guidelines, four items were scored on having a low, high, or unclear RoB. Patient selection, index test (ie, new technology), and reference standard (ie, histopathology) were also assessed in terms of applicability. Initial disagreement between reviewers was resolved by discussion and consensus.

3. Evidence synthesis

3.1. General findings

An overview of the selection procedure is visualised in Figure 1. In total, 616 records were reviewed, of which 35 full-text analyses were performed and a total of 11 articles fulfilled all the selection criteria. In the following, four consecutive sections are described: optical coherence tomography (OCT; n = 1), photodynamic diagnosis (PDD) with 5-aminolevulinic acid (ALA; n = 6), spectroscopy (n = 2), and enhanced microscopy (n = 2).

Table 1 shows the results of the RoB analysis performed with the QUADAS-2 tool of diagnostic studies. No study scored a low RoB on all seven items, whereas four publications had fewer than five items with a low RoB and applicability concerns. All studies had an unclear RoB considering reference standard, since either the reference standard was performed with the knowledge of the index test or no reference to the histopathological protocol was present. The RoB of the index test was unclear in some studies, due to an incomplete description of the interpretation of the index test results. All included technologies were evaluated if requirements were met according to the previously stated criteria. Technical characteristics of all technologies are summarised in Table 2, and an overview of advantages and limitations is provided in Table 3.

3.2. Optical coherence tomography

OCT emits coherent light through tissue, and the reflected light is used to reconstruct a cross-section of the imaged tissue. Light reflections are accordingly reconstructed in a two-dimensional (2D) representation of the tissue architecture, a so-called tomogram [19]. OCT enables real-time evaluation of the entire prostatic circumference, but

