Surgical Guidance in Prostate Cancer: “From Molecule to Man” Translations

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Summary
Given the frequency of the disease and the difficulty of tumor resections, image-guided surgery technologies may aid the surgical management of prostate cancer patients. The “from molecule to man” translation of such approaches is, however, complex and depends on many different features, both from a technical and a practical perspective.
In this issue of *Clinical Cancer Research*, Sonn and colleagues report on a prostate stem cell antigen (PSCA) specific imaging agent for fluorescence-guided surgery (1). Herein the authors rightfully reason that surgical guidance toward the location of prostate cancer may help to improve surgical outcome and to reduce procedure-associated side-effects (2). There are different ways to realize image guided surgery in prostate cancer. While traditional approaches in prostate cancer rely on radiological (e.g. ultrasound) or nuclear medicine (e.g. gamma tracing) guidance, optical guidance technologies are rapidly emerging. Next to fluorescence, a.o. the use of Raman-based guidance technologies is being pursued.

Ideally surgical guidance is realized without the necessity of introducing an imaging agent or by using generic imaging agents. However, in clinical practice specific biomarker targeting imaging agents seem to be required to reproducibly image prostate cancer. Targeted solutions have been generated for e.g. the choline receptor (3), the gastrin-releasing peptide (GRP) receptor (4), and the prostate specific membrane antigen (PSMA) (5). At the moment it seems that, at least in Europe, PSMA-specific small molecules are rapidly becoming the standard-of-care for prostate cancer imaging. Besides being highly efficient, these agents are relatively cheap to produce and can be applied at a micro-dosing level (<100μg or < 30 nmol per patient), features that are favorable for translation and reimbursement. Targeting PSCA, a glycosyl phosphatidylinositol-anchored glycoprotein expressed on the cell surface of prostate cancers, provides a promising alternative. From an economical perspective, however, diabody-based imaging-agents may prove to be less appealing. An assumption that is strengthened by the high dosing levels used for the preclinical proof-of-concept studies (25μg/mouse) (1). This raises the question: Do all targets and developed imaging agents, or only a selected few, have potential for a wide clinical dissemination? In general, (preclinical) reports lack objective selection criteria or appropriate business models to address this issue.

In preclinical subcutaneous tumor models the tumor margins and microscopic invasions rarely reflect the complexity of the clinical situation. This is especially so when optical technologies, which all have a limited signal penetration (6, 7), are evaluated during the dissection of animals. The difference in scale alone (see Figure 1) may already induce a bias. The same is true for the setting and time window wherein the imaging has to be performed and for the (sensitivity of the) modality that can be used to provide such guidance. We illustrate these statements further using two practical applications. First, keeping the true anatomical location of primary prostate cancer in mind, it is clear that this intersects with the urinary pathway (see Figure 1). Quite often imaging-agents, like the one reported by Sonn et. al. undergo renal clearance, a feature that is considered favorable for the compounds toxicity profile. During the dissection of the primary prostate-cancer, however, urine is spilled. If this urine contains even a low amount of the imaging agent, during handling and manipulation, it is likely to generate non-specific signals in the surgical field. Since in this application intraoperative imaging is proposed to help define extracapsular tumor spread, such contaminations could lead to overtreatment. Second, as the authors indicate, the identification of disseminated disease in the lymphatics, provides an alternative application for technologies aiding image-guided resections. Success in this application is, however, largely defined by the
in-depth sensitivity of the imaging-modality used. The lymphatic network is complex and the location of prostate-cancer-derived lymph node metastases is unpredictable. Hence only resection of metastases under the guidance of preoperative (radionuclear) imaging can be envisioned. Since metastases will be embedded within the lymph nodes, which in turn are often surrounded by fat, the limited sensitivity of (endoscopic) real-time intraoperative fluorescence imaging could lead to under-estimation of the tumor spread. In fact, from prostate cancer related studies conducted with a sentinel node-specific hybrid imaging-agent (both radiolabeled and near-infrared fluorescent) we already know that even when imaging-agent accumulation can be confirmed preoperatively using radionuclear imaging, not all sentinel nodes can be resected using *in vivo* fluorescence-guidance (*ex vivo* all proved to be fluorescent) (8).

