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Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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

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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.

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<http://dx.doi.org/10.1016/j.eururo.2015.04.036>

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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 a 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.

Table 1 – Randomized control trials examining multimodal therapy for locally advanced prostate cancer

Study details	Population		Intervention (n)	Median follow-up (yr)	Key findings
	Disease stage	n			
Thompson et al (2009) [7] US multicenter 1988–1997	pT3 N0 M0 ^a	425	RP, then: immediate RT (60–64 Gy prostate; +RT, 214) or observation (–RT, 211)	+RT 12.7 –RT 12.5	Median MFS favored +RT (14.7 vs 12.9 yr; HR 0.71, <i>p</i> = 0.016). NNT to prevent 1 case of metastatic disease at 12.6 yr = 12.2. OS favored +RT (15.2 vs 13.3 yr; HR 0.72, <i>p</i> = 0.023). NNT to prevent 1 death at 12.6 yr = 9.1
Widmark et al (2009) [27] European multicenter 1996–2002	cT3 (78%) N0 M0 PSA <70 ng/ml ^b	875	HT (3-mo LHRH-A then antiandrogen) + RT (70 Gy prostate, 436) or HT alone (439)	7.6	7- and 10-yr CSS favored HT + RT (93.7% and 91.1% vs 88.1% and 76.1%, <i>p</i> < 0.001). 7- and 10-yr OS favored HT + RT (83.5% and 79.9% vs 70.4% and 60.6%, <i>p</i> = 0.004). 7- and 10-yr bPFS ^A favored HT + RT (82.4% and 28.9% vs 74.1% and 25.3%, <i>p</i> < 0.001)
Warde et al (2011) [28] North America and UK multicenter 1995–2005	cT2–4 N0 M0 ^c	1205	HT (lifelong LHRH-A or bilateral orchiectomy) + RT (45 Gy whole pelvis + 20–24 Gy prostate, or 65–69 Gy prostate; 603) or HT alone (602)	6.0	7-yr OS favored HT + RT (74% vs 66%, <i>p</i> = 0.03). 7-yr CSS favored HT + RT (9% vs 79%, <i>p</i> = 0.0001)
Mottet et al (2012) [29] Multicenter France and Tunisia 2000–2003	cT3–4 N0 M0 ^d	264	HT (LHRH-A for 3 yr) + RT (46 Gy whole pelvis + 22–24 Gy prostate, 133) or HT alone (130)	5.6	5-yr bPFS ^A and bPFS ^P favored HT + RT (60.9% and 64.7% vs 8.5% and 15.4%; <i>p</i> < 0.0001 and <i>p</i> < 0.0011, respectively). 5-yr locoregional PFS favored HT + RT (90.2% and 70.8%, <i>p</i> < 0.0001). 5-yr CSS and OS were equivocal
Bolla et al (2012) [8] European multicenter 1992–2001	pT3 pN0 M0 ^e	1005	RP, then immediate RT (60 Gy prostate; +RT, 502) or observation (–RT, 503)	10.6	10-yr PFS favored +RT (60.6% vs 38.2%, <i>p</i> < 0.0001). OS, MFS, and cPFS similar between groups
Wiegel et al (2014) [9] European multicenter 1997–2004	pT3 pN0 M0 ^f	388	RP, then immediate RT (60 Gy prostate; +RT, 194) or observation (–RT, 194)	+RT 9.3 –RT 9.4	10-yr PFS favored +RT (56% vs 35%, <i>p</i> < 0.0001). Patients with pT3b tumors or +surgical margins in –RT group, 10-yr PFS decreased to 28% and 27%, respectively. OS and MFS similar between groups

ADT = androgen deprivation therapy; PFS = progression-free survival; bPFS^A = biochemical PFS, ASTRO definition; bPFS^P = biochemical PFS, Phoenix definition; cPFS = clinical PFS; CSS = cancer-specific survival; CXR = chest x-ray; HT = hormone therapy; LHRH-A = luteinizing hormone-releasing hormone agonist; MFS = metastasis-free survival; NNT = number needed to treat; PLND = pelvic lymph node dissection; PSA = prostatic-specific antigen; RP = radical prostatectomy; RT = external radiation therapy; SV = seminal vesicles.

