



Letter

Multimodal therapy in oligometastatic prostate cancer: A glimpse into the future?



Dear editor,

Since the introduction of radiotracer-labeled prostate-specific membrane antigen (PSMA) targeting positron emission tomography (PET), imaging of prostate cancer (PCa) improved drastically [1,2]. Subsequently, metastases may be detected in earlier stages with possible implications on treatment planning [3]. Here, we described the multimodal treatment approach on a young patient with newly diagnosed metastatic PCa conducted according to the results of repeated PSMA–PET imaging.

In September 2017, a 54-year-old man was referred to our hospital due to newly diagnosed PCa. A biopsy had revealed a Gleason score 4+4 in seven out of 13 cores with an initial prostate-specific antigen (PSA) of 29 ng/mL. Due to equivocal findings on abdominal magnetic resonance imaging (MRI), further ^{68}Ga -PSMA-11 PET/computed tomography (CT) staging was performed revealing multiple metastases to pelvic, as well as retroperitoneal lymph nodes (M1a) (Fig. 1A and B). The patient presented with excellent performance status (ECOG 0) and no relevant comorbidities. According to STAMPEDE data, an inductive chemo-hormonal therapy with six cycles of Docetaxel combined with Leuprolinacetat was initiated [4]. After termination of the chemotherapy, PSA had decreased to 0.02 ng/mL under continuous androgen deprivation therapy (ADT) and no residual disease was detected by a repeated PET/CT imaging using ^{18}F -rhPSMA-7, a probably more sensitive PSMA tracer without urinary excretion (Fig. 1C). In July 2018, the patient underwent open radical prostatectomy with extended pelvic lymph node dissection. Final pathology yielded a ypT3b pN1 (1/15) R0 L1 V0 Gleason 4+4 PCa with postoperatively undetectable PSA. On further follow-up, PSA slowly rose to 0.5 ng/mL in March 2019 under continued ADT. Therefore, ^{18}F -rhPSMA-7 PET/CT was performed, detecting a single intraaortocaval lymph node metastasis (Fig. 1D). After detailed discussion with the patient, salvage lymph node dissection was planned. To assure detection of the suspect lesion, PSMA-radioguided surgery after injection of $^{99\text{m}}\text{Tc}$ -

PSMA investigation and surgery ($^{99\text{m}}\text{Tc}$ -PSMA-I&S) and pre-operative single photon emission computed tomography (SPECT)/CT imaging (Fig. 1E) was performed in April 2019, as previously described [5]. Preoperative PSA was 0.54 ng/mL. Final pathology revealed two lymph node metastases out of seven removed lymph nodes. At 6 weeks after surgery, PSA declined to 0.03 ng/mL.

In patients with newly diagnosed hormone-sensitive metastatic PCa, several studies have recently described survival benefits, when adding docetaxel, abiraterone, apalutamide and enzalutamide to hormonal therapy [4,6–8]. Moreover, radiotherapy directed to the primary in addition to standard of care systemic therapy was shown to improve survival in newly diagnosed metastatic PCa patients with low metastatic burden (<4 bone metastases, no visceral lesions) as compared to standard of care systemic therapy alone [9].

Our patient received primary chemo-hormonal therapy in 2017, and hereafter underwent local therapy with radical prostatectomy due to significant PSA response and complete response on advanced molecular imaging as an individual and multimodal treatment approach [10,11]. However, the sequence in which these modalities should be administered still remains matter of debate. Initiation of systemic therapy prior to local therapy might help to distinguish between patients with potentially less aggressive disease responding well to systemic treatment and who may benefit of additional local treatment compared to patients with systemic disease in whom local therapy might only be considered for palliative local symptom relief.

Unfortunately, in our patient, the PSMA-PET scan triggered by a rising PSA 1 year after termination of the initial chemotherapy revealed a new pelvic lymph node metastasis. Recent data showed promising results of salvage lymph node dissection with radioguided-surgery in initially non-metastatic, then recurrent PCa patients [12]. Specifically, complete biochemical response (PSA <0.2 ng/mL at 4–8 weeks' post-surgery) was demonstrated in 66% of these highly selected patients with a median biochemical recurrence-free survival of 19.8 months. Moreover, patients with low preoperative PSA-values and one single lesion in PSMA-PET imaging were more likely to experience complete biochemical response. Certainly, the mentioned study investigated initially non-metastatic patients with lymph node recurrent disease. Conversely, our patient had metastatic PCa at diagnosis, rather than a metastatic