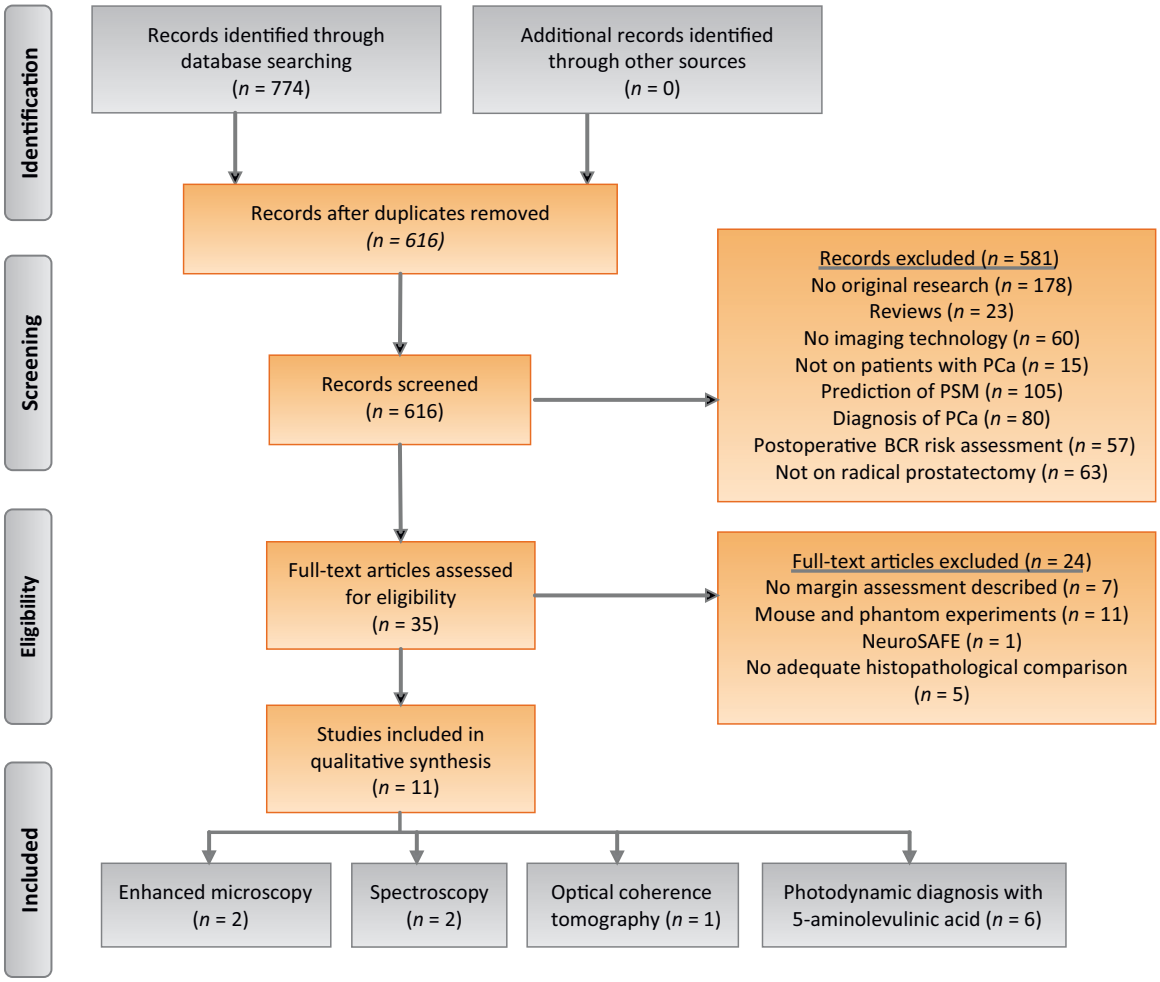

Fig. 1 – Selection workflow query, according to the PRISMA 2009 flow diagram [17]. BCR = biochemical recurrence; NeuroSAFE = neurovascular structure-adjacent frozen-section examination; PCa = Prostate carcinoma; PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis; PSM = Positive surgical margin.

Table 1 – Risk of bias assessment of the included studies obtained with the QUADAS-2 tool [18].

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Dangle [19]							
Ganzer [20]							
Adam [21]							
Inoue [22]							
Fukuhara [23]							
Fukuhara [24]							
Zaak [25]							
Lay [26]							
Morgan [27]							
Lopez [28]							
Wang [29]							

QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies.
White colour indicates low risk, grey unclear risk, and black high risk.

requires careful rinsing of the specimen to remove blood clots and nonprostatic tissue and manual rotation of the specimen. The analysis can be performed within 5 min with a commercially available CE-marked portable machine. OCT is able to assess extraprostatic extension and seminal vesicle invasion, in addition to margin evaluations [19]. Using OCT, Dangle et al [19] observed 21 out of 100 evaluated specimens with PSMs, and a comparison with standard histopathology showed seven true positive and 14 false positive measurements (sensitivity 70% and specificity 84%).

3.3. PDD with 5-ALA

A natural amino acid 5-ALA is converted to photoactive protoporphyrin IX (PpIX) within the cell. This amino acid shows higher accumulation in tumorous tissue compared with healthy tissue and is orally administered 3–4 h prior to surgery for adequate uptake [20–22]. PpIX emits red fluorescence light after excitation with blue light, which can be detected using a commercially available laparoscopic compatible photodynamic camera. The amino acid 5-ALA was evaluated in different small sample size studies (six to 52 patients) and compared with histopathology [20–25]. These studies showed sensitivities ranging from 75% to 82% and specificities between 68% and 88%. The light source can be switched from white to blue light during surgery to excite PpIX, thereby not delaying the operating time [23]. Next, the 5-ALA PDD camera has the same view as the robotic camera, enabling real-time cancer location visualisation in vivo.

3.4. Light reflectance spectroscopy

Spectroscopy visualises the interaction between matter and electromagnetic radiation. Healthy and tumorous tissues are characterised by different tissue properties, regarding nuclear size and cell density [26], enabling tissue discrimination. Light reflectance spectroscopy (LRS) measures the intensity and spectrum of reflected or back-scattered light. Using LRS, 17 specimens were analysed in the study of Morgan et al [27], and PSMs were observed with 86% sensitivity and 85% specificity. Lay et al [26] performed LRS measurements on 50 specimens, of which 197 areas were analysed. LRS was able to detect PSMs in tumours with GS $\geq$ 7 with 91% sensitivity and 93% specificity, in contrast to 65% and 88%, respectively, in specimens with GS 6.

3.5. Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is an endoscopic imaging tool based on standard confocal microscopy. The light beam penetrates at a specific depth at a certain time; from the multiple 2D images obtained, a 3D reconstruction of the specimen can be created. In the study of Lopez et al [28], a 488 nm laser was used for prostate imaging, in concurrence with a Food and Drug Administration–approved fluorophore (sodium fluorescein) intravenously injected 20 min before CLE. Sensitivity and specificity were not mentioned in the study, and no PSM was found.

