Delphi consensus project on prostate-specific membrane antigen (PSMA)-targeted surgery-outcomes from an international multidisciplinary panel

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ORIGINAL ARTICLE

Delphi consensus project on prostate-specific membrane antigen (PSMA)–targeted surgery—outcomes from an international multidisciplinary panel

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Abstract

Purpose Prostate-specific membrane antigen (PSMA) is increasingly considered as a molecular target to achieve precision surgery for prostate cancer. A Delphi consensus was conducted to explore expert views in this emerging field and to identify knowledge and evidence gaps as well as unmet research needs that may help change practice and improve oncological outcomes for patients.

Methods One hundred and five statements (scored by a 9-point Likert scale) were distributed through SurveyMonkey®. Following evaluation, a consecutive second round was performed to evaluate consensus (16 statements; 89% response rate). Consensus was defined using the disagreement index, assessed by the research and development project/University of California, Los Angeles appropriateness method.

Results Eighty-six panel participants (72.1% clinician, 8.1% industry, 15.1% scientists, and 4.7% other) participated, most with a urological background (57.0%), followed by nuclear medicine (22.1%). Consensus was obtained on the following: (1) The diagnostic PSMA-ligand PET/CT should ideally be taken < 1 month before surgery, 1–3 months is acceptable; (2) a 16–20-h interval between injection of the tracer and surgery seems to be preferred; (3) PSMA targeting is most valuable for identification of nodal metastases; (4) gamma, fluorescence, and hybrid imaging are the preferred guidance technologies; and (5) randomized controlled clinical trials are required to define oncological value. Regarding surgical margin assessment, the view on the value of PSMA-targeted surgery was neutral or inconclusive. A high rate of "cannot answer" responses indicates further study is necessary to address knowledge gaps (e.g., Cerenkov or beta-emissions).

Conclusions This Delphi consensus provides guidance for clinicians and researchers that implement or develop PSMA-targeted surgery technologies. Ultimately, however, the consensus should be backed by randomized clinical trial data before it may be implemented within the guidelines.

Keywords Delphi consensus · Prostate cancer · Prostate-specific membrane antigen (PSMA) · Radioguided surgery · Panel meeting

Introduction

The emergence of prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein that is highly overexpressed in prostate cancer (PCa) cells (Fig. 1A), has greatly changed the identification of PCa on imaging. With the incorporation of PSMA-ligand positron emission tomography (PET)/computed tomography (CT) in international guidelines [1], this biomarker has proven its clinical value [2, 3]. Exploitation of imaging biomarkers for surgical guidance is also becoming increasingly popular (Fig. 1B, C), where distinguishing benign tissue from malignant tissue constitutes a challenge. More accurate intraoperative tumor delineation is expected to help advance surgical precision. A recent systematic review on the first efforts in the

