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Original article

Limited prognostic value of preoperative circulating tumor cells for early biochemical recurrence in patients with localized prostate cancer

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Abstract

Introduction: The presence of circulating tumor cells (CTCs) is an established marker for prognosis in men with castration-resistant prostate cancer. A cutoff of ≥5 CTCs/7.5 ml blood in the CellSearch Epithelial Cell Test has been shown to stratify prognostic groups and predict outcome of abiraterone treatment. In contrast, the value of CTC detection in men with localized prostrate cancer before radical prostatectomy (RP) is unknown.

Materials and methods: A total of 152 patients treated with RP between 06/2009 and 09/2009 were included. Peripheral venous blood drawn the day before RP was evaluated for CTCs by the CellSearch system. The detection of CTCs was correlated with prostate-specific antigen (PSA) and the histopathological outcome of the RP specimen. A cutoff of 0 vs. ≥1 CTC/7.5 ml blood was defined as the threshold for positive vs. negative CTC status.

Results: Median age was 62 years and median PSA was 6.7 ng/dl. Staging revealed 62.5% pT2, 26.3% pT3a, and 11.2% pT3b tumors, and high-grade disease (≥Gleason 4 + 3) was determined in 25.6% of patients. CTCs were detected in 17 patients (11%) with a median CTC count/7.5 ml of 1 (range: 1–clusters with >100 epithelial cells) without significant correlations to PSA levels, pT stage, or Gleason scores. Postoperative pT stage was a significant predictor of biochemical recurrence (BCR) in univariable logistic regression models and as a composite measure together with positive CTC counts ($P < 0.0001$). CTC positivity alone tended to have a higher hazard ratio for BCR, but this was not statistically significant ($P = 0.1$). After a median follow-up of 48 months, there was no significant difference in BCR-free survival between patients with or without CTCs ($P = 0.7$).

Conclusion: Using the CellSearch system, we infrequently detected CTCs in patients with localized tumors before RP. The detection of CTCs did not correlate significantly with PSA, disease characteristics, or the development of BCR. However, larger cohorts with extended follow-up are needed to validate our findings.

Keywords: Prostate cancer; Circulating tumor cells; Prostatectomy; Biochemical recurrence

1. Introduction

Prostate cancer (PCa) is the most common malignancy in men, with an estimated 233,000 new cases in 2014 [1]. Its heterogeneity and long course make treatment approaches difficult to fit against under- and over-treatment. Up to 30% of patients treated with curative intent eventually relapse [2]. Since the beginning of the prostate-specific antigen (PSA) era, a significant shift toward organ-confined tumors at diagnosis has been observed in patients with PCa. Major

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advances in the treatment of PCa have led to substantially improved functional and oncologic outcomes. However, still up to one-third of treated men experience a biochemical recurrence (BCR) [2]. Prognostic models including preoperative and postoperative factors have been developed to assess patients at risk for BCR after definite treatment [3,4]. Conventional biomarkers such as PSA have only shown limited potential to predict the natural course of the disease. Although novel biomarkers such as human kallikrein 2 [5], transforming growth factor-beta1, or interleukin-6 soluble receptor [6] have been evaluated in their ability to identify patients at high risk of disease progression after radical prostatectomy (RP), none has succeeded to gain acceptance in routinely used prognostic models.

The presence of circulating tumor cells (CTCs) in peripheral blood has been associated with decreased overall survival in patients treated for metastatic breast, colorectal, lung, or PCa [7–10]. CTCs are used to aid the monitoring of patients with metastatic disease undergoing systemic treatment [11–13]. Large randomized trials have demonstrated the prognostic value of CTCs during the first- and second-line treatment of metastatic PCa with regards to survival [9,14].

Although several studies have tried to determine the value of CTCs in localized PCa, their results have been conflicting and limited by short follow-up periods [15–17]. On this basis, we sought to determine the prognostic value of CTCs for the early development of BCR in a consecutive cohort of RP patients with preoperatively localized disease.