This detectability issue in the clinical setting was in part related to the time available to perform fluorescence-imaging. On top micrometastases, although clinically relevant, are considered too small to be accurately identified using tumor-specific imaging methods and their removal thus still requires lymphadenectomy and/or sentinel lymph node procedures. Given the above-illustrated limitations and practical-challenges, results obtained in mice xenografts merely allow speculation on the clinical potential of prostate cancer specific image guidance technologies.

A mismatch between the lesions identified at preoperative imaging and those identified during surgery can lead to either over- or under-treatment of the patients. Hence it is critical to, in each individual patient, preoperatively validate the specificity of the imaging-agent used for surgical guidance, a concept that has long been applied in radio-guided surgery (9). For example, Maurer and colleagues used ⁶⁸Ga-PSMA-HBED-CC positron emission tomography (PET) to stage patients undergoing salvage lymphadenectomy in recurrent prostate cancer, before using ¹¹¹In-PSMA I&T to resect the lymphatic metastases; single photon emission computed tomography (SPECT) was used to confirm accumulation of ¹¹¹In-PSMA I&T in the PET-positive lesions (10). The success of this approach was largely the result of the ability to plan the resection using three-dimensional imaging and the high in-depth sensitivity of the gamma tracing technology used. Although optical imaging technologies using e.g. the fluorescent dye Cy5 (11), have proven their potential in offering surgical guidance in superficial applications, in-depth validation of their accumulation cannot be realized (7). This suggests that when only an optical agent is available for guidance, the surgeon is blinded towards the efficiency of the tracer accumulation and extensive surgical exploration could be required to search for a signal that may, or may-not, be present.

Theoretically a pair of complementary radio- and optical-agents can be used to link findings in the pre- and intraoperative setting. For this to work both agents need to have identical properties. It is, however, known that conjugating relatively small optical imaging-labels to relatively large antibodies can already effect the pharmacokinetics (12). Such effects depend on the size and properties of the label used, but will likely be more prominent on smaller antibody-fragments, possibly influencing toxicity profiles. Since assessing the pharmacokinetics of optical agents is challenging, this suggests inclusion of a radio- and optical-label on the same imaging-agent is the most efficient way to prevent discrepancies between pre- and intraoperative findings.
For fluorescent agents, improving the photophysical properties may help to increase the sensitivity of detection. The most important features for fluorescence are: i) self-quenching by adjacent dyes, ii) signal intensity of the dye (largely dictated by the absorption coefficient and quantum yield), and iii) the tissue penetration of the fluorescence signal. While shifting to a near-infrared dye may improve the latter, the Cy5-dye used has a superior signal intensity. By having two dyes on a single diabody (1), this signal could be quenched to a certain extent. Of course optimization of the optical properties, should be supplemented by detailed evaluation in vitro (receptor specificity) and in vivo (pharmacokinetics). Only when all these requirements are met, and the compound can be produced under good manufacturing protocols, is a translation to the clinic realistic.

Above we have mainly focused on fluorescence in relation to nuclear medicine technologies. While most of the issues mentioned for fluorescence also apply to the other optical technologies, it appears the alternatives do have specific advantages. With Raman imaging, the sensitivity of detection seems to be high and the imaging agents used are relatively large in size (13). The last feature drives hepatic clearance, which seems to be favorable for applications in primary prostate cancer resection. The large size may limit compatibility with tumor-receptor targeting, but here specific alkyne tags may provide outcome for Raman (14). Which of the optical approaches will in-the-end be clinically most valuable and for what application is yet to be defined.

Considering the frequent presence of positive surgical margins at prostatectomy and the common lymphatic spread of prostate cancer, image guided surgery technologies that help to refine these procedures are in high demand. By performing PSCA targeted fluorescence-guided surgery yet another step has been made towards achieving this goal.

References


Figure 1. Prostate cancer in mice vs. man: the size and anatomical relation between a subcutaneous xenograft mouse tumor model and the clinical situation. The figure also illustrates views of the prostatectomy and the dissection of lymph nodes. On top it illustrates how the urinary pathway (blue) intersects with the primary tumor load (yellow) in the prostate. The anatomical image was generated using the visual body software package (Human anatomy atlas, v3.0.1, Argosy Publishing Inc.).
2.5 cm >25 cm

Lymphatically disseminated disease?

Primary tumor margins?

Figure 1:
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