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EDITORIAL

# Towards molecular imaging-guided intervention theatres in oncology

J. Vonk[1] · S. Kruijff[1,2,3] · R. H. J. A. Slart[1,4] · W. Szymanski[1,5] · M. J. H. Witjes[6] · A. W. J. M. Glaudemans[1]

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Molecular imaging has sparked a transformative revolution in the field of clinical oncology, offering valuable insights into the complex biology of cancer at a molecular level. At the heart of this breakthrough stands positron emission tomography (PET), the cornerstone of molecular imaging that is indispensable in daily clinical practice, playing a major role in diagnosis, staging, and gauging treatment responses [1, 2].

In recent years, the horizon of molecular imaging has expanded, with novel molecular imaging modalities, including non-ionizing variants, emerging from the macroscopic and mesoscopic regime. These techniques often harness optical contrast, offering superior spatial and temporal resolution, portability, and relatively low costs [3]. This wave of innovation promises to enable the visualization of tumors with high precision in clinical scenarios where real-time feedback is crucial for prompt clinical decision-making.

The high specificity and spatial resolution of these imaging methods unlock opportunities to extend the diagnostic applications of molecular imaging into guiding interventional procedures as well. Molecular imaging can now play a pivotal role in guiding interventional procedures across all phases of cancer care, including image-guided biopsy, image-guided surgery, radiofrequency/microwave ablations, and theranostic applications, including image-guided precise pharmacotherapy.

## Image-guided biopsy

At the foundation of cancer treatment lies the need to establish a definitive diagnosis through clinical imaging and the acquisition of tissue samples which still serves as the golden standard for the diagnosis of solid tumors. Typically, biopsies are performed under image guidance, such as ultrasound or computed tomography (CT), as the spatial and temporal tumor heterogeneity requires the sample to be taken from a relevant or representative area to support clinical decision-making. However, in a substantial percentage of biopsies, the obtained tissue material does not show representative material. Furthermore, biopsy of one lesion does not reflect intratumor and intertumoral heterogeneity within one patient. In recent years, the need for high-quality specimens has intensified by the need for mutational analyses, molecular phenotyping and establishment of cell lines for drug development to better tailor the oncological treatment or refrain from further treatment if non-treatable. To this end, image-guided biopsies tend to collect more than one or two samples necessary for conventional diagnostic pathological assessment.

Evidence indicates that the functional tissue contrast (biopsy of areas with increased metabolic activity) obtained with [$^{18}$F]FDG PET/CT-guided biopsies enhances tumor-specificity by successfully obtaining representative tumor tissue [4, 5]. PET/CT-guided biopsy has been successfully used to determine the most metabolic active lesion within a patient. More recently, [$^{68}$Ga]-prostate-specific membrane antigen ([$^{68}$Ga]-PSMA) PET/CT-guided biopsy has been shown to yield a representative prostate biopsy rate of 96% of the cases in patients with prior negative results

✉ J. Vonk
j.vonk@umcg.nl

1 Medical Imaging Center, Department of Nuclear Medicine & Molecular Imaging, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, the Netherlands

2 Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

3 Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

4 Biomedical Photonic Imaging Group, Faculty of Science and Technology, University of Twente, Enschede, The Netherlands

5 Department of Medicinal Chemistry, Photopharmacology and Imaging, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

6 Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

at ultrasound-guided biopsy [6]. However, the widespread application of PET/CT-guided biopsies is hindered by the limited availability of busily occupied camera systems for other clinical purposes, difficulties with biopsy procedures due to the large imaging systems, and high costs.

Integrating ultrasound imaging into a molecular imaging platform allows real-time tracking of the lesion's position and needle motion during procedures with functional and molecular information on the lesion. This approach enables immediate corrections, potentially reducing overall procedure times. Photoacoustic imaging, a non-ionizing technique that uses pulsed light to generate ultrasound waves in the areas where the light is absorbed, shares the detection platform with ultrasound. Combining the rich optical contrast of tumors with ultrasonic spatial resolution, photoacoustic imaging provides a level of detail and resolution higher than other macroscopic or mesoscopic imaging techniques without the use of ionizing radiation and contrast agents [7, 8]. This technology provides both ultrasound and photoacoustic imaging, which is mainly used to visualize vasculature and quantify blood oxygen saturation by differentiating between the distinct optical spectra of oxygenated and deoxygenated hemoglobin. This improved contrast could aid in obtaining high-quality biopsies in for example prostate or thyroid lesions [9, 10]. A proof of principle study showed photoacoustic imaging-guided biopsy allows for simultaneous imaging of functional and molecular contrast, mapping intraprostatic vasculature as well as enhancing contrast of the lesion through visualization of indocyanine green (Fig. 1) [9]. Other techniques to improve the yield of image-guided biopsy include fluorescence imaging. A custom-build biopsy device, allowing pass through of the core needle, was successfully used to differentiate between normal and malignant tissue using indocyanine green as contrast agent [11].