Extended author information available on the last page of the article

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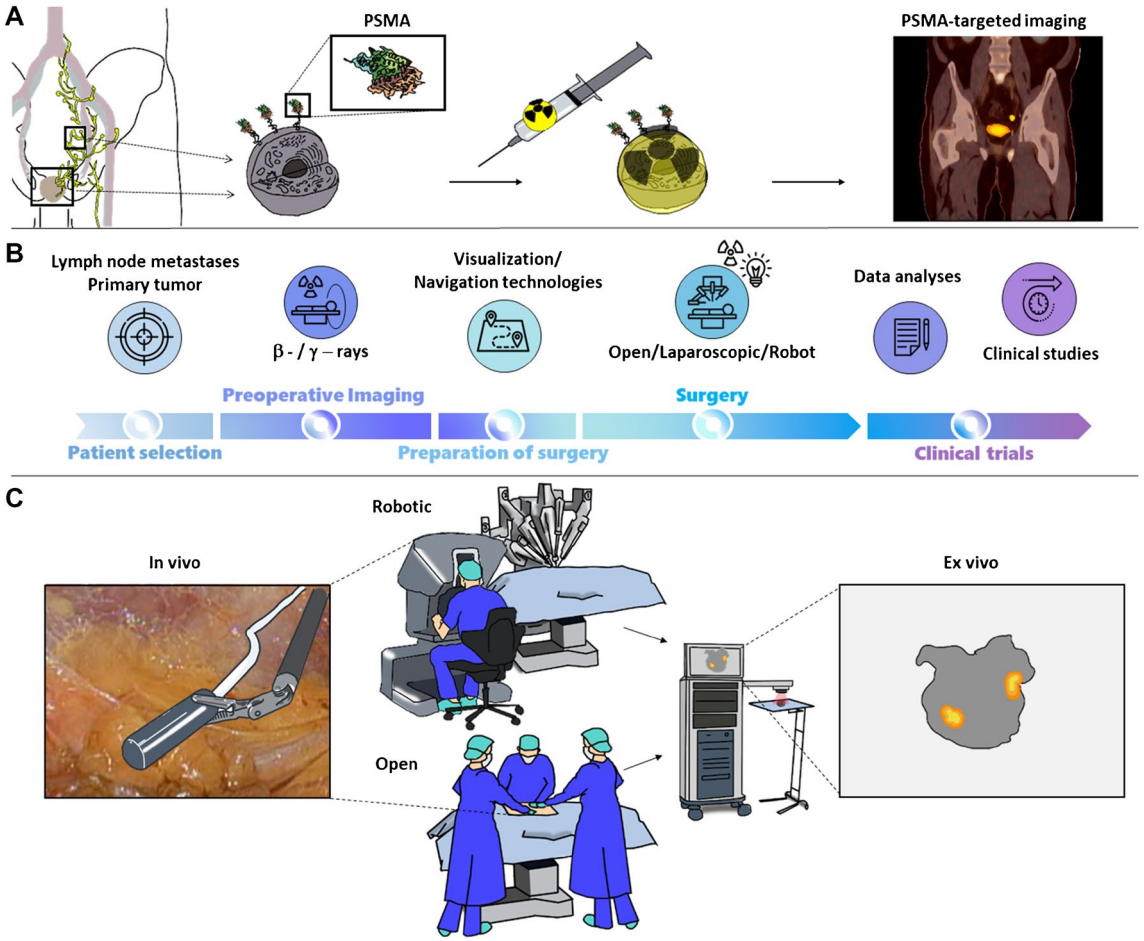

Fig. 1 **A** Prostate-specific membrane antigen (PSMA) targeting. **B** Clinical workflow PSMA-targeted surgery. **C** Surgical settings: Illustration of open and minimally invasive robotic surgery with examples of in vivo drop-in probe and ex vivo specimen imaging (e.g., Cerenkov or fluorescence imaging)

area of PSMA-targeted surgery summarized the results on intraoperative technologies for detecting PSMA expressing PCa cells, both in and ex vivo (total approximately $n = 793$ patients) [4]. This overview of the literature revealed that many of these pioneering studies deviate in (technical) setup and data analysis. Reports using radioguidance facilitated by the tracer [^{99m}Tc]Tc-PSMA-I&S (for imaging and surgery) currently dominate the field [5].

With the exception of two studies (121 and 364 patients) [6, 7], most literature on PSMA-targeted surgery represent smaller, often retrospective, series (range 1–40 patients). This may be related to the novelty of the subject and current reimbursement. Studies describe different types of tracers and detection modalities, each having their own strengths and limitations [4]. Literature on PSMA-targeted surgery also suffers from considerable heterogeneity of definitions and inconsistencies in the reporting of approaches and outcomes such as the cutoff metrics used for a positive signal (signal-to-background ratios (SBR) ranging from 1.5 to 17) [8–10]. Although there appears to be a growing demand for technologies that support PSMA-targeted PCa surgery, criteria for evaluating the outcomes and the optimal approach for future studies are unknown. Furthermore, evidence is lacking to demonstrate the benefits of the technology in improving outcomes for men with PCa such as disease-specific mortality and quality of life. This raises questions about how the technology might affect clinical practice.

In recognition of the importance of consensus on requirements, indications, and assessment criteria, a Delphi consensus was initiated. This widely accepted strategy in the surgical field is employed to establish guidelines based on clinical evidence and is increasingly used for new technologies that have not yet been implemented at a large scale, e.g., for strategies in image-guided surgery [11–13]. By conducting a Delphi consensus project at this early stage of PSMA-targeted surgery development, it becomes possible to identify and address knowledge/evidence gaps and unmet needs. The pursuit of consensus among the

stakeholders in multiple disciplines helps standardize approaches and establish best practices in order to speed up the further maturation of the field. A forward-thinking strategy that helps reduce the chance that patients are subject to sub-optimal treatment paradigms. The objective of this study was to advance insight into the current and future applications of PSMA-targeted surgery early on, and with that help set the stage for future research and clinical implementation.