^a Patients at clinically very low risk of lymph node involvement not required to undergo PLND. All underwent RP, with either extracapsular extension, positive surgical margins, or SV invasion 16 wk before randomization. Undetectable PSA at randomization not required. RT initiated within 10 working days from randomization.

^b PSA <70 ng/ml and negative CXR and bone scan. PSA ≥11 ng/ml underwent PLND (fossa obturatoria). Positive nodal disease excluded. Patients initiated RT after 3 months ADT.

^c At initiation, cT3–4 N0 or X M0. In 1999, inclusion criteria changed to include cT2 with either PSA >40 ng/ml or PSA >20 ng/ml and Gleason >8. Surgical nodal staging allowed, but pN1 excluded. Neoadjuvant ADT within 12 wk of randomization permitted. RT initiated within 8 wk of randomization.

^d RT initiated within 3 mo of randomization.

^e cT0–3 N0 M0 and pT2–3 N0 after RP and ilio-obturator PLND. All underwent RP, with either extracapsular extension, positive surgical margins, or SV invasion, 16 weeks prior to RT. Undetectable PSA at randomization not required. RT initiated at median 90 days after surgery. PFS = biochemical progression (increase in PSA to >0.2 µg/L measured on two occasions ≥2 weeks after nadir), clinical progression, or death.

^f = cT1–3 N0 M0 and pT3–4 pN0 after RP with positive or negative margins. Detectable PSA after RP excluded. RT initiated at median 81 d from surgery. PFS = two consecutive PSA increases.

3.1.2. Changes in tumor biology

There remains a critical need to delineate the molecular features associated with progression to lethal metastatic disease and to outline the sequence of events once metastases have occurred. It would appear a primary tumor is necessary for establishment of metastatic sites. As seen for other tumors, specific upregulation of fibronectin and clustering of bone marrow-derived cellular infiltrates that coexpress matrix metalloproteinases in distant tissue sites before tumor cell arrival are indispensable for the initial

stages of metastasis [20]. Their arrival at distant sites represents early changes in the local microenvironment, termed the *premetastatic niche*, that dictate the pattern of metastatic spread [20]. This theory is complicated by whole-genome sequencing and molecular pathologic analyses. Haffner et al [21] tracked the evolution of a lethal PCa cell clone from the primary tumor to metastasis in a single patient using samples collected during disease progression and at the time of death. Analysis revealed that the lethal clone arose from a small, relatively low-grade cancer focus

in the primary tumor, and not from the bulky, higher-grade primary cancer or from lymph nodes resected at RP. Another group tracked metastatic-specific DNA changes in a patient's PCa lymph-node metastases to a single site of intraductal carcinoma [22]. These findings suggest the importance of developing and implementing molecular prognostic and predictive profiling markers to enhance current pathologic evaluation.

A central tenet of cancer biology is cancer cells leave the primary tumor as circulating tumor cells that seed metastases in distant organs. Data have shown circulating tumor cells can also seed and then colonize their own tumors of origin [23]. Thus, in addition to its role in shedding metastatic cells, the primary tumor may also act as a self-seeding site for circulating tumor cells primed and deposited from established metastatic sites. Genetic interplay may play a role in the migratory behavior in mPCa and in the growth characteristics of the primary tumor [23]. Interruption of this cycle by local treatment of the primary tumor or a metastatic site may alter tumor biology and result in depressed growth or may limit the establishment of new metastatic sites.

In an effort to identify individuals at high risk of early relapse, investigators analyzed bone marrow aspirates from PCa patients to determine the prognostic impact of positive cells detected before surgery and postoperatively [24]. Interestingly, cytokeratin-positive cells detected before surgery were the strongest independent risk factor for early metastasis (within 48 mo), whereas cytokeratin-positive cells detected in bone marrow at 6 mo to 10 yr after RP had no influence on disease outcome [24], providing evidence of the need for a primary tumor for establishment of metastatic niches and the development of clinically identifiable metastases.

The validity of theories on changes in primary tumor biology depends on the presence of disease even after therapy is initiated. Residual tumor in prostate biopsy specimens after RT is a significant prognostic factor in disease-free survival in patients with intermediate- and high-risk PCa [25]. Tzelepi et al [26] provided evidence to support this concept in a novel study that evaluated molecular changes in the primary tumor after aggressive systemic therapy with ADT and docetaxel for 1 yr followed by RP in patients with clinically detected lymph node mPCa. Despite a favorable PSA response, the authors found upregulation of enzymes associated with intracrine androgen synthesis and several other pathways linked to PCa progression. The study highlights the involvement of the primary tumor in disease progression and the potential benefit of local therapy in mPCa.