To ensure that the obtained specimens contain representative tissue for a definitive diagnosis, on-site microscopic evaluations are performed by pathologists or pathology assistants. Alternatively, microscopic molecular imaging modalities could be used to provide non-destructive assessment of obtained samples [12]. This non-destructive pathology not only improves streamline procedures but also enhances the accuracy of pathological analyses, as demonstrated in prostate cancer biopsies [13].

## Image-guided surgery and alternatives

Surgery remains the primary treatment for most solid malignant tumors, with the ultimate goal of resecting the entire tumor bulk (i.e., tumor and metastases, if present) while preserving healthy tissue and functional organs. Unfortunately, incomplete resections (R1) occur frequently, varying by tumor type [14]. These incomplete resections significantly increase the risk of local recurrence and distant metastases, ultimately compromising overall survival. Despite the importance of obtaining a complete resection, no intraoperative tools are available to guide the surgeon in differentiating between tumor and surrounding tissue. Surgeons make an educated guess on the tumor extension based on preoperative imaging and perform surgery accordingly based on visual and tactile feedback.

The advent of hybrid operating rooms has revolutionized image-guided procedures in interventional radiology and vascular surgery. A similar approach can enhance oncological surgery by incorporating appropriate molecular imaging techniques to support the surgeon in achieving complete resections. As in the hybrid operating room, surgeons engaging in image-guided surgery require the collaboration of experts with a solid foundation in molecular imaging. The design of the molecular imaging-guided operating room of the future represents a novel partnership between nuclear medicine specialists and oncological surgeons.

A wide range of imaging techniques have been explored in the operating room to aid in the evaluation of surgical resection margins, including fluorescence imaging, Raman spectroscopy, photoacoustic imaging, specimen PET imaging and radio-guided approaches [15, 16]. Intraoperative imaging before incision allows visualization of subsurface tumor extension and unanticipated satellite lesions or metastases. Moreover, intraoperative imaging of the surgical specimen immediately after resection allows for immediate corrections of inadequate resections, optimizing oncological outcomes. For example, a recent phase II study showed that intraoperative fluorescence molecular imaging can identify inadequate resections with high sensitivity in oral cancer surgery, which can guide intraoperative frozen section analysis to confirm inadequate resections (Fig. 2) [17]. Other imaging modalities for intraoperative margin assessment include specimen[$^{18}$F]FDG PET imaging which is currently evaluated in breast cancer and head and neck cancer surgery. Although technically successful and providing the possibility of quantitative and depth-resolved margin assessment, PET requires more tumor-specific tracers to establish accurate margin assessment [18, 19].

Other opportunities for molecular imaging include improved intraoperative sentinel node localization or nodal staging [20]. This is now regularly performed with nuclear techniques, but using optical imaging instead could also be a good option. This also opens the opportunity to highlight critical structures (e.g., common bile duct, ureters or nerves) to minimize the risk of iatrogenic damage and surgical complications [21].

For tumors that are ineligible for surgical resection, such as unresectable liver tumors or indolent thyroid cancer, where esthetic concerns preclude conventional surgery, minimally invasive techniques are increasingly performed. For

example, in radiofrequency ablation, high-frequency electrical currents are applied to induce thermal destruction of the tumor. The risk of incomplete ablation increases when the fiber is near vasculature as this results in thermal diffusion, the so-called "heat-sink effect" [22]. In this context, molecular imaging techniques can offer functional information on intranodal or perinodal vasculature, which is vital for mitigating this unwanted phenomenon and real-time monitoring of treatment-effect. Preclinical studies in tissue-mimicking phantoms and porcine models demonstrated the potential of photoacoustic imaging for confirming adequate needle placement, visualization of vasculature and the ablation lesion formation, offering real-time evaluation that could guide clinical decision-making [23, 24]. Furthermore, multispectral photoacoustic imaging potentially provides quantitative biomarkers to measure treatment response as tissue optical properties change upon ablation [25].