Methods

Delphi consensus project

The consensus project was conducted in six phases. In the first phase, a steering committee was established comprising 12 experts from across the globe purposively selected to represent urologic end-users (46%), enabling nuclear medicine physicians (31%) and researchers (23%) in the field of image-guided surgery. In an iterative process, the steering committee decided on the topics and wording of the initial 105 statements. To accommodate for difference in backgrounds, statements were included with different levels of complexity and could be answered with "cannot answer." The second phase involved distributing the statements through SurveyMonkey® (Momentive Inc., San Mateo, CA, USA). In the third phase, the answers were analyzed. In the fourth phase, the steering committee met to discuss the need for clarifying certain statements and drafting new ones. The fifth phase consisted of a second round of 16 statements that were distributed to the panel participants, again followed by anonymous answering (89% response rate). The sixth and final phase included the analysis of the answers and drafting of the manuscript. The steering committee guided the project and jointly drafted and authored the manuscript.

Participants and recruitment

Participants were identified through their authorship of studies on PSMA-targeted surgery or other individual relevant experience in this field, independent of the hospital, affiliation, or geographical origin. Industrial participants were invited because their company provided key enabling technologies for PSMA-targeted surgery studies. To avoid bias, two participants per company were invited. Eligible panel participants were invited directly by the steering committee to participate, explaining the projects aim and methodology, and requesting their agreement to participate. Final selection was influenced by the need to achieve an acceptable representation of key stakeholder groups. In total, 86 panel participants answered the statements (62 (72.1%) clinician, 7 (8.1%) industry, 13 (15.1%) scientists, and 4 (4.7%) other), most with a urological background (57.0%), followed by nuclear medicine (22.1%). Further details on participants are available in supplementary 1.

Definition of consensus

The initial statements could be divided into two main categories: clinical and technological. Statements could be scored using a 9-point Likert scale ranging from disagree (1) to agree (9) or "cannot answer" [14]. A median score of 1–3 represented disagreement with the statement, a score between 4 and 6 neutrality on the statement, and a score of 7–9 reflected agreement. Consensus was defined using the disagreement index (DI). DI was assessed using the research and development project (RAND)/University of California, Los Angeles (UCLA) appropriateness method, using the formula: DI = interpercentile range (IPR)/interpercentile range adjusted for symmetry (IPRAS) [14]. IPR was defined as the difference between the 30th and 70th percentiles. The IPRAS was derived using the formula IPRAS = 2.35 + (asymmetry index [AI] × 1.5), where AI was the absolute difference between five and the central point of the IPR. A DI > 1.0 indicated a large dispersion of scores and therefore no consensus. The smaller the DI, the less dispersion, meaning a stronger consensus. The level of dispersion was illustrated by boxplots. The color of the boxplots refers to the median score (1–3 red, 4–6 orange, 7–9 green). Gray reflects "no consensus."

Results/discussion

Molecular targeting methods for PCa surgery

The panel participants concurred that PSMA is, to date, the best available molecular target (median 9.0) (Fig. 1A), but other targets should continue to be explored (median 8.0).

For a surgical roadmap, the panel participants agreed on the use of PSMA-ligand PET scans, ideally undertaken less than 1 month prior to PSMA-targeted surgery (Fig. 2A, B). It was agreed that both ^{18}F- and ^{68} Ga-PSMA-ligand PET tracers can be used interchangeably (median 7.5), thereby addressing the plurality of available PSMA-ligand PET tracers [15]. PSMA-ligand PET could be used to indicate the target location prior to surgery and provide a roadmap to support surgical navigation. While PET was the leading modality in PSMA-targeted surgery, an additional PSMA-ligand SPECT was also considered of value (median 7.0) (Fig. 2A). A secondary roadmap (either PET or SPECT), acquired the day before surgery or on the day of surgery, was scored to be of neutral additional value (median 6.0). Overall, the lesions identified at preoperative imaging were

