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Meeting Report

Precision surgery: the role of intra-operative real-time image guidance - outcomes from a multidisciplinary European consensus conference

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Abstract: Developments within the field of image-guided surgery are ever expanding, driven by collective involvement of clinicians, researchers, and industry. While the general conception of the potential of image-guided surgery is to improve surgical outcome, the specific motives and goals that drive can differ between the different expert groups. To establish the current and future role of intra-operative image guidance within the field of image-guided surgery a Delphi consensus survey was conducted during the 2nd European Congress on Image-guided surgery. This multidisciplinary survey included questions on the conceptual potential and clinical value of image-guided surgery and was aimed at defining specific areas of research and development in the field in order to stimulate further advances towards precision surgery. Obtained results based on questionnaires filled in by 56 panel experts (clinicians: N=30, researchers: N=20 and industry: N=6) were discussed during a dedicated expert discussion session during the conference. The outcome of this Delphi consensus is indicative of the potential improvements offered by image-guided surgery and of the need for further research in this emerging field, that can be enriched by the identification of reliable molecular targets.

Keywords: Image-guided surgery, precision surgery, intraoperative imaging, real-time image guidance

In surgical oncology precision surgery has evolved considerably over the past century, with the gradual introduction of minimally invasive techniques based on combined efforts of surgeons, researchers, and industry. One of the concepts that are being pursued increasingly is image-guided surgery, meaning the use of chemical entities and detection modalities to provide guidance during surgery. The overall aim herein is to achieve complete excision of the cancer, while optimising functional outcomes following the intervention. Key questions in this approach are focused on the precise location of the anatomical target, safety margins and complete excision, while sparing as much healthy tissue as possible. For researchers the challenge lies in improving visualization/identification, either via development and evaluation of novel techniques in the form of e.g., receptor targeted tracers and multiplexing imaging solutions or further perfecting existing ones e.g., sentinel node procedures and gamma detection. While there is plurality of experimental surgical guidance techniques, perhaps the two most widely implemented examples are the use of the fluorescent dye indocyanine green (ICG) for (lymph)angiographic applications facilitated by the intraoperative use of a near-infrared fluorescence camera, and the use of gamma-ray detection probes to identify sentinel nodes that have accumulated a radio-colloid such as ^{99m}Tc-nanocolloid.

The image-guided surgery efforts fall in line with industrial interest based on product development, improvement and dissemination. Obviously, the rise of precision surgery needs to be contributed to a successful combination of all these efforts, but the specific motives and goals that drive development or use of a particular image guidance technique can differ between the different expert groups. Based on the results of a Delphi consensus survey that was conducted during the 2nd European Congress on Image-guided surgery (held at ORSI Academy in Melle, Belgium on 22nd-23rd November 2019) the current and future role of intra-operative image guidance within the field of image-guided surgery was assessed and the differences between the expert groups highlighted (56 participants; 20 researchers (background in translational-, engineering- and clinical based research and experience raging from PhD student to full professor), 30 clinicians (12 urologists, 5 general surgeons, 6 nuclear medicine physicians, 3 radiologists, 2 oncologists, 1 dermatologist, 1 gynaecologist) and 6 representatives from Industry (medical devices; tracer, robotic surgery, endoscopes, navigation) and medical technology (digital projection and digital technology)).

While traditionally pre-operative imaging has guided the planning of interventions, molecular imaging, and in particular image guidance approaches have led to major technological advances in the management of cancer patients [1-3]. Some have even become routine practice in several surgical disciplines [4-7]. By using a combination of surgical planning information and intraoperative imaging data image-guided surgery aims to support localization of the target(s) of interest with respect to the anatomical context, allowing patient-tailored precision surgery [1]. However, while the technology is thriving with continuing innovations in optical imaging (frontrunning in translational developments), identification of molecular targets and development of tissue-specific radioligands and fluorescence conjugated markers [8-10], there is still a paucity of robust high-level evidence of effectiveness in improving outcomes for patients.

