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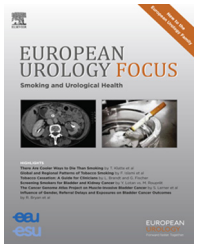


Prostate Cancer

# Interrogating Metastatic Prostate Cancer Treatment Switch Decisions: A Multi-institutional Survey

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## Abstract

*Background:* Evaluation of responses to treatment for metastatic castration-resistant prostate cancer (mCRPC) remains challenging. Consensus criteria based on prostate-specific antigen (PSA) and clinical and radiologic biomarkers are inconsistently utilized. Circulating tumor cell (CTC) counts can inform prognosis and response, but are not routinely used.
*Objective:* To evaluate the use of biomarkers and trends in clinical decision-making in current mCRPC treatment.
*Design, setting, and participants:* A 23-part online questionnaire was completed by physicians treating mCRPC.
*Outcome measures and statistical analysis:* Results are presented as the proportion (%) of physicians responding to each of the options. We used $\chi^2$ and Fisher's tests to compare differences.
*Results and limitations:* A total of 118 physicians (22.1%) responded. Of these, 69.4% treated ≥50 mCRPC patients/year. More physicians administered four or fewer courses of cabazitaxel (27.9%) than for docetaxel (10.4%), with no significant difference in the number of courses between bone-only disease and Response Evaluation Criteria in Solid Tumours (RECIST)–evaluable disease. Some 74.5% of respondents considered current biomarkers useful for monitoring disease, but only 39.6% used the Prostate Cancer Working Group (PCWG2) criteria in clinical practice. PSA was considered an important biomarker by 55.7%, but only 41.4% discarded changes in PSA before 12 wk, and only 39.4% were able to identify bone-scan progression according to PCWG2. The vast majority of physicians (90.5%) considered clinical progression to be important for switching treatment. The proportion considering biomarkers important was 71.6% for RECIST, 47.4% for bone scans, 23.2% for CTCs, and 21.1% for PSA. Although 53.1% acknowledged that baseline CTC counts are prognostic, only 33.7% would use CTC changes alone to switch treatment in patients with bone-only disease. The main challenges in using CTC counts were access to CTC technology (84.7%), cost (74.5%), and uncertainty over utility as a response indicator (58.2%).

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**Conclusions:** A significant proportion of physicians discontinue treatment for mCRPC before 12 wk, raising concerns about inadequate response assessment. Many physicians find current biomarkers useful, but most rely on symptoms to drive treatment switch decisions, suggesting there is a need for more precise biomarkers.

**Patient summary:** In this report we analyse the results of a questionnaire evaluating tools for clinical decision-making completed by 118 prostate cancer specialists. We found that most physicians favour clinical progression over prostate-specific antigen or imaging, and that criteria established by the Prostate Cancer Working Group are not widely used.



## 1. Introduction

The past decade has seen an increase in the therapeutic armamentarium against metastatic prostate cancer, with agents proving survival benefit both in the castrate-resistant (mCRPC) [1–7] and castration-naïve stages [8,9] of the disease. This increased availability of treatment options necessitates improved biomarkers to determine treatment responses more rapidly and facilitate optimised decisions on therapeutic sequencing [10].

Prostate-specific antigen (PSA), bone scans, and Response Evaluation Criteria in Solid Tumours (RECIST) criteria are commonly utilized to evaluate responses and are recommended as outcome measures by the Prostate Cancer Working Group (PCWG2) for clinical trials [11]. However, these biomarkers have significant limitations. In particular, PSA and bone scans do not allow early response assessment, and none of the biomarkers provide patient-level surrogates of clinical benefit [12,13]. This challenge is compounded by the lack of RECIST-evaluable disease in a substantial proportion of patients [14]. For daily clinical practice, existing guidelines do not recommend specific treatment monitoring, an issue addressed by the Advanced Prostate Cancer Consensus conference [15].

The lack of adequate biomarkers may impact the dose intensity of chemotherapy and other anticancer (hormonal, radiopharmaceutical) agents administered in daily clinical practice. The fact that determining disease progression in the absence of clear clinical deterioration is impossible before 12 wk (owing to the possibility of an early PSA or bone scan "flare reaction") in patients with no RECIST-evaluable disease may contribute to both the administration of more chemotherapy cycles to patients with bone-only disease (overtreatment) and a higher reliance on PSA changes for early treatment discontinuation (undertreatment).

Circulating tumour cell (CTC) counts are prognostic and are associated with treatment response in mCRPC patients, with recent studies indicating value as a patient-level surrogate of survival [16,17]. Increasing evidence suggests that CTCs could be utilised to monitor disease progression in mCRPC [18]. However, CTC use is largely limited to academic centres in the setting of clinical trials.

We conducted an online survey of physicians treating mCRPC. The survey focused on how physicians make treatment switch decisions, opinion on response indicators, utilisation of PCWG2 criteria in routine practice, and the value of CTC counts to guide treatment switch decisions. The results will help to inform the design of an international trial and health economic evaluation to improve treatment switch decisions for mCRPC patients to improve outcomes, decrease overtreatment, and maximise resource utilisation.

## 2. Materials and methods

A 23-part online questionnaire, divided in four sections as outlined below, was compiled by the authors (Supplementary Fig. 1):

1. General questions on clinical practice.
2. Familiarity with progression criteria for currently established biomarkers.
3. CTCs and their assessment in patients with advanced prostate cancer.
4. Clinical decision-making using response indicators.

E-mails inviting participation in the survey were sent to 485 UK investigators participating in urologic cancer clinical trials, 29 physician members of the GU Group of the Swiss Group for Clinical Cancer Research, and 20 practising prostate cancer physicians in Australia and New Zealand. A link to the web-based survey (created with SurveyMonkey) was included.

### 2.1. Statistical analyses

Descriptive statistics were used; the proportion (%) of physicians responding to each option is presented. Physicians were classified according to the number of patients they treated ($\geq$50 vs $<$50 patients/year) or recruited to clinical trials ($\geq$25% vs $<$25%), and the number of cycles of docetaxel/cabazitaxel prescribed ($\leq$4, 5–6, $\geq$7 cycles). No pre-existing evidence was used in choosing classification cutoff values. Proportions were compared using a $\chi^2$ test or Fisher's exact test (for cell frequencies $\leq$5). A $p$ value of 0.05 was set as the limit for statistical significance. No adjustment for multiple testing was performed. SPSS version 21 (IBM IBM, Armonk, NY, USA) was used.

## 3. Results

### 3.1. Participant characteristics and their clinical practice

Between November 21, 2014 and December 18, 2014, 118 practising prostate cancer physicians (22.1%) replied. Sections 1, 2, 3, and 4 were completed by, 111, 106, 98, and 89 physicians, respectively. Most respondents (77.1%) practised in the UK. Nearly 70% treated $\geq$50 mCRPC patients/year (Table 1). Most reported prescribing 7–10 courses of docetaxel and 5–6 cycles of cabazitaxel (Fig. 1); there was no difference in the number of courses of either docetaxel ($p(\chi^2_2) = 0.519$) or cabazitaxel ($p(\chi^2_2) = 0.814$) administered to patients with RECIST-evaluable disease compared to patients with bone-only disease. Physicians