3.2. Locally advanced and regional nodal disease

3.2.1. Multimodal therapy for locally advanced prostate cancer identified at RP

The efficacy of multimodal therapy in the treatment of locally advanced PCa has been established in large RCTs (Table 1). In general, RT following RP consistently improved freedom from biochemical recurrence (BCR) and local

control outcomes with or without ADT [7–9]. Mature studies have demonstrated that post-RP RT improved OS and metastasis-free survival [7], while other subgroup analyses revealed only patients with high-risk features or positive surgical margins after RP appeared to benefit from adjuvant RT [8,9,30].

3.2.2. Local therapy in occult nodal disease

Many large retrospective studies have examined local therapy of the primary tumor, with or without subsequent ADT, in occult nodal disease (Table 2). The majority of these studies examined patients with clinically localized disease undergoing staging pelvic lymph node dissection (PLND) before planned RP. If pelvic nodes were positive on frozen section analysis, surgeon discretion drove decisions to proceed with or abort RP. The studies consistently showed improved outcomes when local therapy, in the form of RP or subsequent RT to the primary tumor, was used.

To contextualize these data, it is important to acknowledge the significant limitations of these predominantly institutional retrospective studies. It is not possible to adequately control for selection bias of the treating surgeon in the decision to proceed with RP in positive nodal disease. Furthermore, neoadjuvant and adjuvant treatments were inconsistently reported and varied between studies. Finally, lymph node burden was reported inconsistently (eg, number of positive nodes vs largest diameter). This is particularly important, as several retrospective reviews found lymph node burden dichotomized outcomes in occult node-positive disease (Table 3).

3.2.3. Multimodal therapy in occult nodal disease and clinically positive nodal disease

The use and timing of adjuvant treatments in occult nodal disease have been investigated in both retrospective and prospective studies (Table 4). Spiess et al [46] reviewed cases of immediate hormone therapy versus observation after PLND and RP. The series was small and identified similar metastasis-free survival, cancer-specific survival (CSS), and OS between the two groups. These results are overshadowed by a prospective, randomized study by Messing et al [45] in which patients with positive lymph nodes after PLND and RP experienced significantly improved clinical PFS, CSS, and OS when randomized to immediate versus delayed hormonal therapy, although the delayed hormonal therapy was administered at the time of symptomatic bone metastases. In the setting of occult nodal disease at PLND and aborted RP, Schröder et al [50] showed that delayed hormonal therapy was noninferior compared to immediate hormonal therapy in a prospective randomized, albeit underpowered, study. Aggressive local therapy seems to be effective in this setting as well. Two retrospective studies showed the addition of RT and ADT after local therapy with RP and PLND improved survival in occult nodal disease, regardless of the number of positive lymph nodes removed at PLND [47,48]. Improved CSS in the retrospective review by Abdollah et al [49] was limited to patients with intermediate- and high-risk nodal disease. As all three retrospective reviews were performed at the