3.6. Structured illumination microscopy

Structured illumination microscopy (SIM) is an optical sectioning technique using wide field illumination. In the study by Wang et al [29], a video-rate SIM (VR-SIM) is used to record images of the entire circumference in 24 patients. Each tissue frame is stitched together, to get a circumferential image of the entire prostate specimen. VR-SIM was able to detect a PSM in three of the four histologically confirmed cases, which had a size of >1 mm. In one case, VR-SIM detected a PSM that was not confirmed by histopathology

Table 2 – Characteristics of the included articles.

Technology and author		Safe to use	No. of patients	In vivo/ ex vivo	T category (% of patients)	PSM (%)	Distinguishes signal based on	NVB assessment	Min. invasive	FOV
OCT	Dangle[19]	Some heat generation	100	Ex vivo	T2 85% T3 15%	10	Microstructure	Yes	Future	2.7 mm
5-ALA PDD	Ganzer[20]	Side effects, FDA approved	24	In vivo/ex vivo	T2 37.5% T3a 33% T3b 25%	33	Fluorescence of PpIX	Possible	Yes	Camera view
	Adam[21]	Side effects, FDA approved	39	In vivo	T2 42% T3 58%	33	Fluorescence of PpIX	Possible	Yes	Camera view
	Inoue[22]	Side effects, FDA approved	6	In vivo	T1c 50% T2a 17% T2b 17% T2c 17%	0	Fluorescence of PpIX	Possible	Yes	Camera view
	Fukuhara [23]	Side effects, FDA approved	16	In vivo/ex vivo	T1c 68.8% T2a 25% T3a 6.25%	0	Fluorescence of PpIX	Possible	Yes	Camera view
	Fukuhara[24]	Side effects, FDA approved	52	In vivo	T1c 65% T2a 17% T2b 13% T3a 4%	2	Fluorescence of PpIX	Possible	Yes	Camera view
	Zaak[25]	Side effects, FDA approved	16	In vivo	GS 2–4: 10% 5–7: 80% 8–10: 10%	13	Fluorescence of PpIX	Possible	Yes	Camera view
LRS	Lay[26]	Yes	50	Ex vivo	Gleason ≥7 88% T3 45%	58	Cell density & nucleus size	Not yet	Future	1 mm
	Morgan [27]	Yes	17	Ex vivo	Intermediate to high-grade Gleason 7	59	Cell density & nucleus size	Future	Future	1 mm
CLE	Lopez[28]	Yes	21	In vivo	T2a,b,c T3a	NS	Microscopic changes	Yes	Yes	2.6 mm
SIM	Wang[29]	Yes	24	Ex vivo	T2a 5% T2c 53% T3a 32% T3b 10%	17	Microscopic changes	Yes	No	1.3 μm

Technology and author		Commercially available	Resolution	Sensitivity (%)	Specificity (%)	Time	Compromising conditions	Depth penetration
OCT	Dangle[19]	Yes	10–20 μm	70	84	1.5 s per image, <5 min	No perfusion blood clots	1–2 mm
5-ALA PDD	Ganzer[20]	Yes	NS	75	88	Real time	Heat and blood	NS
	Adam[21]	Yes	NS	75	88	Real time	Heat and blood	NS
	Inoue[22]	Yes	NS	NS	NS	Real time	Heat and blood	NS
	Fukuhara[23]	Yes	NS	82	68	Real time	Heat and blood	NS
	Fukuhara[24]	Yes	NS	75	87	Real time	Heat and blood	NS
	Zaak[25]	Yes	NS	50[a]	100[a]	Real time	Heat and blood	NS
LRS	Lay[26]	No	NS	91	93	No real-time data processing	Blood and inflammation	2 mm
	Morgan[27]	No	NS	86	85	NS	Perfusion	2 mm
CLE	Lopez[28]	Yes	1 μm	NS	NS	10 min	Blood and debris	60 μm
SIM	Wang[29]	No	1.3 μm	75[a]	93.8[a]	1 h	NS	Cell layer

5-ALA = 5-aminolevulinic acid; CLE = confocal laser endomicroscopy; FDA = Food and Drug Administration; FOV = field of view; GS = Gleason score; LRS = light reflectance spectroscopy; NS = not specified; NVB = neural vascular bundle assessment; OCT = optical coherence tomography; PDD = photodynamic diagnosis; PpIX = photoactive protoporphyrin IX; PSM = positive surgical margin; SIM = structured illumination microscopy.

[a] Sensitivity and specificity were not mentioned in the article, but calculated from the obtained numbers. The PSM rate was based on histopathological findings. Safe to use indicates if there were any issues regarding the patient or personnel safety that should be taken into consideration.

Table 3 – Main advantages and limitations of the included technologies.

