available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer

*Editorials on pp. 795–796 and on pp. 797–799 of this issue*

# Treatment of the Primary Tumor in Metastatic Prostate Cancer: Current Concepts and Future Perspectives

***Christopher E. Bayne*** [a], ***Stephen B. Williams*** [b], ***Matthew R. Cooperberg*** [c], ***Martin E. Gleave*** [d], ***Markus Graefen*** [e], ***Francesco Montorsi*** [f], ***Giacomo Novara*** [g], ***Marc C. Smaldone*** [h], ***Prasanna Sooriakumaran*** [i,j], ***Peter N. Wiklund*** [i], ***Brian F. Chapin*** [b,*]

[a] *Department of Urology, The George Washington University, Washington, DC, USA;* [b] *Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [c] *Departments of Urology and Epidemiology and Biostatistics, University of California, San Francisco, CA, USA;* [d] *The Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada;* [e] *Martini-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [f] *Division of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy;* [g] *Department of Surgery, Oncology, and Gastroenterology–Urology Clinic, University of Padua, Italy;* [h] *Division of Urologic Oncology, Fox Chase Cancer Center-Temple University Health System, Philadelphia, PA, USA;* [i] *Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden;* [j] *Surgical Intervention Trials Unit, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK*

**Article info**

***Article history:***
Accepted April 22, 2015

***Associate Editor:***
Giacomo Novara

***Keywords:***
Prostatic neoplasms
Neoplasm metastasis
Prostatectomy
Chemotherapy
Survival

**Abstract**

***Context:*** Multimodal treatment for men with locally advanced prostate cancer (PCa) using neoadjuvant/adjuvant systemic therapy, surgery, and radiation therapy is being increasingly explored. There is also interest in the oncologic benefit of treating the primary tumor in the setting of metastatic PCa (mPCa).
***Objective:*** To perform a review of the literature regarding the treatment of the primary tumor in the setting of mPCa.
***Evidence acquisition:*** Medline, PubMed, and Scopus electronic databases were queried for English language articles from January 1990 to September 2014. Prospective and retrospective studies were included.
***Evidence synthesis:*** There is no published randomized controlled trial (RCT) comparing local therapy and systemic therapy to systemic therapy alone in the treatment of mPCa. Prospective studies of men with locally advanced PCa and retrospective studies of occult node-positive PCa have consistently shown the addition of local therapy to a multimodal treatment regimen improves outcomes. Molecular and genomic evidence further suggests the primary tumor may have an active role in mPCa.
***Conclusions:*** Treatment of the primary tumor in mPCa is being increasingly explored. While preclinical, translational, and retrospective evidence supports local therapy in advanced disease, further prospective studies are under way to evaluate this multimodal approach and identify the patients most likely to benefit from the inclusion of local therapy in the setting of metastatic disease.
***Patient summary:*** In this review we explored preclinical and clinical evidence for treatment of the primary tumor in metastatic prostate cancer (mPCa). We found evidence to support clinical trials investigating mPCa therapy that includes local treatment of the primary tumor. Currently, treating the primary tumor in mPCa is controversial and lacks high-level evidence sufficient for routine recommendation.


* Corresponding author. Department of Urology, The University of Texas MD Anderson Cancer Center, Unit 1373, 1515 Holcombe Blvd, Houston, TX 77030, USA. Tel. +1 713 7923250; Fax: +1 713 7944824.
E-mail address: bfchapin@mdanderson.org (B.F. Chapin).

http://dx.doi.org/10.1016/j.eururo.2015.04.036
0302-2838/

## 1. Introduction

Although the incidence of de novo metastatic prostate cancer (mPCa) identified at initial diagnosis has declined with time in the era of prostate-specific antigen (PSA)-based early detection efforts, survivability after presentation is more complex [1–3]. The current standard treatment for de novo mPCa is systemic treatment directed at the androgen axis, with surgical castration or androgen deprivation therapy (ADT) with or without an antiandrogen agent [4,5]. Multimodal therapy with combined use of chemotherapy seems to substantially improve survival and may become a more standard option in hormone-sensitive mPCa [6].