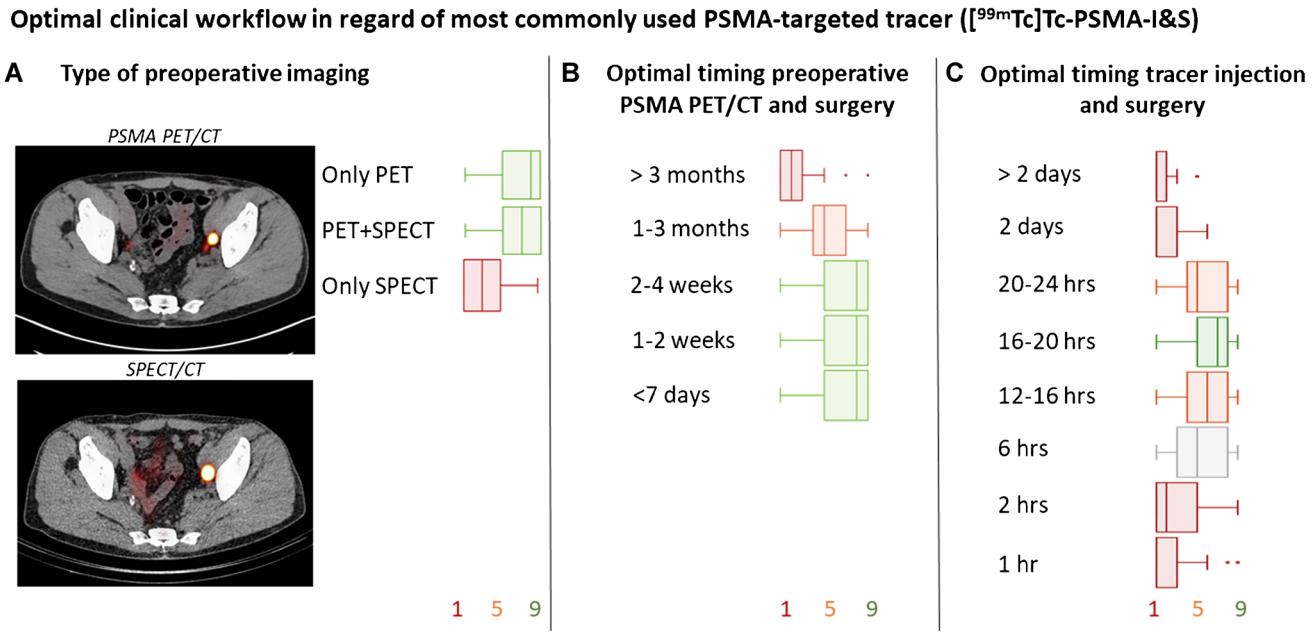

Fig. 2 Optimal clinical workflow in regard of most commonly used PSMA-targeted tracer ([^{99m}Tc]Tc-PSMA-I&S). **A** Left, top image: PSMA PET/CT, bottom image: SPECT/CT. Right: level of consensus of only SPECT/CT, both PET and SPECT or only SPECT as preferred type of preoperative imaging. **B** Level of consensus on optimal timing between preoperative PSMA PET/CT and surgery. **C** Level of consensus on optimal timing between tracer injection and surgery. Scale: 9-point Likert scale. Legend: red = disagree (median 1–3), orange = neutral (median 4–6), green = agree (median 7–9), and gray = no consensus

considered leading for PSMA-targeted surgery. The intraoperative identification of additional lesions was considered a bonus as it may support the identification of lesions < 3 mm since these are easy to miss on preoperative imaging [16].

Based on the available data from [^{99m}Tc]Tc-PSMA-I&S, a time range of 16–20 h between injection and surgery was regarded as optimal for the clinical workflow (Fig. 2C). However, as tracers may differ in imaging signature and pharmacokinetic properties, the timing between injection of the tracer and surgery may differ accordingly, and it was agreed that this should be determined for each tracer separately. The panel participants concurred that next to the pharmacokinetics, the quantity of PSMA tracer injected has influence on lesion staining, timing of administration, and background signal (median 8.0). A recent study using the fluorescent PSMA analogues OTL78, which used a therapeutic dosing range, indicates that the sensitivity and specificity of staining are highly dependent on the quantity of tracer administered [17].

Indications for PSMA-targeted surgery

Despite the limited evidence provided thus far [4], the panel participants were neutral on the statement that PSMA-targeted surgery has already proven its value in routine patient care, hereby taking into consideration that routine care is depended on the geographical origin of the panel participants.

Use of PSMA targeting strategies differs in clinical requirements and evidence for primary and salvage surgery [4]. Where indicated, the statements therefore addressed primary cancer surgery separately from salvage surgery (Fig. 3A). There was consensus on the value of PSMA targeting during nodal identification in both primary and salvage surgery, especially outside the standard surgical template, with the strongest consensus for nodes surrounding the rectum, the bladder, and the aortic bifurcation. Despite literature describing use of PSMA targeting for margin detection during primary prostatectomy [8, 10, 18–20], no consensus was reached on its value (median 6.0, DI = 1.01). The view on the value of PSMA targeting technologies for the assessment of resection margins during salvage prostatectomy was neutral (Fig. 3A). Local recurrence, however, was seen as an indication that could benefit from a PSMA-targeted approach. This statement is supported by the recent report of Knipper et al. [21].

