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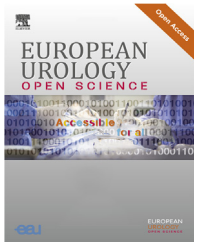

European Association of Urology

Brief Correspondence

Possible Role of Circulating Tumour Cells for Prediction of Salvage Lymph Node Dissection Outcome in Patients with Early Prostate Cancer Recurrence

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Abstract

Promising oncological results have been reported for salvage lymph node dissection (SLND) with prostate-specific membrane antigen–radioguided surgery (PSMA-RGS) in patients with prostate cancer (PCa) recurrence. We performed a proof-of-principle study assessing circulating tumour cells (CTCs) as a prognostic marker in patients undergoing SLND. Twenty consecutive patients with recurrent PCa treated with PSMA-RGS during April–July 2019 for PSMA-positive LNs were evaluated. Preoperative CTC counts were assessed using the US Food and Drug Administration–approved CellSearch system. Biochemical recurrence (BCR)-free survival (BFS) and therapy-free survival (TFS) were evaluated using the Kaplan-Meier method. Overall, three patients (15%) were CTC-positive. Postoperatively, CTC-positive patients had more pathologically positive LNs (median 8 vs 2) without a difference in overall LN count. During median follow-up of 10.1 mo, 14 patients experienced BCR and five received further therapy. In Kaplan-Meier analyses, median BFS was 1.4 versus 4.3 mo and median TFS was 10.3 mo versus not reached for CTC-positive versus CTC-negative patients. The main limitations are the small number of patients, the retrospective design, and short follow-up. Our pilot study suggests that CTC-positive patients seem to have worse pathological and short-term oncological outcomes. Therefore, further validation of this biomarker for treatment decision-making before local salvage therapy could be of value.

Patient summary: We looked at outcomes for lymph node dissection in patients with recurrence of prostate cancer. We found that outcomes appear to be worse when circulating tumour cells (CTCs) can be measured in the blood preoperatively. We conclude that detection of CTCs indicates spread of tumour cells via the blood, which may limit the benefit of lymph node dissection. Thus, CTCs should be investigated in further studies as a potential marker to help in selecting patients who could benefit from lymph node dissection if their prostate cancer recurs.

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In recent years, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has become the routine imaging modality for biochemical recurrence (BCR) of prostate cancer (PCa) [1]. Even at very low prostate-specific antigen (PSA) levels at BCR, metastatic sites can be detected [2,3]. This evolution fuelled the desire for local targeted treatment approaches such as salvage lymph node dissection (SLND). In this context, it has been reported that PSMA-radioguided surgery (PSMA-RGS) can improve intraoperative detection [4]. Promising oncological outcomes with this approach have been reported. In the largest series of 121 patients, a complete biochemical response (postoperative PSA <0.2 ng/ml) was observed in 66% of patients. Not surprisingly, low PSA and a single lesion on PSMA PET were associated with longer median BCR-free survival (BFS) without any additional therapy (14 mo) [5]. Although complication rates are moderate, harms and benefits must be critically weighed, as SLND is currently considered an experimental individual treatment approach. Therefore, further parameters, such as biomarkers, are necessary to discriminate between potentially successful SLND candidates with localised metastatic lesions and patients with a high risk of systemic disease that warrants systemic treatment.

Circulating tumour cells (CTCs) have been described as biomarkers for prognosis, patient stratification to therapy, and prediction of treatment response in patients with solid cancers [6]. CTCs originate from the primary tumour and/or metastases and can be detected in peripheral blood [7]. CTC enumeration using the CellSearch system is already an established independent prognostic marker in metastatic castration-resistant PCa [8]. We therefore aimed to assess CTCs in patients undergoing SLND for recurrent PCa.

In total, 20 consecutive patients treated with PSMA-RGS during April–July 2019 for PSMA-positive lymph node recurrent (pelvis and retroperitoneum) PCa were evaluated. CTC counts were assessed using the US Food and Drug Administration–approved CellSearch system as previously described [7]. All patients were informed about the experimental nature of salvage surgery and the additional use of the ^{99m}Tc-PSMA-I&S ligand for PSMA-RGS as previously described [4]. All patients provided informed consent for the procedure and for data analysis. The retrospective analysis was approved by the institutional review board. BFS (defined as PSA < 0.2 ng/ml without further PCa-specific treatment) and therapy-free survival (TFS, defined as survival without further PCa-specific treatment) were

Table 1 – Characteristics of 20 consecutive patients treated with PSMA-RGS during April–July 2019