Table 2 – Retrospective series examining local therapy in occult nodal disease

Study details	Population		Intervention (n)	Median follow-up (yr)	Key findings
	Clinical stage	n			
Frazier et al (1994) [31] US single center 1975–1989	Stage A–B	156	Staging PLND, then completed RP (+RP; 42) or aborted RP (–RP; 114). Both groups received ADT	Unknown	Overall median CSS and median CSS for patients with 1–2 +LNs both favored +RP (11.2 vs 5.8 yr, $p = 0.005$; 10.2 vs 5.9 yr, $p = 0.015$). No difference for patients with >3 +LNs
Frohmlüller et al (1995) [32] German single center	T1–3	139	Staging PLND, then RP + ADT (52) or ADT alone (87)	RP + ADT 4.3 ADT 4.7	10-yr OS and nonprogression rates favored RP + ADT (50.8% vs 29.7%, $p = 0.067$; 35.8% vs 14.6%, $p = 0.0023$). QoL measures favored RP + ADT
Cadeddu et al (1997) [33] US single center 1983–1995	T1–3a	168	Staging PLND, then completed RP (+RP; 127) or aborted RP (–RP; 41). 19 patients from each group cross-matched ^a	+RP 5.2 –RP 5.4	5- and 10-yr CSS favored +RP (91% and 61% vs 63% and 45%, $p = 0.006$). Cross-matched analysis with trend towards 5- and 10-yr DSS advantage for +RP (93% and 56% vs 58% and 34%, $p = 0.09$). Note: RP not preformed in setting of gross or multiple +LNs; LN burden greater in –RP
Ghavamian et al (1999) [34] US single center 1967–1995	T1–4	903	Staging PLND, then RP + orchiectomy (RP + O; 382) or orchiectomy alone (O; 79). 79 patients from each group cross-matched ^b	8.3	OS and CSS advantage for RP + O at 10 yr (66% and 79% vs 28% and 39%, $p < 0.001$). After 1987, trend towards CSS advantage for RP + O (79% vs 63%, $p = 0.19$). Benefit of RP independent of number of +LNs ($p = 0.53$)
Zagars et al (2001) [35] US single center 1984–1998	T1–3	255	Staging PLND, then immediate ADT (183) or ADT + RT (72) ^c	ADT 9.4 ADT + RT 6.2	Of patients accrued after 1987, ADT + RT experienced improved NED rate (78% vs 30%, $p < 0.001$), freedom from metastasis (83% vs 46%, $p < 0.001$), and survival rate (78% vs 57%, $p = 0.039$)
Engel et al (2010) [36] German multicenter 1988–2007	T1–4	938	Staging PLND, then completed RP (+RP; 688) or aborted RP (–RP; 250). Majority of patients received adjuvant or salvage hormone ablation	5.6	5- and 10-yr OS favored +RP (84% and 64% vs 60% and 28%). Fewer in +RP had ≥ 4 +LNs (17.2% in +RP vs 28% in –RP). After adjusting for age, PSA, clinical stage, number of +LNs, and WHO grade, RP was independent predictor of survival ($p < 0.0001$)
Steuber et al (2010) [37] European single center 1992–2004	T1–3	176	Staging PLND, then completed RP (+RP; 108) or aborted RP (–RP; 50). 38 patients from each group cross-matched ^d	8.2	5- and 10-yr cPFS favored +RP (77% and 61% vs 61% and 31%, $p = 0.005$). 5- and 10-yr CSS favored +RP (84% and 76% vs 81% and 46%, $p = 0.001$). 5- and 10-yr OS favored +RP (79% and 69% vs 80% and 42%, $p = 0.002$). Treatment (+RP vs –RP) and number +LNs were significant predictors of cPFS, CSS. In cross-matching, cPFS, CSS significantly favored +RP

ADT = androgen deprivation therapy; cPFS = clinical progression-free survival; CSS = cancer-specific survival; +LN = cancer-positive lymph node; NED = no evidence of disease; OS = overall survival; PLND = pelvic lymph node dissection; PSA = prostatic-specific antigen; RP = radical prostatectomy; RT = external radiation therapy; QoL = quality of life; WHO = World Health Organization.

^a Patients cross-matched for preoperative PSA, clinical T stage, age at diagnosis, +LN burden (largest LN metastasis and percentage +LN), and length of follow-up.

^b Patients cross-matched for preoperative PSA (after 1987), clinical grade and stage, age and year at surgery, and total number of +LNs. Orchiectomy performed within 3 mo and usually at time of RP.

^c ADT and RT each begun within 3 mo of PLND. ADT = orchiectomy, luteinizing hormone-releasing hormone agonist, or diethylstilbestrol and megestrol acetate (in earlier patients). External RT = 60–78 Gy to prostate.

^d Overall, 9% of +RP and 92% of –RP patients received adjuvant hormone therapy. Patients cross-matched for presurgical PSA groupings (0–10, 10–20, 20–30, 30–40, 40–50, 60–70, >70 ng/ml), clinical T stage, and number of +LN (≤ 2 vs > 2).

same institutions, there is some overlap of identical patients [47–49].