In general, it was considered valuable to identify lesions that lay deeper below the tissue surface, in addition to the identification of superficial lesions. This is in line with the reliance on PSMA-ligand PET as a surgical roadmap (see clinical workflow, Fig. 1B). While there was consensus that PSMA targeting strategies should facilitate open, laparoscopic, and robotic surgery, the consensus on its

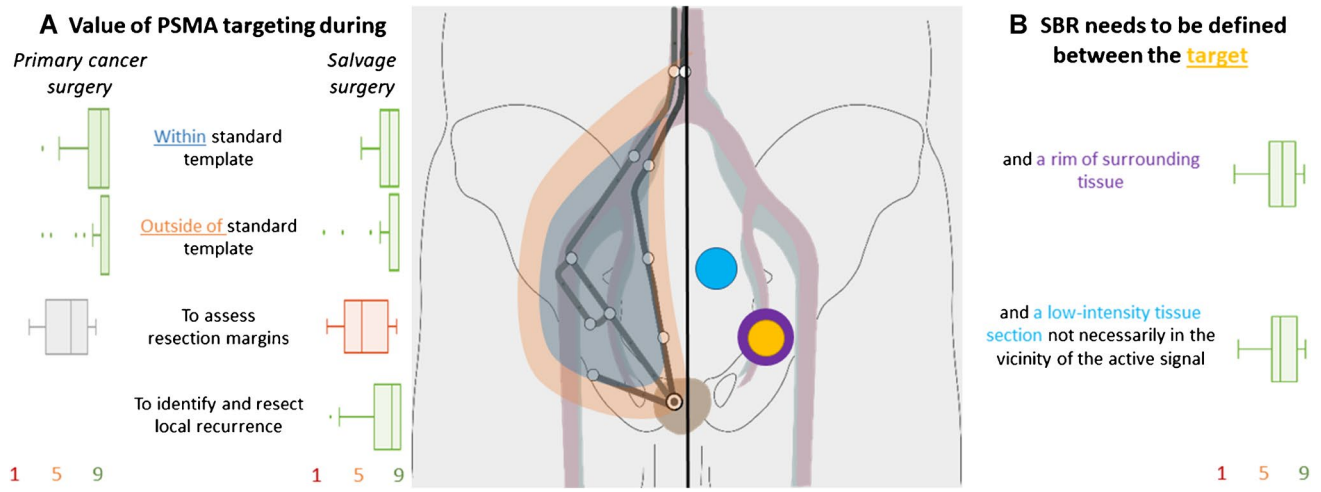

Fig. 3 **A** Level of consensus on the value of PSMA targeting during primary or salvage surgery in different settings. **B** Level of consensus on how to define the signal-to-background ratio (SBR). Scale: 9-point Likert scale. Legend: red = disagree (median 1–3), orange = neutral (median 4–6), green = agree (median 7–9), and gray = no consensus

value in the latter setting was the most evident (median 9.0 with a DI = 0.0). This is contrary to the current predominant literature of PSMA-targeted approaches in open surgery [4] (Fig. 4A). In particular, (real-time) in vivo guidance technologies were considered useful (median 7.0). Complementary value was seen in ex vivo specimen analysis (median 8.0), in line with the outcomes reported in a general Delphi consensus on image-guided surgery [13]. In this back table setup, the (margins of) excised tumor specimens are analyzed for PSMA expressing tissue.