Variable	Overall	CTC-negative	CTC-positive	*p* value
Patients, *n* (%)	20 (100)	17 (85)	3 (15)	
Median age at RGS, yr (IQR)	64.5 (60.5–68.2)	61 (59–68)	67 (67–68)	0.2
Median follow-up, mo (IQR)	10.1 (7.8–16.4)	9.8 (7.6–15.9)	10.3 (9.1–16.4)	0.7
PTx, *n* (%)				
Radical prostatectomy	19 (95)	16 (94.1)	3 (100)	0.8
Irreversible electroporation	1 (5)	1 (5.9)	0 (0)	
Median year of PTx (IQR)	2016 (2014–2017)	2015 (2013–2017)	2016 (2016–2017)	0.3
Median PSA before PTx, ng/ml (IQR)	7.6 (4.6–11.1)	7.5 (5–10.7)	10 (7.3–11.2)	0.7
pT stage at radical prostatectomy, *n* (%)				
pT2	8 (40)	6 (35.3)	2 (66.7)	0.7
pT3a	4 (20)	4 (23.5)	0 (0)	
pT3b	7 (35)	6 (35.3)	1 (33.3)	
Not assigned	1 (5)	1 (5.9)	0 (0)	
pGG at radical prostatectomy, *n* (%)				
I–II	8 (40)	6 (35.3)	2 (66.7)	0.8
III	6 (30)	5 (29.4)	1 (33.3)	
IV–V	5 (25)	5 (29.4)	0 (0)	
Not assigned	1 (5)	1 (5.9)	0 (0)	
pN stage at radical prostatectomy, *n* (%)				
pN0	15 (75)	14 (82.4)	1 (33.3)	0.2
pN1	2 (10)	1 (5.9)	1 (33.3)	
pNX	2 (10)	1 (5.9)	1 (33.3)	
Not assigned	1 (5)	1 (5.9)	0 (0)	
Surgical margin at radical prostatectomy, *n* (%)				
R0	14 (70)	13 (76.5)	1 (33.3)	0.2
R1	5 (25)	3 (17.6)	2 (66.7)	
Not assigned	1 (5)	1 (5.9)	0 (0)	
Radiotherapy after radical prostatectomy, *n* (%)				
No	8 (40)	6 (35.3)	2 (66.7)	0.7
Yes	12 (60)	11 (64.7)	1 (33.3)	
Median time from PTx to PSMA-RGS, mo (IQR)	37.1 (20.8–63.9)	48.8 (21.3–72.8)	31.5 (20.7–34.3)	0.4
Median PSA before PSMA-RGS, ng/ml (IQR)	0.9 (0.5–1.6)	0.9 (0.5–1.2)	1.5 (1.2-2.9)	0.2
PSMA-positive lesions, *n* (%)				
1	12 (60)	10 (58.8)	2 (66.7)	0.9
2	7 (35)	6 (35.3)	1 (33.3)	
3	1 (5)	1 (5.9)	0 (0)	
Extent of PSMA-RGS, *n* (%)				
Pelvic surgery	15 (75)	13 (76.5)	2 (66.7)	0.9
Pelvic and retroperitoneal surgery	5 (25)	4 (23.5)	1 (33.3)	
Median lymph nodes removed, *n* (IQR)	16 (8.8–19.2)	16 (8–20)	16 (14.5–17)	1
Median positive lymph nodes, *n* (IQR)	2.5 (1–8)	2 (1–7)	8 (4.5–11.5)	0.4

PSMA = prostate-specific membrane antigen; RGS = radioguided surgery; CTC = circulating tumour cell; IQR = interquartile range; PTx = primary treatment; pGG = pathological Gleason grade group.