A high level of agreement was reached between the experts on the conceptual potential of image-guided surgery (**Table 1**; Q1-4). This was based on the notion that image guidance can improve surgical outcome and that the impact of image guidance will further expand over an increasing number and type of surgical interventions. In addition, image guidance is thought to help promote minimally invasive surgery and to reduce potential overtreatment. This is directly in line with the potential of image guidance to improve target delineation in order to reduce positive surgical margins, and the intention to preserve delicate anatomical structures (e.g., nerve-sparing surgery during prostatectomy, [11]). An interesting difference between end-users and developers arose on how image guidance should be further developed (Q5, Q6, Q8, Q9). While clinicians stressed that not all types of surgery will require additional image-guidance and integration of image guidance into currently standard surgical procedures and logistics would be preferred (Q5), the standpoint from researchers and industry leaned more towards "anything is possible". Herein revision of current surgical procedures based on image-guidance methodologies would not be excluded straight away (Q8). With providing the best treatment in mind, clinicians proved to be most keen on using the intraoperative imaging information to further refine existing procedures. The fact that technology developers were more conservative, could suggest a difference in opinion on the unmet clinical need. However, the general consensus was that when added to existing surgical procedures, image guidance methods should enhance and not replace routine surgical imaging (Q9). Herein clinicians, who hold direct responsibility for their patients, proved more cautious than researchers and industry who consider the clinicians as beneficiaries of new technologies. Researchers and industry do not have a direct accountability or responsibility and tend to be

Table 1. Key statements of the modified Delphi process to define the role of image guidance during surgery

Item	Level of agreement within clinicians (n=30)	Level of agreement within researchers (n=20)	Level of agreement within industries (n=6)	Overall level of agreement (n=56)
Conceptual potential of image-guided surgery				
1. Surgical outcomes could be improved by image guided surgery	94% (28/30)	95% (19/20)	100% (6/6)	95% (53/56)
2. Image guidance will impact on an increasing number of surgeries	90% (27/30)	100% (20/20)	100% (6/6)	95% (53/56)
3. Image guidance should help to promote minimally invasive surgery and to reduce potential overtreatment	100% (30/30)	90% (18/20)	83% (5/6)	95% (53/56)
4. Imaging guidance can provide value (can tick multiple answers):				
- by improving target delineation in order to minimize positive surgical margins	94% (28/30)	95% (19/20)	100% (6/6)	95% (53/56)
- by preserving delicate anatomic structures such as nerves	97% (29/30)	100% (20/20)	100% (6/6)	98% (55/56)
5. Image guidance should be developed further and integrated in excising surgical procedures	90% (27/30)	80% (16/20)	83% (5/6)	86% (48/56)
Actual clinical value of image-guided surgery				
6. Innovations in image guidance should focus on:				
- realizing a high specificity	57% (17/30)	50% (10/20)	67% (4/6)	55% (31/56)
- realizing a high sensitivity, even when this negatively impacts the specificity	43% (13/30)	50% (10/20)	33% (2/6)	45% (25/56)
7. Image guided surgery has already proven its value in patient care	80% (24/30)	80% (16/20)	83% (5/6)	80% (45/56)
8. Today surgical procedures should be revised based on image guidance technologies:				
- Yes	67% (20/30)	45% (9/20)	33% (2/6)	55% (31/56)
- No	6% (2/30)	25% (5/20)	33% (2/6)	16% (9/56)
- Unable to answer	27% (8/30)	30% (6/20)	33% (2/6)	29% (16/56)
9. When added to existing surgical procedures, image-guided surgery methods should enhance and not replace routine surgical imaging	93% (28/30)	80% (16/20)	83% (5/6)	87% (49/56)
10. For lesion targeted procedures to be effective, surgical guidance technologies should target exactly the same lesions as identified at preoperative imaging	100% (30/30)	90% (18/20)	83% (5/6)	95% (53/56)
11. Image guidance should support identification of local metastases to at least the level provided by preoperative imaging levels	97% (29/30)	70% (14/20)	67% (4/6)	84% (47/56)
12. Intraoperatively there is a demand for technologies that help identify superficially located (<1 cm beneath the surface) lesions and also deeper lying lesions	83% (25/30)	80% (16/20)	100% (6/6)	84% (47/56)
13. Which kind of image-guided surgery should we use in daily clinical practice (multiple answers are possible)?				
- intraoperative ultrasound	80% (24/30)	80% (16/20)	100% (6/6)	82% (46/56)
- radioguidance	77% (23/30)	80% (16/20)	100% (6/6)	80% (45/46)
- fluorescence imaging	87% (26/30)	85% (17/20)	100% (6/6)	87% (49/56)
- 3D printing models	37% (11/30)	10% (2/20)	17% (1/6)	25% (14/56)
- 3D reconstruction	50% (15/30)	35% (7/20)	100% (6/6)	50% (28/56)
- augmented reality	57% (17/30)	65% (13/20)	100% (6/6)	64% (36/56)
14. Image guidance only has value when it provides directional guidance towards the target in vivo (i.e.: tumour) or around the target in vivo (e.g.: nerves):				
- Yes	40% (12/30)	50% (10/20)	33% (2/6)	43% (24/56)
- No	60% (18/30)	40% (8/20)	67% (4/6)	54% (30/56)
- Unable to answer	0/30	10% (2/20)	0/6	3% (2/56)
15. Ex vivo back table tissue imaging (imaging of the tissue removed outside the patient) is considered image guided surgery when it influences the surgical procedure	97% (29/30)	95% (19/20)	83% (5/6)	95% (53/56)