Traditionally, surgical treatment has been reserved for patients with organ-confined and, more recently, pelvic-confined PCa [7–9]. The fundamental oncologic principle in treating mPCa patients systemically rather than locally is that malignant tumor cells have already entered the systemic circulation and established metastatic sites. Therefore, local therapy (including external radiation therapy [RT], brachytherapy, and radical prostatectomy [RP]) has potential for harm (eg, side effects) without a clearly defined benefit. By contrast, there is a growing body of evidence indicating that for other malignancies (eg, metastatic ovarian, gastrointestinal, and kidney cancers) treatment of the primary tumor in addition to systemic therapy improves survival outcomes [10–14].

There is currently no level 1 evidence suggesting local therapy of the primary tumor in mPCa provides a survival advantage. However, in recent years there has been a paradigm shift in the treatment of patients with locally advanced PCa and/or occult node-positive disease. Prospective studies have demonstrated improved progression-free survival (PFS) and overall survival (OS) for multimodal treatment of locally advanced PCa (Table 1). In addition, retrospective cohorts and population-based studies of occult nodal disease have shown survival advantages in mPCa patients treated with local therapy. Furthermore, post hoc analyses of prospective studies have revealed improved outcomes for with local therapy in patients who eventually develop mPCa [15,16].

Owing to the heterogeneity of concepts and data published in the literature, this review was not conducted according to a systematic protocol but is rather a narrative review of the literature examining the role of local therapy in mPCa. We also describe current theories on local control in mPCa and explain the rationale for designing an randomized controlled trial (RCT) to evaluate the impact of local treatment as an integrated treatment strategy.

## 2. Evidence acquisition

### 2.1. Materials and methods

#### 2.1.1. Information sources and eligibility criteria

The Medline, Medline In-Process, and Scopus databases were searched for all original articles published from January 1990 to September 2014 on the topic of interest. Medline was searched through PubMed. The inclusion criteria were (1) original article, (2) English language, (3) accessibility to the full manuscript, and, when applicable, (4) availability of Kaplan-Meier/Cox regression-derived results on PCa outcomes. As there are no current prospective RCTs published on the topic of local therapy in mPCa, we subjectively evaluated the current literature regarding its relevance to the topic.

#### 2.1.2. Search strategy

We searched using the controlled vocabulary of the Medical Subject Heading database and open text. The algorithm applied used (“prostate” OR “prostatic”) AND (“cancer” OR “carcinoma” OR “tumour” OR “tumor” OR “neoplasm”) AND (“metastatic” OR “metastasis” OR “advanced” OR “high risk” OR “high-risk” OR “lymph node” or “nodal”) AND (“local therapy” OR “cytoreductive” OR “cytoreduction” OR “surgery” OR “prostatectomy” OR “radiation therapy” OR “radiotherapy”). All selected articles were further searched to identify additional relevant articles.

## 3. Evidence synthesis

### 3.1. Efficacy theories

#### 3.1.1. Tumor debulking

The theory on the oncologic benefit of tumor debulking in patients diagnosed with mPCa has been studied both in vivo and ex vivo. Investigators have evaluated the integration of systemic therapy and local control in a preclinical mouse model with promising results [17,18]. Kadmon et al [17] used a PCa cell line that uniformly resulted in metastatic lung colonies. The mice were treated with either single-dose chemotherapy, surgical excision of the primary tumor, or a combination of tumor excision and postoperative single-dose chemotherapy. Tumor excision followed by postoperative chemotherapy resulted in a decrease in the number of metastatic sites in the lungs and substantially prolonged survival. Grinis et al [18] also found a significant decrease in metastatic lung lesions in mice treated with resection of the primary lesion, further establishing a preclinical model incorporating local therapy.

In a clinical setting, Qin et al [19] investigated patients with hormone-sensitive mPCa treated with ADT with and without transurethral resection of the prostate (TURP) as a symptom-relieving procedure. Preliminary results showed patients who underwent TURP had a significantly lower PSA nadir (median 0.15 vs 0.82 ng/ml, $p = 0.015$) and a longer time to PSA nadir (11.2 vs 6.4 mo, $p < 0.001$). Control patients who did not receive TURP were more likely to develop hormone-refractory PCa ($p = 0.007$). For the data published thus far, there is no significant difference in disease-specific survival or OS between the groups [19]. These studies suggest treating the primary tumor in mPCa has a plausible role; however, further research in humans is warranted to discern appropriate candidates for local therapy.