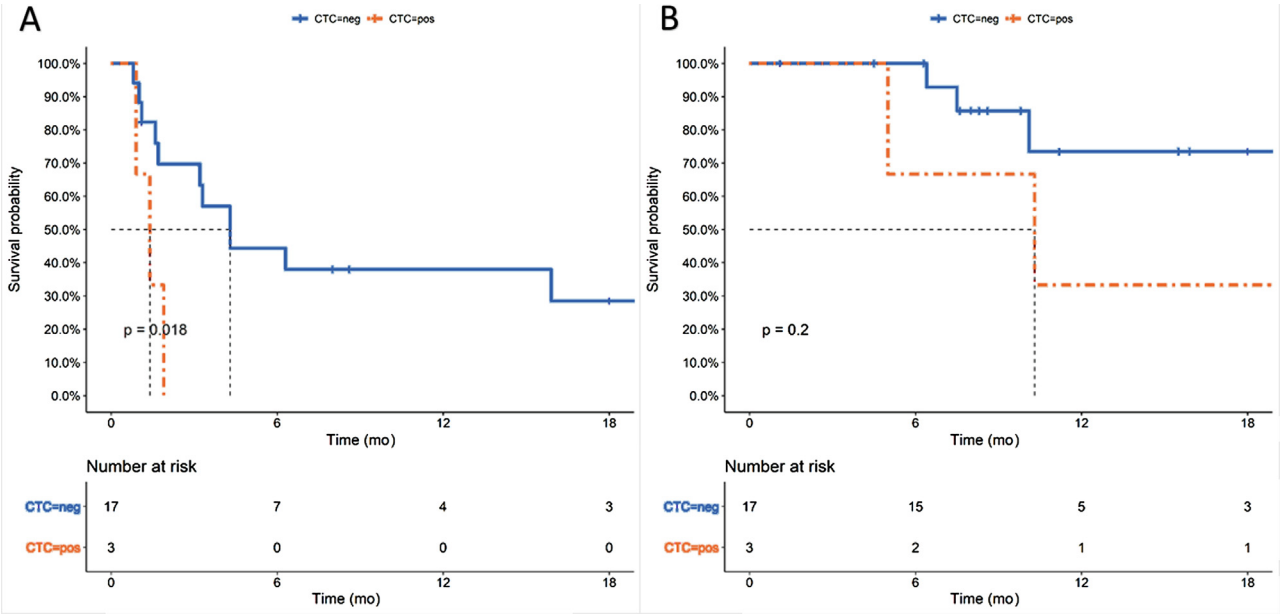

Fig. 1 – Kaplan-Meier plots depicting (A) biochemical recurrence-free survival (prostate-specific antigen <0.2 ng/ml, without additional prostate cancer–specific therapy) and (B) therapy-free survival by circulating tumour cell (CTC) status among 20 patients treated with prostate-specific membrane antigen (PSMA)-radioguided surgery (RGS) in a tertiary referral centre between April and July 2019.

evaluated. Descriptive statistics included the frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuous variables. Kaplan-Meier plots were used to graphically depict BFS and TFS after salvage surgery. For all statistical analyses, R v3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used. All tests were two-sided, with the level of significance set at $p < 0.05$.

Overall, 20 consecutive patients were included (Table 1). Of these, three patients (15%) were CTC-positive (Supplementary Fig. 1). CTC-positive (2–3 CTCs/7.5 ml) patients presented with slightly higher PSA before PSMA-RGS (1.5 vs 0.9 ng/ml in CTC-negative patients) but no difference in the number of positive lesions on PSMA PET imaging was observed (median 1 vs 1 in CTC-negative patients). Postoperatively, CTC-positive patients had more positive lymph nodes on final pathology assessment (median 8 vs 2 in CTC-negative patients) while no difference in overall lymph node count was observed. During median follow-up of 10.1 mo (interquartile range 7.8–16.4), 14 patients experienced BCR and five received further therapy. In Kaplan-Meier analyses, median BFS was 1.4 mo for CTC-positive patients versus 4.3 mo for CTC-negative patients ($p = 0.018$). Median TFS was 10.3 mo for CTC-positive patients versus not reached for CTC-negative patients ($p = 0.2$; Fig. 1).

Since CTCs have been described as an independent prognostic marker in metastatic castration-resistant PCa, we aimed to assess CTCs in patients with early recurrent PCa receiving SLND. We found worse clinical and pathological parameters in the CTC-positive group. Moreover, short-term oncological outcomes were inferior in the CTC-positive group. To the best of our knowledge, we are the first to describe these observations.

Since SLND remains an individual approach, thorough patient counselling is extremely important. Clinical variables such as PSA levels and the number of PET-positive lesions may help in guiding treatment decisions [9]. Nonetheless, further tools for decision guidance are eagerly awaited. In this context, biomarkers may be able to detect micrometastatic spread not yet visible on novel molecular imaging. Consequently, they may serve as gate-keepers in patients otherwise clinically deemed suitable for metastasis-directed therapy, such as SLND [10]. Thus, in cases with biomarker positivity, systemic therapy may be the primary treatment recommendation in the future, with discussion of a multimodal approach that includes additional local therapy only for selected cases. The liquid biopsy approach includes, besides CTCs, various other analytes such as circulating nucleic acids and extracellular vesicles. However, to the best of our knowledge these biomarkers have so far not been assessed as prognostic markers in patients with recurrent PCa before SLND [6].

Several limitations of our study need to be mentioned. First and foremost, our cohort included only 20 patients overall and only three patients were CTC-positive. Thus, univariable and multivariable analyses of further factors predicting relapse could not be performed. Moreover, we only report on short-term oncological outcomes. In addition, the CellSearch system was used for CTC counting, which may not be as sensitive in capturing CTCs as other methodologies [11,12].

Nonetheless, we believe that CTCs (and potentially other liquid biomarkers as well) are a promising tool that deserves further attention when considering salvage therapy approaches in BCR PCa. The results from this pilot study motivated us to initiate a prospective clinical trial with the aim of identifying predictive biomarkers for successful sal-

vage surgeries for PSMA-positive limited metastatic PCa recurrences (BioPoP, NCT04324983).

Author contributions: Tobias Maurer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Maurer, Knipper.
Acquisition of data: Maurer, Riethdorf, Werner.
Analysis and interpretation of data: Knipper, Maurer.
Drafting of the manuscript: Knipper, Maurer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Knipper.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.09.017.

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