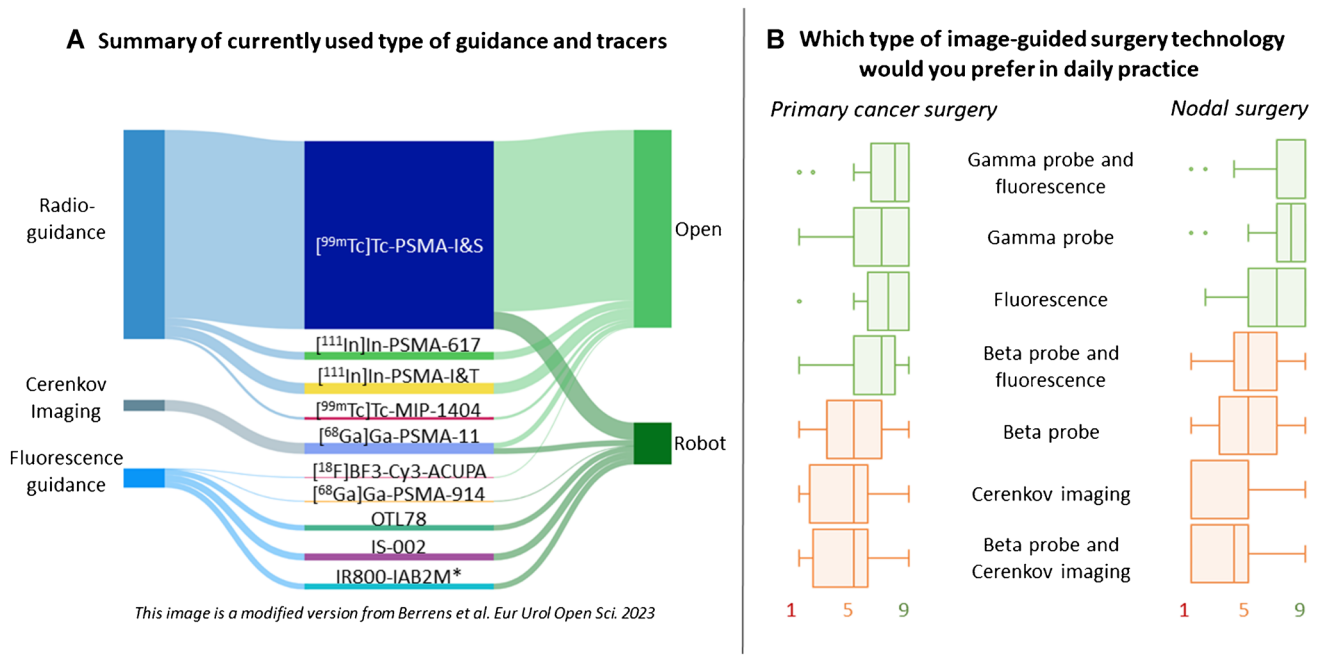

Fig. 4 **A** Summary of currently used types of PSMA-ligand guidance and their distribution over open and robotic surgery [4]. **B** Level of consensus on which type of guidance would be preferred in daily practice (ranked based on declining consensus of nodal surgery) on a 9-point Likert scale. Legend: red = disagree (median 1–3), orange = neutral (median 4–6), green = agree (median 7–9), and gray = no consensus. *not yet published

Guidance modalities

There are a variety of technologies that can be used to help realize PSMA-targeted surgical guidance, ranging from radioactive to optical approaches [9, 10, 18, 22]. While it is often argued that non-ionizing methods are preferred, the panel participants remained neutral when asked whether non-radioactive guidance approaches are preferred over radioactive approaches (median 6.0). Combined with the strong consensus that radioactive PSMA ligands provide a valid method for PSMA-targeted surgery (median 8.0), this indicates that the exposure to ionizing radiation during guided surgery is not considered to be an issue. It should be noted that this view could be region specific, but radiation burden on patient and personnel for ^{99m}Tc-based technologies is minimal [23, 24].

Gamma-emission provides in-depth guidance (> 10 cm), while fluorescence, Cerenkov, and beta-emission provide superficial guidance (< 1 cm) only [18, 25]. The depth at which a signal can be detected constitutes a fundamental feature for the impact that a technology can offer during either nodal resections (in-depth signal detection most desirable) and primary tumor margin detection (superficial signal detection desirable). When asked which guidance technology was preferred for radical prostatectomy, the panel participants most strongly agreed on the use of a hybrid combination of gamma- and fluorescence-guidance, or fluorescence-guidance only (Fig. 4B). Interestingly, panel participants did not reach consensus on whether the in-depth nature of gamma-guidance supported resection margin evaluation. In addition, in primary tumor margin evaluation, a hybrid combination of beta- and fluorescence-guidance was valued, while use of a beta-probe only resulted in a neutral response. Use of Cerenkov also yielded a neutral response; hereby, it is worth mentioning that Cerenkov imaging is only employed ex vivo. The statements regarding the use of Cerenkov or beta-probes generated exceptionally high cannot answer rates (27–47%). This indicates more education is needed regarding the use of these technologies for PSMA-targeted surgery applications, something recently attempted by Costa et al. [26]. The panel participants answered neutral on whether the location of the tumor lesion affects the choice of imaging modality (median 6.0).