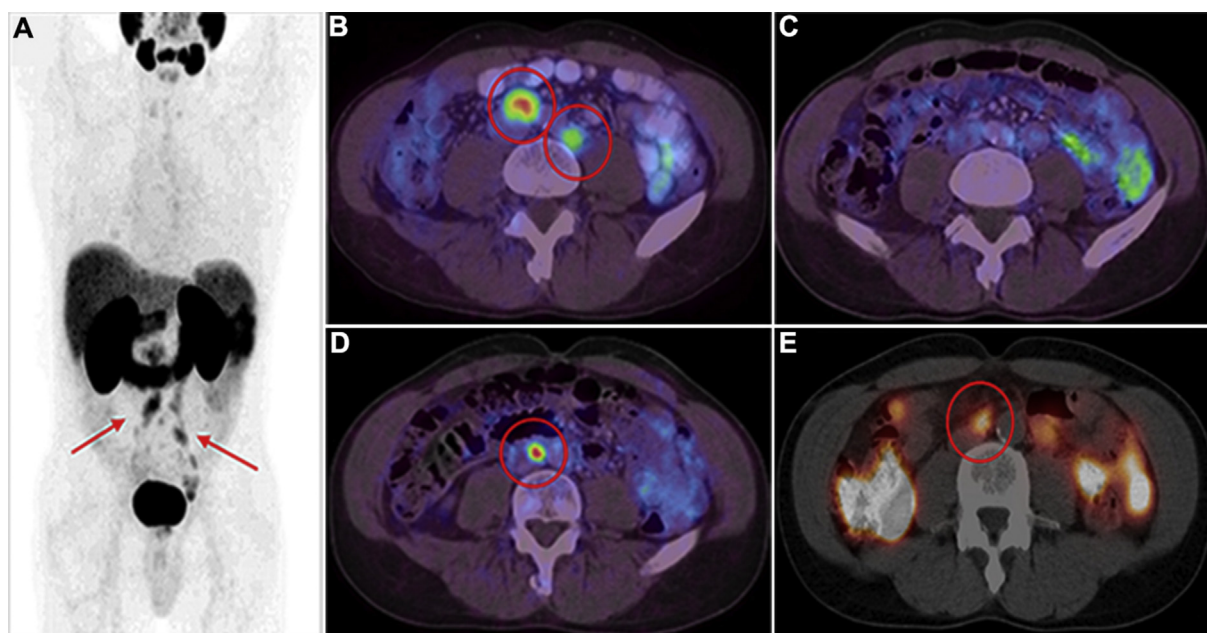


Figure 1 PSMA PET and SPECT imaging. (A) Initial ^{68}Ga -PSMA-11 PET (maximum-intensity-projection) showing bilateral pelvic, as well as retroperitoneal lymphatic dissemination (arrows); (B) Example of initial retroperitoneal lymph node metastasis (circles; axial ^{68}Ga -PSMA-11 PET/CT fusion image); (C) Complete remission of lymph node metastasis after chemo-hormonal therapy (axial ^{18}F -rhPSMA-7 PET/CT fusion image); (D and E) Solitary recurrent retroperitoneal lymph node metastasis after radical prostatectomy (D. Axial ^{18}F -rhPSMA-7 PET/CT fusion image; E. Axial $^{99\text{m}}\text{Tc}$ -PSMA-I&S SPECT/CT fusion image obtained prior to PSMA-radioguided salvage surgery). PSMA, prostatespecific membrane antigen; PET, positron emission tomography; SPECT, single photon emission computed tomography; CT, computed tomography; $^{99\text{m}}\text{Tc}$ -PSMA-I&S, $^{99\text{m}}\text{Tc}$ -PSMA investigation and surgery.

recurrence after initial definitive local therapy. However, previous data suggested a potential survival benefit of metastasis-directed therapy [13–15].

One common limitation of most previously published trials concerning treatment modalities in newly diagnosed metastatic PCa is the use of conventional imaging techniques. With PSMA-based PET imaging, sensitivity and specificity increased tremendously in comparison to conventional imaging [2]. Therefore, earlier metastatic stages may be detectable, rendering comparisons to metastatic stages diagnosed by conventional imaging possibly difficult. In consequence, in metastatic patients diagnosed by PSMA-PET imaging, intensified active treatment may be considered more frequently in the future [3]. However, there are several unsolved questions. It is unknown if the extension of lymphadenectomy (or radiotherapy) should follow the extension of metastasis of initial PET/CT to potentially avoid undertherapy. Moreover, it is unclear if survival may be prolonged by intensified treatment modalities. Nonetheless, although cure may not be possible in advanced stages, as visible by very low persisting PSA levels in the presented case, use of ADT may be delayed, which in itself has morbidity and mortality. Further studies are needed to find optimal treatment combinations and sequences including systemic, as well as local therapy options for these patients.

To date, the optimal sequence of treatments in newly diagnosed metastatic PCa with low metastatic burden is unclear, especially in patients diagnosed by PSMA-based PET imaging. In our experience, as highlighted in the presented case, a multimodal approach with systemic, as well as local (*i.e.* surgical and radiotherapeutic) treatment may

be considered in selected patients to achieve potentially longer survival. Ideally, such patients should be included in clinical trials.

Author contributions

Study concept and design: Tobias Maurer.

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Drafting of manuscript: Sophie Knipper.

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Conflicts of interest

The authors declare no conflict of interest.

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