Technology	Advantages	Limitations
OCT [19]		
	- NVB assessment - Fast acquisition	- Learning curve for interpretation - Hampered by the presence of blood and nonprostatic tissue - Small FoV
5-ALA PDD [20–25]		
	- Applicable in vivo using a light switch - Real time	- Learning curve for interpretation - Compromised by heat - Preparation time - Some side effects
LRS [26,27]		
	- Unambiguous result - Surgical cavity assessment - Minimisation of impairment of the signal due to absorption by blood - Real-time data acquisition	- Small FoV - No real-time data processing
CLE [28]		
	- NVB assessment - In vivo usage - Fast acquisition - 3D reconstruction of the specimen - Micron scale resolution	- Hampered by the presence of blood - Preparation time - Lower signal intensity due to resolution
SIM [29]		
	- NVB assessment circumferential image of the entire prostate specimen	- Learning curve for interpretation - Manual rotation to scan the circumference

5-ALA = 5-aminolevulinic acid; CLE = confocal laser endomicroscopy; 3D = three dimensional; FoV = field of view; LRS = light reflectance spectroscopy; NVB = neural vascular bundle assessment; OCT = optical coherence tomography; PDD = photodynamic diagnosis; SIM = structured illumination microscopy.

and one PSM was missed by VR-SIM. Sensitivity and specificity were not specified in the article; however, calculation using the published data resulted in 75% sensitivity and 94% specificity.

4. Discussion

Intraoperative margin assessment contributes to reduction of PSMs in PCa surgery. This systematic review provides an overview of current possibilities for intraoperative margin assessment, including five different technologies. All included technologies are based on optical imaging of cellular differences between cancerous and normal tissue. Technologies such as OCT and LRS seem to be promising, although these still face drawbacks before clinical implementation is possible. So far, none of these techniques affect clinical decisions as they are used only in research situations.

A RoB assessment of all selected studies was performed with the QUADAS-2 tool. A few points of consideration were extracted from this assessment. The first observation was the general lack of studies with a methodology to answer our research question. Since most studies were still in the feasibility phase, they failed to compare their results properly with standard histopathology. Second, several studies performed their reference test (ie, histopathology) not blinded for the results of the index test (ie, new technology). This may result in a RoB regarding the sensitivity and specificity, since it is possible that assessors alter histopathology results based on the technology's suggestions. On the contrary, marking of suspicious locations based on the technology results enabled a direct comparison with histopathology in that specific location.

Previous reviews on technologies for surgical margin assessment in other tumour types predicted, in 2014, an increase in the clinical use of these technologies [30–33]. Currently, only NeuroSAFE is used for PCa in daily practice in specific institutions, and one could ask why these technologies are not incorporated on a more frequent basis. This might be directly related to the strict histopathological definition of PSMs in PCa, which is "tumour on ink". Hence, to be as precise as histopathology, a technology should

assess margins with a depth resolution of one cell layer, which is challenging for the described intraoperative imaging technologies. In general, the sensitivity and specificity of the included technologies are inferior to the 93.5% sensitivity and 98.8% specificity of NeuroSAFE. However, the technologies included in this review are evaluated in limited sample sizes (range 6–100 patients) and are still under development. Next to that, with the introduction of new techniques, a learning curve is common and could result in suboptimal detection rates. Still, the results were promising with specificities above 84% (except for those of Fukuhara et al [23]) and sensitivity ranging from 50% to 91%.

Real-time tumour visualisation during PCa surgery may improve patient outcome and survival by assisting towards a more radical resection, while preserving vital normal tissues. The trifecta of surgical outcome includes cancer control, sexual function, and presence of continence. The first two can be evaluated if intraoperative margin assessment is combined with nerve-sparing surgery, for example, using the OCT, CLE, and SIM techniques to assess the neural vascular bundle. Furthermore, easy incorporation in clinical routine requires a user-friendly technology and unambiguous interpretation of the results. A learning curve was required to distinguish OCT signals between tumour and normal tissue due to variations in prostate anatomy. This applies for 5-ALA as well, where training is required for the subjective interpretation of 5-ALA PDD [20,21]. In contrast, since spectroscopy technologies are based on computer-based algorithms, the conclusion will not primarily depend on user interpretation [26,27].