## Theranostic capabilities

Numerous novel molecular imaging modalities use light for the generation of contrast. Light has unique advantages as an external stimulus for treatment, offering high spatiotemporal precision and the capacity to modulate the power and wavelength of the light source. Due to this adaptability, phototherapies (i.e., light-based) promise great tumor-specificity by confining the volume of illumination to the tumor region and the administration of tumor-specific light-responsive agents [26]. In photodynamic therapy, exogenous photosensitizers generate cytotoxic reactive oxygen species upon light irradiation. This therapeutic approach is already used in clinical practice, facilitating curative or palliative treatment of actinic keratosis, basal cell carcinomas and small squamous cell carcinomas [27, 28]. In parallel, photothermal therapy

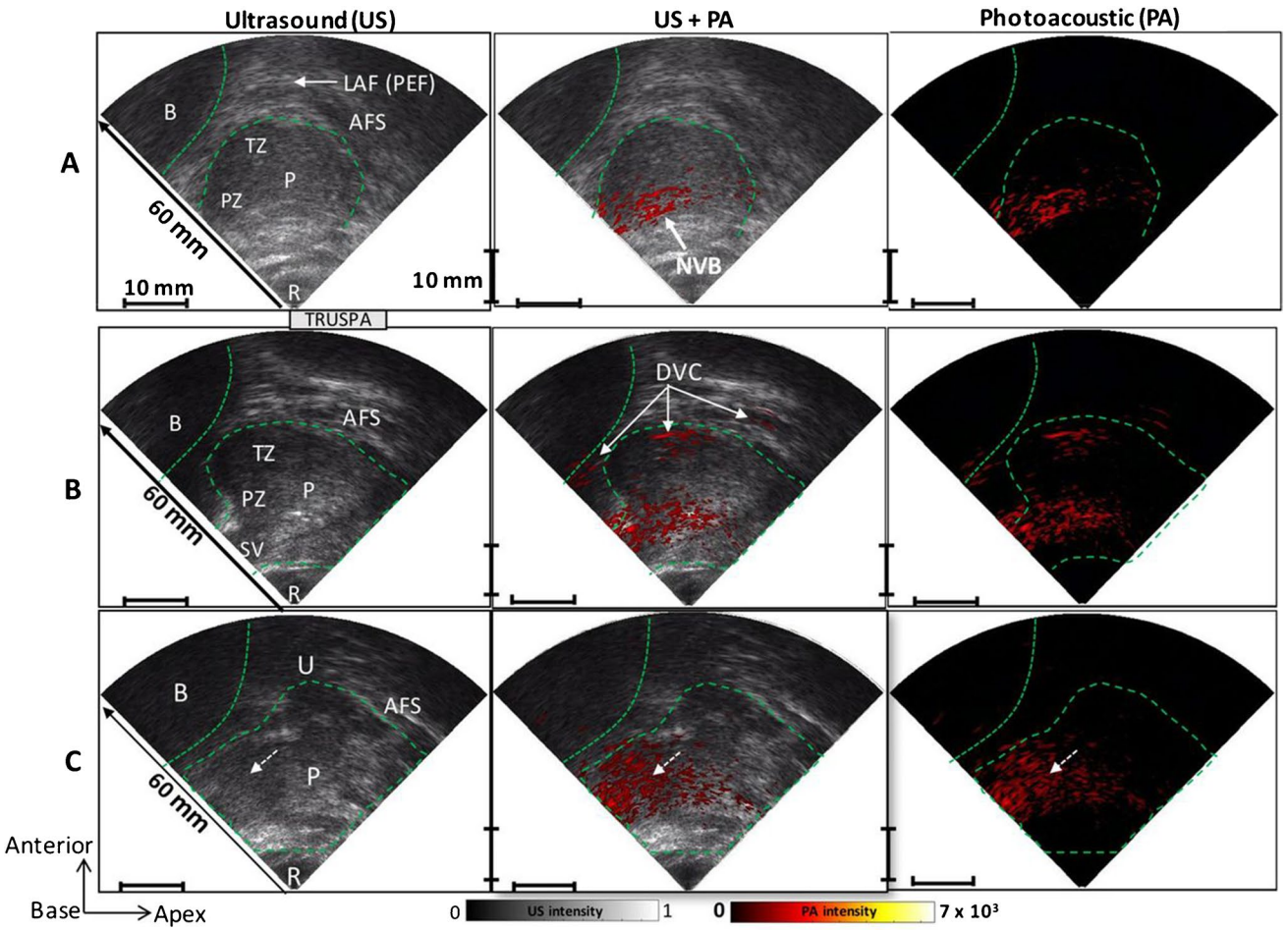


**Fig. 1** Molecular imaging-guided biopsy. In vivo hybrid ultrasound-photoacoustic imaging of the human prostate. A) Photoacoustic contrast identifies the neurovascular bundle (NVB) in de posterior peripheral zone. B, C) Photoacoustic contrast identifies vascular structures in surrounding organs as well in the hypoechogenic mass in the peripheral zone at the left base of the prostate. Abbreviations: P, prostate; R, rectum; B, bladder; U, urethra; P, peripheral zone; TZ, transition zone; SV, seminal vesicle; NVB, neurovascular bundle; AFS, anterior fibromuscular stroma; DVC, dorsal vascular complex; LAF, levator ani fascia; PEF, parietal endopelvic fascia

relies on the administration of exogenous absorbers that convert the optical absorption energy into heat, causing hyperthermia in tumor cells. Its potential has been shown in multiple solid tumors in mouse models, showcasing selective thermal ablation of tumor cells with minimal effects on surrounding healthy tissue [29].

In this era, pharmacotherapy is increasingly tumor-specific due to the development of bioactive compounds targeting hallmarks of cancer. Yet, true tumor-selectivity remains challenging as the pharmacological targets are also expressed in healthy tissue [30], which necessitates the development of a truly localized, image-guided pharmacotherapy. In this