There is a lack of data on the use of multimodal therapy in clinically positive nodal disease identified on imaging at diagnosis. Current standard treatment regimens for clinically positive nodal disease include RT and immediate ADT. This is largely based on the study by Lawton et al [51], who reported a retrospective subset analysis of RTOG 85–31, a prospective RCT investigating the timing of ADT to RT

administration in the treatment of clinically positive nodal PCa. The analysis compared patients with biopsy-proven positive lymph nodes who received immediate or delayed ADT along with external RT. All study endpoints, including absolute survival, CSS, metastatic failure, and biochemical control, favored immediate ADT after RT [51]. While this does not address the critical question of the degree of benefit, if any, of RT addition in this clinical scenario, these data serve as a basis for contemporary clinical guidelines

Table 3 – Retrospective studies identifying lymph node burden as a predictor of outcome in local therapy for occult nodal disease

Study details	Intervention (n)	PLND extent	Median LN removed / follow-up (yr)	Key findings
Daneshmand et al (2004) [38] US single center 1972–1999	PLND and RP (235), then minority (31%) AHT	External iliac chain Obturator fossa	19 / 11.4	5- and 10-yr cPFS favored 1 (89% and 70%) and 2 +LNs (81% and 73%) vs >5 +LNs (62% and 49%, $p = 0.042$). 5- and 10-yr OS favored 1 (94% and 75%) and 2 +LNs (96% and 74%) vs >5 +LNs (76% and 49%, $p < 0.005$). 10-yr cPFS favored LND <20% vs >20% (72% vs 47%, $p = 0.0001$)
Boorjian et al (2007) [39] US single center 1988–2001	PLND and RP (507), then majority (89.7%) AHT	Not standardized	19 / 10.3	Total +LNs (≥ 2 vs 1) an independent predictor of metastatic progression (HR 1.9, $p = 0.003$) and CSS (HR 2.2, $p = 0.001$)
Fleischmann et al (2008) [40] Swiss single center 1989–2002	PLND and RP (102). No adjuvant hormones until symptomatic progression	External iliac chain Obturator fossa Internal iliac chain	21 / 7.6	Diameter of largest +LN metastasis (≥ 6 vs <6 mm) an independent predictor of negative bPFS (HR 2.0, $p = 0.002$), CSS (HR 3.1, $p = 0.007$), and OS (HR 2.9, $p = 0.004$)
Schumacher et al (2010) [41] Swiss single center 1989–2007	PLND (≥ 10 LNs) and RP (122). AHT in 50% (69% for ≥ 3 +LNs)	External iliac chain Obturator fossa Internal iliac chain	22 / 5.6	10-yr CSS favored ≤ 2 vs ≥ 3 +LNs (78.6% vs 33.4%, $p < 0.001$). Total +LNs (HR 1.4, $p < 0.001$) and ≥ 3 +LNs (HR 5.7, $p < 0.001$) independent predictors of negative outcome
Briganti et al (2009) [42] US and Italian multicenter 1988–2003	PLND and RP, then ART + AHT (171) or AHT alone (532)	External iliac chain Obturator fossa Internal iliac chain	13.9 (mean) / 9.4	15-yr CSS favored ≤ 2 vs > 2 (84% vs 62%, $p < 0.001$). > 2 +LNs an independent predictor of improved CSS (HR 1.9, $p = 0.002$)
Touijer et al (2014) [43] US single center 1988–2010	PLND and RP (369)	Extended PLND	15 / 11.9	Total +LNs (≥ 3 vs 1) an independent predictor of biochemical recurrence (HR 2.6, $p = 0.0001$) and distant metastasis (HR 2.5, $p = 0.003$)
Seiler et al (2014) [44] Swiss single center 1989–1999	PLND and RP (88)	External iliac chain Obturator fossa Internal iliac chain	21 / 15.6	7/39 (18%) and 18/39 (46%) patients with 1 +LN remained free of PSA relapse and clinical progression, respectively. All 49 patients with ≥ 2 +LNs experienced PSA relapse and 5/49 remain free of clinical progression. Total +LNs (≥ 2 vs 1) an independent predictor of worse CSS (HR 3.2, $p = 0.001$)

AHT = adjuvant hormone therapy; ART = adjuvant external radiation therapy; bPFS = biochemical progression-free survival; cPFS = clinical progression-free survival; CSS = cancer-specific survival; HR = hazard ratio; LN = lymph node; +LN = cancer-positive LN; LND = LN density (+LN / total LNs removed); OS = overall survival; PLND = pelvic lymph node dissection; RP = radical prostatectomy.

[4,5]. Recent data (presented in abstract form) from the STAMPEDE trial, which evaluated local therapy with RT to the primary tumor in clinically positive nodal disease, demonstrate improved OS in the group receiving RT compared to systemic therapy with ADT alone (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.31–0.84) [52].