more biased towards the technologies that they themselves develop.

The more conservative integration of image guidance into standard operating procedures might give less room for new wild scientific ideas or new product markets, but on the other hand helps maintain the clinical standard. It also helps define the complementary value of a new technology. Examples of successful expansion of already clinically accepted concepts are the use of the hybrid tracer ICG-^{99m}Tc-nanocolloid for intraoperative identification of the sentinel node (combining radioguidance and intraoperative fluorescence imaging; [1, 6, 12]) and the use of a drop-in gamma probe instead of a rigid gamma probe during robotic surgery (improving the degrees of freedom and thus intraoperative utility; [3, 13]).

There was somewhat more debate on the actual clinical value provided by image-guidance technologies (**Table 1**, Q6-15). Despite popular statements such as "*seeing is believing*", there was no consensus on specificity and sensitivity of the various technologies discussed (Q6). Intriguingly, specificity was not considered critical by any of the expert groups, which seems to contradict with the consensus that oversampling should be avoided (Q3). This perhaps suggests that the technical aspects behind imaging sensitivity and specificity are not widely understood. Logically one could argue that achieving high specificity is the only means to assure the right tissue is resected but may demand more training in data interpretation skills for the operating surgeon. On the same note, focussing on detection sensitivity means it will be easier to interpret the surgical field, but will increase the false positive rate. The differences in response between the expert groups (but also within the expert groups) show that timely definition of requirements will be crucial during the development process of a novel image guidance technique, as this can have great impact on the eventual clinical utility.

A relatively high level of confidence was expressed in the value of image-guidance in patient care (Q7). This choice came somewhat as a surprise as additional value has only been demonstrated in a limited number of indications [6, 14, 15] and most respondents agreed that additional assessment was required on oncological outcome. Realizing that image guidance is a relatively new technology, and that assessment of oncological outcome requires a multi-year evaluation, it can be expected that more will be known on the added value of image guidance techniques in the near future. First results on the added value of combined radio- and fluorescence guidance during sentinel node biopsy procedures in prostate and penile cancer are promising [14, 15], showing improved detection of positive nodes and potentially lower recurrence rates with subsequent optimization of patient management. Similar large cohort assessments in other indications are currently ongoing, and these studies provide an example for future assessment of novel image guidance technologies.