When asked which guidance technology was preferred for lymph node dissection, the response changed slightly (Fig. 4B). For this indication, there was consensus on the use of gamma- and/or fluorescence-guidance. While lesion location on preoperative imaging was considered essential for the selection of the best imaging modality, there was no consensus on whether the superficial nature of fluorescence imaging allows accurate identification of nodal metastases (median 5.0, DI = 1.15). There was a strong consensus to use radio-gamma and hybrid-gamma supporting approaches (median 8.0 and 9.0, respectively) and a neutral view on the use of the hybrid combination of beta- and fluorescence-guidance (median 5.0) or beta-probe combined with Cerenkov imaging (median 4.0). Again, only Cerenkov and only beta-emissions scored neutral including a high percentage of "cannot answer" (29–43%).

When asked about what type of readout was preferred (quantitative or qualitative and visual or acoustic), the strongest consensus was on a quantitative and visual image-based readout (median 8.0 and 7.0, respectively). As a quantitative readout is affiliated with radioguidance (gamma and beta), while an image-based readout is affiliated with optical technologies (fluorescence and Cerenkov), only hybrid approaches appear to tick both boxes.

Besides the choice of a modality, the surgeon's ability to use image-guided technology during surgery also is critical. For example, the integration of the Firefly fluorescence camera in the da Vinci surgical system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) has paved the way for the pursuit of robotic fluorescence-guidance applications [27]. In extension to this, the operating surgeon should be able to autonomously select and control the modalities needed to implement PSMA-targeted surgery instead of, e.g., the bedside assistant (median 8.0). There was consensus that guidance modalities are preferably integrated in existing surgical instruments but it appears that more research is needed on this topic. This need for integration aligns with technical concepts such as intelligent robotics that are currently under investigation [28, 29].

Performance assessment

In the gathering of evidence for PSMA-targeted approaches, it was agreed that it is important to assess the impact on the success of the surgical procedure. Oncological outcomes (e.g., surgical margins, biochemical recurrence, disease-free survival) were defined as the most valuable endpoint (median 9.0), followed by improvement in dexterity and decision-making (median 8.0) and complications (median 7.0). There was a neutral view on the role of length of surgery or blood loss as endpoints (median 5.0). On top of this, the panel participants agreed on the need for technologies that support scoring of proficiency in the use of PSMA technologies. A trend that is in line with the use of proficiency scoring in urological training programs and the relation between outcomes and surgical quality [30, 31].

When asked whether specificity should be central even when sensitivity is reduced, the opinion was neutral (median 6.0), and the answers were scattered (DI = 0.97). There was consensus that sensitivity is preferred, even when this reduces specificity (median 7.0). It is worth noting that the widely employed method of ^{99m}Tc-PSMA radioguidance exhibits greater specificity than sensitivity [9, 32, 33].

Recent studies describe fluorescent PSMA ligands to exhibit the same, although this was highly dose dependent [17, 34]. Further enquiries revealed that there was a strong consensus that during primary tumor resection false-positive signal needs to be avoided (median 8.0). During lymph node dissection, false positivity was voted on to be less of an issue (median 7.0).

There was consensus on the need to define SBR values during surgery and that these values are critical for decision-making, a finding that is supported by earlier literature [35]. In line with the variations of SBR assessments reported in literature [8, 9], there was no consensus on the best way to perform SBR measurements; variations considered were the individual target versus the direct surrounding rim of tissue, or all the targets versus a distant low-intensity tissue (Fig. 3B). As SBRs are the driving factor for a surgeon's ability to isolate a target from its background environment, one can question the value of measures that rely on SBRs based on distant low-intensity tissue. Although in current clinical practice the ex vivo SBR is often taken into account [32, 36], it was agreed that the SBR should be measured in vivo (median 8.0). There was a preference for SBR > 2 as cutoff for detection, and it was mutually understood there is a need to standardize the way SBRs are measured and reported. Hence, it seems more studies are required that address the role of SBR values during PSMA-targeted surgery. During primary tumor resection, background signal coming from the intestines was considered acceptable (median 7.0). On background signal coming from urine, however, no consensus was reached (median 4.0, DI = 1.36). Here, one should realize that urine can contaminate the operating field during prostatectomy [37]. It should be noted that literature on PSMA-targeted surgery rarely describes the idea, development, exploration, assessment, and long-term study (IDEAL) framework criteria [4, 38]. Logically, adopting the IDEAL criteria would improve standardization.

Before the individual PSMA-targeted surgery strategies put forward in feasibility studies can be accepted as valid treatment option, individual tracers and modalities need to be independently analyzed, preferably in prospective randomized controlled trials (RCTs). Multicenter RCTs with identical procedures (median 9.0), or with the same procedure but different tracers (median 8.0), and different modalities (median 7.0) were considered valuable. There was strong consensus that clinical data acquisition needs to be standardized (median 8.0). The panel participants remained inconclusive, however, on whether the data that is gathered on one specific PSMA targeting tracer provides sufficient evidence to support the use of alternative PSMA targeting tracers for the same indication (median 5.0, DI = 0.97). Further studies are thus required to define how, e.g., higher dose fluorescence approaches [17] relate to micro-dosing based radioguided approaches [7, 21, 39].

