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The DETECT Trial: Are We on the Verge of Precision Surgery in Primary Prostate Cancer?

Tobias Maurer[1,2], Christian Thomas[3], and Boris Hadaschik[4]

[1]*Martini-Klinik Prostate Cancer Center, University Hospital Hamburg–Eppendorf, Hamburg, Germany;* [2]*Department of Urology, University Hospital Hamburg–Eppendorf, Hamburg, Germany;* [3]*Department of Urology, University Hospital Dresden, Dresden, Germany; and* [4]*Department of Urology, University Hospital Essen, Essen, Germany*

The DETECT trial presented by Schilham et al. in *The Journal of Nuclear Medicine* constitutes one of the first prospective trials on prostate-specific membrane antigen (PSMA) radioguided surgery (RGS) in primary prostate cancer patients (*1*). Thus, we first would like to congratulate the authors for their efforts in the design, execution, and subtle analysis of this study that proved the feasibility and safety of this still-novel approach during robotic pelvic lymphadenectomy with or without primary prostatectomy in patients with prostate cancer and evidence of lymphatic spread on preoperative PSMA PET imaging. However, in this context and especially concerning the role of lymph node dissection, some aspects deserve further discussion.

The intricate lymphatic drainage pathways of the prostate pose a challenge in the treatment of prostate cancer because cancer cells might disseminate to atypical regions not covered in established surgical templates. Traditional extended lymph node dissection often falls short in addressing spread to locations such as the bladder pedicle and the deep internal, pararectal, or presacral regions. Sentinel procedures have been proposed to make up for this shortcoming and may detect slight atypical lymphatic spread; however, the tracers used for these approaches are not tumor-specific and often are even combined with an extended pelvic lymph node dissection rather than replacing it (*2*).

Pelvic lymph node dissection causes morbidity while remaining of inconclusive oncologic value, as robust evidence from long-term studies, even in primary high-risk disease, is lacking (*3*). Although pelvic lymph node dissection represents a diagnostic tool and may conciliate patients, this uncertainty about its oncologic value is even more troublesome in patients without evidence of lymphatic spread on final histopathology postoperatively. Thus, there is still much controversy on the value of and indications for lymph node dissection in prostate cancer patients. Increased use of modern imaging with PSMA PET has led some countries to omit lymphadenectomy in patients without evidence of lymph node metastases, whereas other guidelines still emphasize the value of extended lymph node dissection in patients with an elevated risk of metastasis in preoperative clinical nomograms.

The advent of PSMA PET imaging in primary prostate cancer has substantially augmented our ability to discern lymphatic involvement compared with conventional cross-sectional imaging (*4*). Still, the challenge remains to intraoperatively detect those tumor-infested lymph nodes reliably. The development and introduction of PSMA RGS into clinical practice may at least partly close this gap by enabling real-time molecular detection of prostate cancer lesions during surgery through in vivo and ex vivo γ-probe measurements (*5*). Undoubtedly, this technique holds promise in improving surgical accuracy and completeness.

Despite these advancements, PSMA PET lacks sensitivity for small metastases, and PSMA RGS may still overlook small lymph node metastases, as Schilham et al. accurately analyzed using postoperative PSMA PET imaging (*1*). Particularly, in patients with PSMA PET–positive pelvic lymph node metastases at primary diagnosis, there is a risk of further additional slight lymphatic spread. This understaging may be substantially higher than in the setting of biochemical recurrence, when, additionally, the prostate-specific antigen value, its dynamics, and other clinical parameters can be taken into consideration and correlated with the PSMA PET–positive tumor volume. This ability enables careful patient selection to avoid early treatment failure.

Patients with PSMA PET–positive lymph nodes at primary staging harbor a considerable risk of aggressive tumor biology requiring additional treatments besides surgery (*6*). In this clinical scenario, a renaissance of neoadjuvant treatment strategies may be expected. Several studies are investigating such neoadjuvant treatment strategies in prostate cancer patients with an elevated risk profile. First, emerging data suggest an oncologic benefit (*7,8*), but data from registration trials are still pending. Neoadjuvant treatment approaches lead to shrinkage of lymph node metastases, impeding detectability by molecule-targeted PSMA RGS and rendering such surgical approaches futile. At present, evidence for an oncologic benefit is best for radiotherapy in combination with androgen receptor pathway inhibition in patients with pelvic lymph node metastases.

At the same time, PSMA PET leads to more sensitive detection of lymph node metastases, and this early oligometastatic stage might be an opportunity for surgery alone. For sure, the primary setting offers an opportune environment for surgeons to familiarize themselves with the intricacies of the PSMA RGS procedure, especially in learning its limitations and in navigating to anatomically challenging locations, as compared with the setting of biochemical recurrence after primary radical prostatectomy or radiation therapy, in which surgery might be even more complicated. Recent developments in hardware technology, such as the design of novel γ-probes

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For correspondence or reprints, contact Tobias Maurer (t.maurer@uke.de).
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for robotic surgery as compared with rigid laparoscopic γ-probes, might further facilitate those surgical procedures within the confined space of the small pelvis (*9*). Furthermore, advancements in tracer design and labeling, such as with ^{99m}Tc instead of ^{111}In, will expand its availability because ^{99m}Tc is an inexpensive and readily available radiotracer with a favorable half-life and less radiation exposure than ^{111}In (*10*).

Besides these limitations and open questions regarding patient selection and the oncologic benefits of surgery, the presented DETECT trial and its thoughtful evaluation underscore the potential of PSMA RGS, and we thus want to applaud the authors again for conducting this important clinical trial. Challenges persist, and they urge us as a scientific community to delve more deeply into refining the technique of PSMA-targeted surgery, exploring alternative tracers, and conducting rigorous trials to decipher the true impact of this technique on long-term oncologic outcomes to ultimately improve patient outcomes and shape the future landscape of surgical prostate cancer management.

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