3.3. Effect of local and systemic therapy in mPCa

3.3.1. Effect on symptomatic progression

One of the overriding hypotheses for local therapy of the primary tumor is that it may prevent or delay the onset of clinical symptoms from local progression. According to retrospective data for occult nodal disease, the incidence of symptomatic disease progression eventually requiring palliative surgical intervention is lower in patients who undergo initial RP than in those treated with systemic therapy alone [53–55]. Steinberg et al [53] reviewed 120 cases of node-positive PCa according to the modality

of the initial treatment and local recurrence. Local progression requiring surgical intervention occurred in 3% of men treated with RP, compared to 24% and 23% of men treated with RT and expectant management, respectively. A more recent retrospective review of 192 cases of occult node-positive PCa treated with RP, RP and ADT, or ADT alone after PLND revealed a significantly lower incidence of symptomatic local relapse in men treated with RP and ADT (6.5%) versus RP or ADT alone (10.3% and 44.6%, respectively) [54]. In men with localized PCa who received local treatment and eventually progressed to castration-resistant PCa, 32.6% (20% treated with RP vs 46.7% treated with RT) eventually developed symptoms secondary to local disease progression or recurrence compared to 54.3% of men with intact primary tumors at the time of mPCa diagnosis [55].

Prostatic invasion of the ureters, bladder, or bladder outlet can result in incapacitating symptoms that significantly degrade a patient's quality of life in advanced disease. In a Swedish cohort of men who died with PCa between

Table 4 – Study series examining multimodal therapy in occult nodal disease

Study details	Population		Intervention (n)	Median follow-up (yr)	Key findings
	Nodal stage	(n)			
Messing et al (2006) [45] Randomized control US multicenter 1988–1993	cN0, pN+ after PLND	98	PLND, then RP and immediate HT (goserelin monthly or orchiectomy; 47) or deferred HT (51)	11.9	Immediate ADT showed improvement in cPFS (HR 3.42, $p < 0.0001$), CSS (HR 4.09, $p = 0.0004$), and OS (HR 1.84, $p = 0.04$) with 5- and 10-yr CSS 4% and 13% for immediate HT and 24% and 41% for delayed HT. Significance in endpoints maintained after controlling for Gleason score
Spies et al (2006) [46] Retrospective review US single center 1982–2001	cN0, pN+ after PLND	100	PLND, then RP and immediate HT (30) or observation (70; 23 receiving delayed HT and 47 no HT)	5.2	Delayed HT given for biochemical failure. Immediate and delayed HT had similar metastatic-free survival ($p = 0.549$), CSS ($p = 0.843$), and OS ($p = 0.843$). Delayed HT group had significantly higher median PSA and biopsy Gleason score. Unclear how HT administered
Da Pozzo et al (2009) [47] Retrospective review Italian single center 1988–2007	cN0, pN+ after PLND	250	PLND and RP, then adjuvant HT (LHRH-A) + RT (median 66.6 Gy prostatic bed [26%] or whole pelvis [74%]; 129) or HT alone (121)	7.6	5-, 8-, and 10-yr bPFS and CSS insignificantly favored HT + RT. RT + HT vs HT alone an independent predictor of bPFS (HR 0.49, $p = 0.002$) and CSS (HR 0.38, $p = 0.009$)
Briganti et al (2011) [48] Retrospective review US and Italian multicenter 1986–2002	cN0, pN+ after PLND	364	PLND and RP, then adjuvant RT (median 50.4 Gy whole pelvis with prostate bed boost to median 68.4 Gy) + HT (majority orchiectomy or complete blockade; 117) matched and compared to HT alone (247)	7.9	Patients cross-matched for age at surgery, pT stage, Gleason score, surgical margin status, number of +LNs, and length of follow-up. 5-, 8-, and 10-yr CSS and OS favored RT + HT (95%, 91%, 86%; and 90%, 84%, 74%) vs HT alone (88%, 78%, 70%; and 82%, 65%, 55%; $p = 0.004$). CSS and OS curves significantly favored RT + HT for patients with ≤ 2 and > 2 +LNs (all $p \leq 0.04$)
Abdollah et al (2014) [49] Retrospective review US and Italian multicenter 1988–2010	cN0, pN+ after PLND	1107	PLND and RP, then adjuvant HT (majority orchiectomy or complete blockade) + RT (median 45–50.4 Gy whole pelvis with prostate bed boost to median 66.6–70.2 Gy from 1988 to 2010; 386) or HT alone (721)	+RT 8.4 -RT 7.1	8-yr OS favored HT + RT (87.6% vs 75.1, $p < 0.001$). 8-yr CSS similar between groups. +RT associated with more favorable CSS (HR 0.37, $p < 0.001$). When stratified by risk, only two groups benefited from +RT: (1) ≤ 2 +LNs, Gleason 7–10, pT3b/pT4, or +surgical margins (HR 0.3, $p = 0.002$); (2) 3–4 +LNs (HR 0.21, $p = 0.02$)