context, photopharmacology has emerged as a method in which UV, visible and Near-IR light is used for remote activation of drug activity [31]. Considering recent advances in controlling molecular function also with deeper penetrating photons of high wavelengths [32], this approach is perfectly set to be synergized with molecular imaging methods described in this editorial.

In photothermal therapy and photopharmacology, the light used for thermal ablation or drug activation yields theranostic capabilities: the absorption of light causes simultaneous generation of pressure or ultrasound waves for hybrid photoacoustic imaging. As such, the effect of photothermal therapy and photopharmacology have the potential to be monitored in real-time based on the changes in tumor size or signal intensity.

## Outlook

Now that the potential for of molecular imaging for peri-procedural use has been shown across various medical domains, the pivotal question remains: How can we seamlessly transition these innovations into routine clinical practice? The convergence of biology, chemistry, pharmacy, physics, and engineering has been the driving force behind advances in the preclinical phases. As such, long-term and dedicated multidisciplinary effort is the linchpin for conducting comparative clinical studies and laying the groundwork for integrating peri-procedural molecular imaging in clinical practice.

Understanding the distinctive demands of peri-procedural molecular imaging is the first step in this transformative process. In diagnostic imaging, the highest spatial resolution and image contrast is often desired, tolerating long image acquisition times. Conversely, peri-procedural imaging demands real-time information during biopsies or radiofrequency to ensure accurate needle guidance. For image-guided surgery, the acquisition time can be extended to a few minutes without disturbing the surgical workflow.

Radiologists, through their close collaboration with nuclear medicine and overlap of disciplines, are likely early adopters of peri-procedural imaging. However, translating these molecular technologies requires specific training of imaging physicians for the interpretation of new acquired functional or molecular information. The logistical