One performance aspect that was considered too early to investigate is the learning curve. This is because only a very limited selection of the participants had enough clinical experience to define which metrics define procedural proficiency. In line with the consensus on the value of dexterity and decision-making analysis, studies are now emerging on technologies that can objectively assess these features during PSMA-targeted surgery [40]. Following further growth of performance assessment technologies, the impact of learning curves on PSMA-targeted surgery could be addressed in future consensus activities.

Conclusions

While conducted at an early phase in clinical implementation, the present Delphi consensus project provides guidance for clinicians and researchers that have an interest in pursuing PSMA as a surgical biomarker in PCa. Key stakeholders from urology, nuclear medicine, research, and industry, with experience in PSMA-targeted surgery, were involved. As the different participants often applied the technology in a different setting (e.g., primary vs salvage surgery) or using different technologies (e.g., radio- or fluorescence-guided surgery), a balanced view of the field could be provided. This project demonstrated areas of consensus, identified disagreements, highlighted ongoing knowledge gaps, and revealed unanswered clinical needs. Consensus indicated that PSMA-ligand PET/CT is ideally undertaken within 1 month before surgery. The preferred time between injection of tracer and surgery seems to be 16–20 h. The timing should, however, be determined per tracer, imaging signature, and in relation to the pharmacokinetics and dosing. In vivo guidance and SBR measurements are preferred, with an additional value of ex vivo confirmation. Looking at indication, the strongest consensus was found for the use of PSMA-targeted guidance in nodal surgery outside of the template, independent of primary or salvage setting. As imaging modality, a hypothetical hybrid combination of gamma- and fluorescence guidance yielded the strongest consensus. The answers also clearly indicated knowledge gaps in areas such as Cerenkov, the use of beta-emission, or their combination (high percentages of "cannot answer"), suggesting more education and research are needed to assess the value of these unconventional approaches. Regarding the value of PSMA as biomarker in surgical margin assessment, the view was neutral or inconclusive. Again, indicating more evidence is needed before widespread clinical implementation is pursued. For gathering evidence, the field should move beyond feasibility, and future emphasis should be on well-designed RCTs with the same procedures using standardized values and relevant endpoints to improve outcomes in patients receiving surgical

treatment for their PCa. This Delphi consensus project provides a valuable reference by addressing clinical needs and recommendations for research and clinical trials.

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Author contribution Study design by ACB, FWBvL, and HGvdP. Drafting of the statements by ACB, EM, FWBvL, HGvdP, HAdB, JMS, MNvO, MS, PD'O, PRC, PS, PJvL, SV-S, TB, and TM. The authors ACB, D. DDR, EM, FWBvL, HGvdP, KH, MNvO, PD'O, PJvL, RVO, SV-S, SK, TB, and TM discussed the first round of statements and drafted the second round. Material preparation, data collection, and analysis were performed by ACB, FWBvL, and HGvdP. All authors critically revised the previous versions of the manuscript and approved the final manuscript.

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Data availability The statements from round 1 and 2 can be found in the supplementary material.

Declarations

Conflict of interest TM had a consulting role in the past at ROTOP Pharma, GEMoAb, Astellas, Blue Earth Diagnostics, and is ongoing consulting for Advanced Accelerator Applications International S.A, Novartis, Telix, Axiom and ABX. TM has received speaker fees from Bayer, Sanofi-Aventis, Astellas, and Philips. PDS has a consulting role at Angiodynamics. KH reports personal fees from Bayer, SIR-TEX Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Fusion, Immedica, Onkowissend.de, Novartis, Molecular Partners, ymabs, Aktis Oncology, Theragnostics, Pharma15, Debiopharm, AstraZeneca, and Janssen. Personal fees and other from Sofie Biosciences, non-financial support from ABX, and grants and personal fees from BTG. JMS is an employee and stockholder of Intuitive Surgical, Inc. PRC contributed to a clinical trial from Intuitive Surgical, Inc. All other authors declared that they have no conflicts of interest. FCH is a Chief Investigator at the Cancer Research UK Programme and financially supported by investigation of novel molecular imaging techniques for precision surgery and genomic characterization of high-risk prostate cancer grant (CR-UK A18444).

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