Most included studies, except for the 5-ALA PDD and CLE studies, are currently only performed ex vivo; yet all hold potential for in vivo usability. CLE images were acquired in vivo, though image analysis and interpretation were performed afterwards [28]. A general obstacle for in vivo usage is the influence of the surgical conditions on image acquisition. For example, the 5-ALA signal is compromised by heat [21,23,24]. Thus, the use of diathermy should be avoided in critical areas. To overcome this effect, the specimen can be prepared using a cold knife without electric devices [23]. Besides that, the signal of multiple technologies (5-ALA, OCT, and CLE) is hampered by the presence of blood. Hence, careful rinsing of the prostate is required, complicating actual in vivo usage. However, research into different wavelengths that do not overlap with the heme peak may overcome this problem. This could be performed, for example, using a specific wavelength range for LRS (700–850 nm), which minimises impairment of the signal due to absorption by blood [26,27]. Finally, OCT images can be altered by nonprostatic tissue through tissue interference and long periods without perfusion [19].

A shared disadvantage of all described techniques includes long assessment times, due to either long-lasting data processing or long acquisition times to assess the entire prostate with a small field of view (FoV). Spectroscopy, OCT, and microscopic techniques all have an FoV of <5 mm; therefore, scanning the prostate circumference can take up to 1 h. Full assessment of the prostate using a technology should be within 35 min to compete with intraoperative time constraints and to improve upon NeuroSAFE [11–13]. With future technical developments, the aforementioned technologies should be able to reduce assessment times. Preparation time needs to be considered when using fluorescent dyes with 5-ALA and CLE, as imaging should be performed 3–4 h and within 20 min after administration, respectively [20–22,28]. Additionally, some side effects of 5-ALA have been reported [21], resulting in several contraindications for the oral use and restriction from sunlight after surgery to avoid skin reactions [20,23,24].

If a PSM is detected ex vivo by an optical technology, one of the problems is to map the PSM back to the surgical cavity to resect additional tissue. This mapping can be difficult due to changes in the surgical field, thus a limiting factor for ex vivo imaging. Ideally, the technology would assess margins within the surgical cavity, for example, using LRS that has the ability to measure the surgical cavity besides the excised specimen [26,27]. Based on all previous mentioned advantages and drawbacks, currently no technique is optimal for intraoperative PSM detection in PCa. Therefore, the search for alternative technologies persists, and is likely to end up in the use of fluorescent or radioactive markers to enhance signal intensities.

4.1. *Alternative and future technologies*

This review focused on the clinical applicability of intraoperative margin assessment, and several innovative technologies are developed for optical guidance during PCa surgery. Another strategy to decrease positive margins includes surgical experience, preoperative selection, preoperative models, and radioguided surgery [34–36]. Investigations in the latter area are already on-going, as well as in combination with augmented and virtual reality [37,38]. Promising other techniques that are still in a preclinical development stage include fluorescence coupled to tumour-targeted probes, such as the prostate-specific membrane antigen (PSMA). Tumour-targeting ligands to near-infrared (NIR) fluorophores are already studied in (pre)clinical trials in other cancer types. PSMA is often overexpressed by PCa cells, and the ligand can be bound to an infrared fluorescent dye or Cy5 dye. This dye has absorption and emission wavelengths in the NIR and far red ranges, enabling fluorescence imaging using a fluorophore [30,39,40]. PSMA can also be coupled to ^{68}Gallium, enabling Cerenkov luminescence imaging during surgery using positron emitting properties of ^{68}Gallium. This technique has shown promising results in a preclinical setting [41].

5. Conclusions

In conclusion, several technologies are suggested to overcome the problem of postsurgery PSMs in PCa. Despite promising specifications of the technologies mentioned, many struggle to find implementation in the clinic. Surgical conditions hampering the signal, long acquisition times, and accurate comparison with histopathology are mutual challenges. Furthermore, large clinical trials are needed to

investigate the added value of each technology in terms of improved patient outcome and cost effectiveness, before incorporating margin assessment into clinical practice. Finally, improvements of the techniques are required to enhance implementation of intraoperative assessment of surgical margins.

Author contributions: Judith olde Heuvel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: olde Heuvel, Bhairosing, de Wit-van der Veen.
Acquisition of data: olde Heuvel, Bhairosing, de Wit-van der Veen, Huizing.
Analysis and interpretation of data: olde Heuvel, de Wit-van der Veen, Huizing, Slump, van der Poel, van Leeuwen.
Drafting of the manuscript: olde Heuvel, de Wit-van der Veen, Huizing.
Critical revision of the manuscript for important intellectual content: olde Heuvel, de Wit-van der Veen, Huizing, Bhairosing, van der Poel, van Leeuwen, Stokkel, Slump.
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Appendix A. Supplementary data

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