In the current clinical practice, preoperative imaging (e.g., CT or MRI) provides the benchmark for patient selection and planning of a surgical approach. The general consensus was that for intraoperative decision making to be effective, identical features as shown on preoperative imaging should be visualized during surgery (Q10). This can be made possible via two different strategies; the use of hybrid tracers that allow direct correlation between preoperative identification and intraoperative detection based on two different signals emitted by the same tracer (e.g., combined radioactive labelled markers (limited by spatial resolution) and fluorescence-guidance (limited by tissue penetration) to obtain a high level of intraoperative resolution [1, 16]), while a two-tracer strategy (e.g., PSMA-mediated diagnostics (^{68}Ga PET) and radioguided surgery (^{99m}Tc gamma tracing) [17]) that is focussed on targeting of the same tumour-related receptor has also shown to be feasible. Interestingly, the outcome of Q11 (the need for in depth target identification) and Q12 (the value of superficial imaging) show there is still debate on the fundamental aspects underlying image guidance technologies. Where clinicians lean towards dissecting lesions of which the location could be non-invasively established prior to surgery, the other two groups see more value in lesions that become visible during the resection itself. Here opinions seem to be biased by either the clinical availability of and experience with a particular image guidance method and specific research interest within academia or industry. Again, this indicates the possibility of a discrepancy between medical needs and the interests that drive the technological developments.

Generally, ultrasound, radioguidance and fluorescence imaging were identified as modalities that are currently used for intraoperative guidance in different surgical specialties (Q13). However, despite the reliance on preoperative roadmaps (Q9-11), three-dimensional (3D) reconstruction/planning approaches such as navigation and augmented reality display (i.e., the overlaying of 3D virtual models on the operative field in real time) were not unanimously considered as valuable modalities for routine intraoperative image-guided surgery (Q13). This is at odds with the extensive use of such technologies in neurosurgery and orthopaedics, which are especially based on their high potential in providing surgical guidance [7, 18]. An explanation for this discrepancy might lie in the fact that navigation and augmented reality displays are still mainly restricted to applications wherein bony structures can be used as a reference, while soft tissue applications are emerging, but are not yet as widely adopted [19, 20]. Moreover, in the latter tissue movement and deformation limit the current use of 3D preoperative models. Printing of 3D models was also not considered useful for providing intraoperative image guidance by most of the respondents, while their added value for patient counselling, surgical planning and education was acknowledged [21].

While the current trend in surgery goes towards application of tissue sparing resections (such as nerve-sparing surgery) that focus on decreasing the level of surgical-induced side-effects, the value of image-guidance herein was also not unanimously underlined (Q14). This might be caused by the fast progression that is currently been made in tracer and hardware development, and multicolour fluorescence/hybrid approaches [3, 22, 23]. In the latter, complementary tracers are used to highlight different anatomical features that can be discriminated during the same intervention. However, these are still not widely available in the clinic and these approaches are still mainly applied in a clinical trial setting [22-24]. 95% of respondents stated that ex vivo assessment of surgical specimens (back-table tissue imaging) - such as the principle of frozen section biopsy for histopathological evaluation of surgical resection margins [25] - is considered an intrinsic component of image-guided surgery when the imaging results could directly influence the surgical procedure (Q15). Application of this approach has been intensified recently, providing an intermediate step in the translation of novel fluorescence-guided applications [24, 26, 27].

In summary, this international Delphi consensus conference represents, to our knowledge, the first multidisciplinary attempt to achieve consensus on the current role and the future directions of intraoperative image-guided surgery. As there is little that can be argued against the concept of advancing patient care via precision surgery, consensus was easily reached about the potential improvements offered by image-guided surgery. Contradictory views on critical issues such as sensitivity, specificity and outcomes can be considered a point of concern for advancement of the field. It highlights the importance of more interactions among, and understanding between, product developers and end-users. Surely, we should be developing technologies in the context of addressing patient-centred unmet clinical needs, rather than pursue technical concepts in search of sterile applications. Overall, the expert panel agreed that intraoperative imaging should complement the pre-operative roadmaps defined by radiological mapping. Modalities that digitally translate preoperative information into the surgical theatre, such as overlay technologies, were viewed less favourably compared to technologies that offer real-time imaging. At the same time, ex vivo specimen imaging following surgical excision was considered of complementary value for precision surgery when decision-making during an intervention can be directly influenced.

Conclusions

The outcome of this Delphi consensus seems to be indicative to the need for further intensified research and development in this important and emerging field of technology. Something that can be enriched by the identification of reliable molecular targets. Key issues of added value in improving clinical outcomes were highlighted and must be taken into consideration in the design of the next generation, as well as evaluation and validation in well-conducted clinical trials.

Disclosure of conflict of interest

None.

