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Original article

Circulating tumor cells in patients with advanced urothelial carcinoma of the bladder: Association with tumor stage, lymph node metastases, FDG-PET findings, and survival

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Abstract

Background: There are currently no methods in clinical use that can detect early systemic dissemination of urothelial tumor cells.

Objective: To evaluate measurement of circulating tumor cells (CTCs) as a biomarker for disseminated disease in patients with advanced bladder cancer.

Design, setting, and participants: Between March 2013 and October 2015, 88 patients were prospectively included in the study: 78 were scheduled for radical cystectomy (RC) ± perioperative chemotherapy and 10 treated with palliative chemotherapy. The CellSearch CTC test was further assessed in this context by investigating expression of epithelial cell adhesion molecule (EpCAM) in primary tumors obtained at cystectomy from an independent cohort of 409 patients.

Outcome measurements and statistical analysis: Presence of CTCs was tested for association with tumor stage, lymph node metastases, metastatic disease on [18 F]-fluorodeoxyglucose-positron emission tomography (FDG-PET), and cancer-specific and progression-free survival.

Results: CTCs were detected in 17/88 patients (19%). In 61 patients who underwent FDG-PET-computed tomography (CT), a statistically significant association with presence of CTCs was found for radiological metastatic disease but not for normal PET-CT results (12/35 [34%] vs. 2/26 [8%], $P = 0.014$). After a median follow-up time of 16.5 months (95% CI: 9.6–21.4), presence of CTCs was associated with an increased risk of progression among patients treated with RC with or without perioperative chemotherapy ($n = 75$, $P = 0.049$). A multivariate analysis adjusted for clinical tumor stage, clinical lymph node status, and age showed that CTCs were an independent marker of progression ($n = 75$; hazard ratio = 2.78; 95% CI: 1.005–7.69; $P = 0.049$) but not of cancer-specific death ($P = 0.596$). In 409 cystectomised patients, more than 392 (96%) of the bladder tumors expressed EpCAM.

Conclusions: CTCs were present in 19% of patients with advanced urothelial tumors and were associated with metastatic disease on FDG-PET-CT and with increased risk of disease progression after RC. A significant portion of urothelial cancer cells do express EpCAM and can thus be identified using EpCAM-antigen–based CTC detection methods.

Keywords: Bladder cancer; Circulating tumor cells; Urothelial carcinoma of the bladder; FDG-PET-CT; EpCAM

1. Introduction

Urothelial carcinoma of the bladder (UCB) is the fifth most common cancer in Europe and a significant cause of morbidity and mortality throughout the world [1]. The standard of care for patients with muscle-invasive UCB

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consists of neoadjuvant chemotherapy with radical cystectomy (RC) [2]. Despite extensive surgery, the 5-year survival rate is only about 50% after RC, most likely because of dissemination of the disease before surgery [3]. At present, there are no methods in clinical use that can detect early dissemination of tumor cells, although neoadjuvant chemotherapy is used to increase survival by targeting undetected micrometastatic disease [4–6]. Therefore, a method that can detect disseminated disease at an early stage would constitute a valuable tool for selecting patients for chemotherapy.

In this context, we prospectively examined whether the detection of circulating tumor cells (CTCs) is associated with tumor stage, lymph node metastasis, and [18 F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) findings in a heterogeneous population of patients with advanced urothelial tumors and survival in patients treated with RC with or without perioperative chemotherapy. To further assess the consequences of epithelial cell adhesion molecule (EpCAM) expression for the CellSearch CTC test, we also investigated EpCAM expression in primary tumors from cystectomised patients in a separate but similar cohort.

2. Patients and methods

2.1. Study population

Between March 2013 and October 2015, 88 patients (Table 1) with histopathologically confirmed UCB were evaluable in the present investigation as an extension of a previous pilot study [7]. The following were eligible for inclusion: patients with advanced urothelial tumors (pT1-T4, pN0-N3, or M0-M1) who underwent RC with or without preoperative chemotherapy, and patients who were scheduled for palliative chemotherapy. Patients who had radiological locally advanced disease (T4b or N+) and were considered for RC with curative intent received induction chemotherapy with 4 to 6 courses of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC), whereas neoadjuvant chemotherapy was administered as 3 courses of ddMVAC in patients with no evidence of lymph node involvement (T2-T4aN0). Palliative chemotherapy was administered as ddMVAC or gemcitabine/cisplatin. Staging included standard histopathological staging after transurethral resection and computed tomography (CT) scanning of the thorax, abdomen, and pelvis. In selected patients with a cT3b tumor or a T2 tumor with hydronephrosis or other high-risk features, an FDG-PET-CT scan was also performed according to current institutional practice [8].

Exclusion criteria were high-risk prostate cancer (according to the D'Amico risk categories) or other concomitant malignancies. Patient characteristics of the study cohort are listed in Table 1. The treatment cohort with preoperative chemotherapy also included patients receiving induction chemotherapy (i.e., chemotherapy aimed at reducing macroscopic disease burden before surgery, as opposed to neoadjuvant chemotherapy, which is administered to eliminate micrometastases) [9]. The Regional Ethical Review Board in Lund, Sweden, approved the study (EPN 2013/76).

Table 1
Patient characteristics

Parameter	Value, *n* (%)
Total patients	88
Median age (IQR) at CTC-analyses	73 (67–76)
Sex	
Male	68 (77.2)
Female	20 (23.7)
cTNM-classification	
cT1	7 (8.0)
cT2	54 (61.3)
cT3	21 (23.8)
cT4	6 (6.8)
cN positive	32 (36.3)
pTNM-classification	
pTis	6 (8.0)
pTa	3 (4.0)
pT0	20 (26.7)
pT1	3 (3.4)
pT2	18 (24.0)
pT3	15 (20.0)
pT4	10 (13.3)
FDG-PET-CT performed	61
Metastases (N+/M1) on PET	35/61 (57.4)
Median CTC-number (range: 1–105)	3
Treatment cohort	
Cystectomy alone	34 (45.3)
Cystectomy with adjuvant chemotherapy	5 (6.7)
Cystectomy with neoadjuvant chemotherapy	25 (33.3)
Cystectomy with induction chemotherapy	11 (14.7)
Curative external radiation beam therapy	1
Other[a]	2
Palliative chemotherapy	10
Number of MVAC-cycles	
1	3
2	6
3	19
4	4
5	4
6	4
Men with prostate cancer in the cystectomy specimen	18 (24)
Low risk	13
Intermediate risk	4
High risk (excluded)	1
Margin status	
Positive	4
Negative	71
Patient status at end of follow-up after radical cystectomy	
Alive	71 (80.7)
Progressed	13
Dead	17 (19.3)

IQR = interquartile range; TNM = tumor, node, metastates.
[a]One patient progressed before cystectomy could be performed and one patient suffered a fatal pulmonary embolism before cystectomy could be performed.