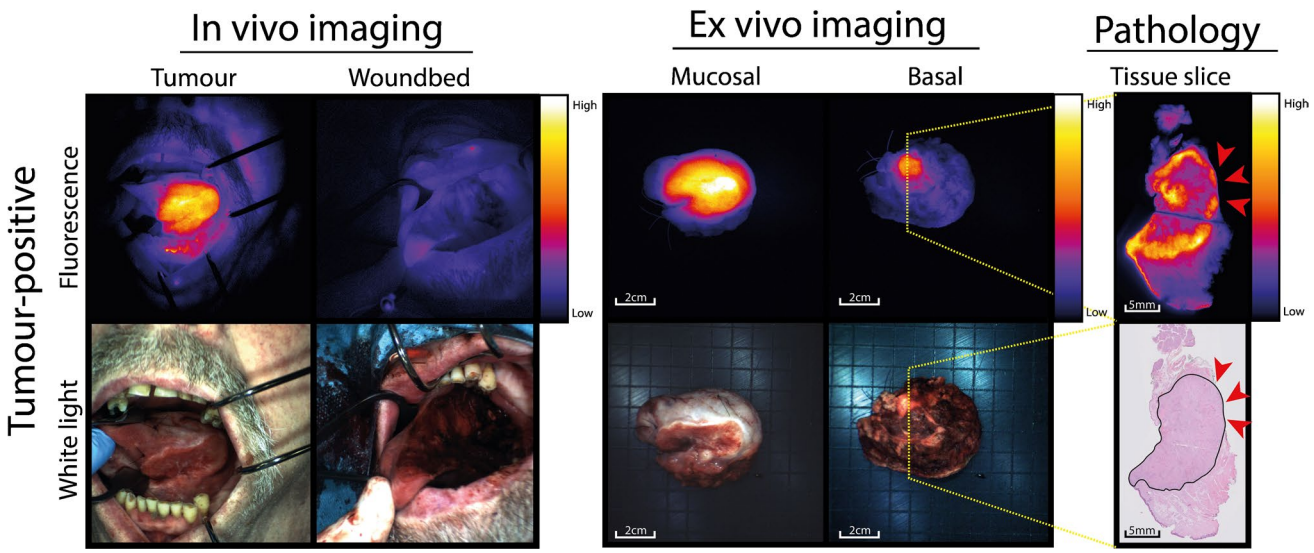


**Fig. 2** Molecular imaging-guided surgery. Epidermal growth factor receptor-targeted fluorescence molecular imaging during oral cancer surgery. In vivo fluorescence molecular imaging shows a sharply demarcated fluorescent lesion, informing on tumor extension prior to excision. After excision, no fluorescence signal is detected in the wound bed. Subsequent intraoperative imaging of the freshly excised surgical specimen identifies a fluorescent spot at the basal margin. The cross-sectional image of the corresponding tissue slice shows fluorescence signal extending in the surgical margin, and was found to be a tumor-positive margin as determined by standard of care histopathology

challenges can be surmounted: biopsies based on cross-sectional imaging may require dedicated and mobile PET/CT devices, while other techniques such as optical or photoacoustic imaging offer more flexible bed-side procedures.

Image-guided intervention rooms is the next step in the right direction for molecular imaging. This envisages a new collaborative platform where molecular imaging specialists and surgeons work together to guide surgery, not only in the oncological setting, but also in case of infections, e.g., infected prosthetic material where surgeons need metabolic information to be able to define the extent of infection and which parts of the foreign body material have to be removed. Surgeons pursuing image-guided surgery need partners who can support them with a proven platform and long-standing experience on adopting sound and reliable methodological development in clinical adaptation. Achieving this vision demands not only technical advancements but also development of generic targeted contrast agents (e.g., using experience in radiotracer development) and establishing high-scale tracer production, preoperative tracer administration, and standardized image acquisition and image analysis. Ideally, this data is truly quantitative and can be integrated with preoperative imaging and molecular pathological analysis of the surgical specimen, advancing our biological understanding of cancer.

Last decades, our deepened understanding of light and light-tissue interactions has revealed the theranostic capabilities of light. Although current developments of light-based theranostics are still limited to preclinical efforts, its transformative promise is likely to be fulfilled soon as in for example image-guided surgery. Whereas the use of molecular imaging during interventions may incur additional costs due to the purchase of new equipment or use of contrast agents, it may be cost effective by reducing inconclusive biopsies or incomplete surgeries and radiofrequency ablations. Reducing these unwanted outcomes not only prevent repeat procedures, but also spare patients from postoperative therapies to correct for suboptimal outcomes. This patient-centric approach underscores the potential impact of molecular imaging, reinforcing the importance of its continued development and integration into routine clinical practice.

## Conclusion

With exciting advancements in molecular imaging techniques, often offering unprecedented spatiotemporal resolution and portability, the role of molecular imaging in oncological care can be extended into the guidance of interventional procedures. The real-time availability of functional or molecular information promises to transform clinical decision-making, particularly in scenarios where real-time feedback is paramount. The integration of molecular imaging in interventions in daily oncological practice can enhance both the accuracy and efficiency of these procedures. The clinical significance of molecular imaging is undeniable, with major opportunities unfolding in image-guided biopsy, image-guided surgery or ablation, and the rapidly evolving field of theranostics. Notably, the possible impact of molecular imaging in guiding surgical interventions has already been shown. To fully unlock the potential of molecular-imaging guided interventions, the collaborative spirit, adaptive training approaches, and transformative promises of emerging technologies provide a roadmap for achieving seamless clinical adoption. As these molecular imaging technologies advance, they urge to become indispensable in guiding oncological interventions and expanding their applications in theranostics.

**Data availability** Not applicable.

## Declarations

**Ethical approval** Not applicable to this Editorial.

**Informed consent** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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