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References

[1] van Leeuwen FWB, Schottelius M, Brouwer OR, Vidal-Sicart S, Achilefu S, Klode J, Wester HJ and Buckle T. Trending: radioactive and fluorescent bimodal/hybrid tracers as multiplexing solutions for surgical guidance. J Nucl Med 2020; 61: 13-19.

[2] Yoon JW, Chen RE, Kim EJ, Akinduro OO, Kerezoudis P, Han PK, Si P, Freeman WD, Diaz RJ, Komotar RJ, Pirris SM, Brown BL, Bydon M, Wang MY, Wharen Re Jr and Quinones-Hinojosa A. Augmented reality for the surgeon: systematic review. Int J Med Robot 2018; 14: e1914.

[3] van Oosterom MN, Rietbergen DDD, Welling MM, van der Poel HG, Maurer T and van Leeuwen FWB. Recent advances in nuclear and hybrid detection modalities for image-guided surgery. Expert Rev Med Devices 2019; 16: 711-734.

[4] Follacchio GA, Monteleone F, Meggiorini ML, Nusiner MP, de Felice C, de Vincentis G and Liberatore M. Radio-localization of non-palpable breast lesions under ultrasonographic guidance: current status and future perspectives. Curr Radiopharm 2017; 10: 178-183.

[5] Jenkinson MD, Barone DG, Bryant A, Vale L, Bulbeck H, Lawrie TA, Hart MG and Watts C. Intraoperative imaging technology to maximise extent of resection for glioma. Cochrane Database Syst Rev 2018; 1: cd012788.

[6] Kleinjan GH, van Werkhoven E, van den Berg NS, Karakullukcu MB, Zijlmans H, van der Hage JA, van de Wiel BA, Buckle T, Klop WMC, Horenblas S, Valdés Olmos RA, van der Poel HG and van Leeuwen FWB. The best of both worlds: a hybrid approach for optimal pre- and intraoperative identification of sentinel lymph nodes. Eur J Nucl Med Mol Imaging 2018; 45: 1915-1925.

[7] Miner RC. Image-guided neurosurgery. J Med Imaging Radiat Sci 2017; 48: 328-335.

[8] Hernot S, van Manen L, Debie P, Mieog JSD and Vahrmeijer AL. Latest developments in molecular tracers for fluorescence image-guided cancer surgery. Lancet Oncol 2019; 20: e354-e367.

[9] Joshi BP and Wang TD. Targeted optical imaging agents in cancer: focus on clinical applications. Contrast Media Mol Imaging 2018; 2018: 2015237.

[10] van Leeuwen FW, Hardwick JC and van Erkel AR. Luminescence-based imaging approaches in the field of interventional molecular imaging. Radiology 2015; 276: 12-29.

[11] Kleinjan GH, Sikorska K, Korne CM, Brouwer OR, Buckle T, Tillier C, van der Roest RCM, de Jong J, van Leeuwen FWB and van der Poel HG. A prediction model relating the extent of intraoperative fascia preservation to erectile dysfunction after nerve-sparing robot-assisted radical prostatectomy. J Robot Surg 2019; 13: 455-462.

[12] Bugby SL, Lees JE and Perkins AC. Hybrid intraoperative imaging techniques in radioguided surgery: present clinical applications and future outlook. Clin Transl Imaging 2017; 5: 323-341.

[13] Meershoek P, van Oosterom MN, Simon H, Mengus L, Maurer T, van Leeuwen PJ, Wit EMK, van der Poel HG and van Leeuwen FWB. Robot-assisted laparoscopic surgery using DROP-IN radioguidance: first-in-human translation. Eur J Nucl Med Mol Imaging 2019; 46: 49-53.

[14] Dell'Oglio P, de Vries HM, Mazzone E, Kleinjan GH, Donswijk ML, van der Poel HG, Horenblas S, van Leeuwen FWB and Brouwer OR. Hybrid indocyanine green-(99m)Tc-nanocolloid for single-photon emission computed tomography and combined radio- and fluorescence-guided sentinel node biopsy in penile cancer: results of 740 inguinal basins assessed at a single institution. Eur Urol 2020; 78: 865-872.