bPFS = biochemical progression-free survival; cPFS = clinical progression-free survival; CSS = cancer-specific survival; HT = hormone therapy; HR = hazard ratio; LHRH-A = luteinizing hormone-releasing hormone agonist; +LN = cancer-positive lymph node; OS = overall survival; PLND = pelvic lymph node dissection; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = external radiation therapy.

1988 and 1990 after treatment with noncurative intent, men who died of PCa required significantly more palliative interventions (including TURP, palliative radiation, and upper tract interventions) and hospital days at the end of life than patients with PCa who died of other causes (61% vs 29%, $p < 0.001$; 37 vs 10 d, $p < 0.0001$, respectively) [56]. Symptoms can be particularly prominent if primary PCa treatment involved RT or ADT alone, with 50–60% of these patients eventually developing symptoms as a result of upper or lower urinary tract obstruction [57].

It has been observed that palliative cystoprostatectomy in advanced PCa can improve symptoms. Thirty-eight patients with bladder invasion by locally advanced PCa, including 17 patients with local recurrence after primary RT, were treated with palliative cystoprostatectomy at MD

Anderson between 1995 and 2003 [58]. The incidence of local symptoms improved significantly after surgery (89% vs 21%, $p < 0.001$). While substantial improvement was observed, this was not without risk, as 13% of patients experienced a rectal injury and 24% had to undergo a secondary surgical procedure because of complications. The median CSS for the cohort after palliative cystoprostatectomy was 31 mo. To the best of our knowledge, survival after palliative cystoprostatectomy has not been compared to other palliative options in published series.

3.3.2. Prior local therapy

The effect of prior local therapy with either RP or RT in the setting of subsequent development of mPCa has been explored. Thompson et al [15] performed a post hoc analysis

of the Southwest Oncology Group (SWOG) 8894 trial, which randomized 1286 men with mPCa to either orchiectomy alone or orchiectomy with flutamide. They compared patients who received either RP or RT before trial enrollment to men who did not receive any prior local therapy. Prior RP was associated with a statistically significant decrease in the risk of death relative to those who did not undergo RP (HR 0.77, 95% CI 0.53–0.89; $p = 0.014$). A separate pooled analysis of data from nine clinical trials investigating men with progressive PCa while on ADT despite castrate testosterone found no association between improved survival and previous RP [59]. Aside from the post hoc nature, there are other limitations to both studies that limit their generalizability. These results should be viewed as hypothesis-generating, and further studies are needed to discern the role of local therapy, specifically RP, in mPCa.

Several population-based studies have analyzed the effect of local therapy in mPCa [60–62]. Culp et al [60] used data from the Surveillance, Epidemiology, and End Results (SEER) registry for 2004–2010 to identify men diagnosed with mPCa who underwent local therapy (RP or BT). The 5-yr OS and predicted CSS were both significantly higher in patients undergoing RP (67.4% and 75.8%, respectively) or BT (52.6% and 61.3%, respectively) compared to patients who did not undergo local therapy (22.5% and 48.7%, respectively, $p < 0.001$). Factors associated with decreased CSS in patients undergoing local therapy included clinical stage T4, high-grade disease, PSA ≥ 20 ng/ml, age ≥ 70 yr, and pelvic lymphadenopathy.

Following their analysis showing local therapy has been used in Sweden for metastatic disease [63], Sooriakumaran et al reviewed 18 352 PCa cases presenting with PSA > 50 ng/ml and compared men undergoing local RP or RT with those who were put on initial ADT alone (P. Sooriakumaran, personal communication). After a number of statistical adjustments to adjust for baseline differences in the cohorts, they found that patients in the ADT group were approximately three times more likely to die from PCa over the 15-yr follow up period than those in the local therapy group, with no significant differences in other-cause mortality. However, an important omission from the studies by Culp et al and Sooriakumaran et al is the lack of subgroup stratification and discernment of clinical and pathologic predictors for survival in mPCa treated with local therapy.