2. Materials and methods

Between June and September 2009, 152 patients scheduled for RP at our institution gave their written informed consent to participate. The study received approval from the local ethics committee. We included patients >18 years of age with histologically confirmed PCa. Patients with prior or adjuvant hormonal treatments were excluded. Preoperative full blood samples (7.5 ml) were taken on the day before surgery in CellSave tubes (Veridex, Raritan, NJ). The CellSearch assay was used as previously described [8,18]. The detection of CTCs was correlated with PSA and the histopathological outcome of the RP specimen. Presence (0 vs. $\geq$1/7.5 ml blood) of CTCs was assessed to predict BCR. This cutoff was chosen as localized disease is more likely to have lower numbers of CTCs than metastatic PCa and is in accordance with previous studies [15,17]. BCR was defined as 2 consecutive PSA measures of >0.2 ng/ml. Follow-up data were available for 135 men. Kaplan-Meier and univariate Cox Regression analysis were performed to evaluate the association between the presence of CTCs, pathological characteristic, and BCR. Additionally, studies of CTC count $\geq$2, $\geq$4, $\geq$20, and $\geq$100 were performed to evaluate prognostic significance at higher thresholds. Further sensitivity analyses evaluated the association of the composite measure of pT stage and CTC positivity with the prediction of BCR. All statistical analyses were performed using the R-statistical package (R Foundation for Statistical Computing, Vienna, Austria), with a 2-sided significant level set at $P<0.05$.

3. Results

In descriptive analyses (Table 1), the mean (median/interquartile range [IQR]) age of patients was 63.2 (46–75) years. Mean (median/IQR) PSA was 6.6 (0.04–87) ng/dl, and 95 (62.5%), 40 (26.3%), and 17 (11.2%) patients had pT2, pT3a, and pT3b tumors, respectively. High-grade disease defined by a Gleason score $\geq 4+3$ and higher was found in 39 patients (25.9%), and 10 (6.6%) patients harbored lymph node metastasis.

CellSearch analysis revealed CTC positivity for 17 patients (11.2%) with a median CTC count of 1/7.5 ml (range: 1–clusters with $>$ 100 epithelial cells) (Table 2). No significant differences were found between groups with 0 vs. $\geq$1 CTC with respect to PSA ($P = 0.6$), pT stage, Gleason grade ($P = 0.8$ both), or nodal status ($P = 0.5$), repectively. The majority of CTC-positive patients had pT2 and pN0 disease in the final pathologic specimen.

After a mean (median/IQR) follow-up of 44.3 (48/36–60) months, BCR-free survival for patients with 0 vs. $\geq$1 CTCs was 68 % and 72%, respectively ($P = 0.66$). Patients with localized disease (pT2) had a significantly higher BCR-free survival than patients with pT3a and pT3b disease ($P < 0.0001$, Fig 1). Pathological stage $\geq$pT3 alone and in the composite measure with CTC positivity was a positive predictor of BCR ($P < 001$). A CTC count $\geq$1 alone did not

Table 1
Descriptive statistics of 152 RP patients, stratified by $\geq$1 CTC vs. no detectable CTC

	Overall	CTC-negative (%)	CTC-positive $\geq$1 (%)	*P*
Patients	152	135 (88.8)	17 (11.2)	
Age, median (IQR)	63.2 (46–75)	64 (58–69)	63 (57–68)	0.9
PSA, median (IQR)	6.65 (5.1–12)	6.6 (5–12)	8.6 (5.4–13.5)	0.6
PT stage (%)				
pT2	95 (62.5)	86 (63.7)	12 (70.6)	0.8
pT3a	40 (26.3)	35 (25.9)	4 (23.5)	
$\geq$pT3b	17 (11.2)	14 (10.4)	1 (5.9)	
Gleason score (%)				
$\leq 3+3$	35 (23)	30 (22.2)	5 (29.4)	0.8
$3+4$	78 (49.4)	69 (51.1)	7 (41.2)	
$4+3$	32 (21.0)	30 (22.2)	3 (17.6)	
$\geq 4+4$	7 (4.6)	6 (4.4)	2 (11.8)	
pN status (%)				
pNx	46 (30.3)	40 (29.6)	3 (17.6)	0.6
pN0	96 (63.3)	86 (63.7)	13 (76.5)	
pN1	10 (6.6)	9 (6.7)	1 (5.9)	