[15] Mazzone E, Dell'Oglio P, Grivas N, Wit E, Donswijk M, Briganti A, van Leeuwen F and van der Poel H. Diagnostic value, oncological outcomes and safety profile of image-guided surgery technologies during robot-assisted lymph node dissection with sentinel node biopsy for prostate cancer. J Nucl Med 2021; 62: 1363-1371.

[16] Kleinjan GH, van Werkhoven E, van den Berg NS, Karakullukcu MB, Zijlmans H, van der Hage JA, van de Wiel BA, Buckle T, Klop WMC, Horenblas S, Valdes Olmos RA, van der Poel HG and van Leeuwen FWB. The best of both worlds: a hybrid approach for optimal pre- and intraoperative identification of sentinel lymph nodes. Eur J Nucl Med Mol Imaging 2018; 45: 1915-1925.

[17] Maurer T, Robu S, Schottelius M, Schwamborn K, Rauscher I, van den Berg NS, van Leeuwen FWB, Haller B, Horn T, Heck MM, Gschwend JE, Schwaiger M, Wester HJ and Eiber M. (99m) Technetium-based prostate-specific membrane antigen-radioguided surgery in recurrent prostate cancer. Eur Urol 2019; 75: 659-666.

[18] Jud L, Fotouhi J, Andronic O, Aichmair A, Osgood G, Navab N and Farshad M. Applicability

of augmented reality in orthopedic surgery - a systematic review. BMC Musculoskelet Disord 2020; 21: 103.

[19] van Oosterom MN, Meershoek P, Kleinjan GH, Hendricksen K, Navab N, van de Velde CJH, van der Poel HG and van Leeuwen FWB. Navigation of fluorescence cameras during soft tissue surgery-is it possible to use a single navigation setup for various open and laparoscopic urological surgery applications? J Urol 2018; 199: 1061-1068.

[20] van Oosterom MN, van der Poel HG, Navab N, van de Velde CJH and van Leeuwen FWB. Computer-assisted surgery: virtual- and augmented-reality displays for navigation during urological interventions. Curr Opin Urol 2018; 28: 205-213.

[21] Pietrabissa A, Marconi S, Negrello E, Mauri V, Peri A, Pugliese L, Marone EM and Auricchio F. An overview on 3D printing for abdominal surgery. Surg Endosc 2020; 34: 1-13.

[22] van Beurden F, van Willigen DM, Vojnovic B, van Oosterom MN, Brouwer OR, der Poel HGV, Kobayashi H, van Leeuwen FWB and Buckle T. Multi-wavelength fluorescence in image-guided surgery, clinical feasibility and future perspectives. Mol Imaging 2020; 19: 1536012120962333.

[23] van den Berg NS, Buckle T, Kleinjan GH, van Der Poel HG and van Leeuwen FW. Multispectral fluorescence imaging during robot-assisted laparoscopic sentinel node biopsy: a first step towards a fluorescence-based anatomic roadmap. Eur Urol 2017; 72: 110-117.

[24] de Vries HM, Bekers E, van Oosterom MN, Krakullukcu MB, van der Poel HG, van Leeuwen FWB, Buckle T and Brouwer OR. c-MET receptor-targeted fluorescence on the road to image-guided surgery in penile squamous cell carcinoma patients. J Nucl Med 2022; 63: 51-56.

[25] Preisser F, Theissen L, Wild P, Bartelt K, Kluth L, Kollermann J, Graefen M, Steuber T, Huland H, Tilki D, Roos F, Becker A, Chun FK and Mandel P. Implementation of intraoperative frozen section during radical prostatectomy: short-term results from a German tertiary-care center. Eur Urol Focus 2021; 7: 95-101

[26] Buckle T, van Alphen M, van Oosterom MN, van Beurden F, Heimburger N, van der Wal JE, van den Brekel M, van Leeuwen FWB and Karakullukcu B. Translation of C-met targeted image-guided surgery solutions in oral cavity cancer-initial proof of concept data. Cancers (Basel) 2021; 13: 2674

[27] Hekman MCH, Rijpkema M, Langenhuijsen JF, Boerman OC, Oosterwijk E and Mulders PFA. Intraoperative imaging techniques to support complete tumor resection in partial nephrectomy. Eur Urol Focus 2018; 4: 960-968.