Gratzke et al [62] analyzed data from the Munich Cancer Registry regarding the role of RP in mPCa. Between 1998 and 2010, 1538 mPCa patients underwent RP. Patients who underwent RP had an OS rate of 55%, compared to 21% for patients with no RP ($p < 0.01$). Unfortunately, no data on comorbidity and external RT, or on the timing and dosage of systemic therapy were reported. Finally, there was no information regarding tumor volume or the extent and location of bone metastasis.

3.4. Patient selection and risk stratification for clinical trials

At present there is no evidence to suggest who might benefit from local therapy of the primary tumor in mPCa.

Trials are under way in an attempt to determine if local therapy confers any benefit in mPCa. These trials will be informative on how to best select patients who would benefit most from local therapy.

An optimal design of a clinical trial would include known prognostic features to allow for patient selection and better risk stratification among treatment arms. PSA is one of the strongest prognostic indicators for PCa at all stages. In mPCa, the PSA nadir after ADT initiation is a predictor of poor survival. Data from a SWOG trial suggested that PSA progression by a median of 6 mo while on ADT heralds clinical progression [64]. These findings were further confirmed by data from SWOG 9346, which identified 1345 patients with mPCa treated with a 7-mo induction course (step 1) with goserelin and bicalutamide [65]. At the end of the induction period, responding patients (judged by a stable or declining PSA level of ≤ 4 ng/ml in months 6 and 7 of treatment) were randomly assigned to intermittent or continuous ADT (step 2) [65]. After controlling for prognostic factors, patients with post-induction PSA > 4 ng/ml had significantly worse median OS compared to those with PSA ≤ 0.2 or 0.2–4 ng/ml ($p < 0.001$). An ADT induction period of 6 mo for risk stratification of patients and identification of early progressors seems to be a reasonable approach.

A lead time for systemic therapy has been used in neoadjuvant and presurgical systemic therapies in many clinical trials evaluating novel agents in advanced PCa. Data garnered during this time period may provide prognostic information that can be used for risk stratification for trials or possibly predictive factors for selecting subsequent therapy. There have also been efforts to provide a morphologic characterization of patients who received preoperative systemic treatment to provide a post-therapy histologic classification, as Gleason score cannot be used in such a setting [66]. Efstathiou et al [66] provided an in-depth histologic classification in such patients based on hierarchical clustering analysis: group A, characterized by a predominance of cell clusters, cell cords, and isolated cells; group B tumors, characterized by intact and fused small glands; and group C, characterized by tumors with any degree of cribriform growth pattern or intraductal tumor spread. A cribriform or intraductal spread morphology and positive surgical margins were stronger predictors of biochemical relapse than pathologic stage in multivariate analysis. Interestingly, it was shown that intraductal disease harbored the monoclonal genetic origin of metastatic-specific DNA changes in one patient [22,67]. While further validation is needed, classification and identification of such patients may provide a prognostic tool before or after receipt of local therapy for mPCa.

Metastatic tumor volume in patients with mPCa has also been regarded as a surrogate for oncologic outcome. In the much-anticipated Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), 790 men with mPCa were randomized to ADT with or without six cycles of docetaxel [68]. The primary endpoint was OS, with median OS of 57.6 mo in the ADT plus docetaxel arm and 44.0 mo in the

ADT arm (HR 0.49, 95% CI 0.37–0.65; $p < 0.0001$) [6]. The difference in men with high-volume disease was 49.2 versus 32.2 mo, respectively (HR 0.60, 95% CI 0.45–0.81; $p < 0.0006$) [6]. Although median OS was not reached in men with low-volume disease, findings from the study suggest an improved benefit for combination treatment in patients with high-volume disease. Further results are pending; however, mPCa patients were further stratified for these data, which may prove crucial in selecting patients to undergo neoadjuvant chemotherapy before considering RP. With improved systemic therapies and an ever-changing standard of therapy, the design of a clinical trial evaluating local therapy should allow for changes in systemic therapy as advances are made.

Clinical features characteristic of small-cell prostate carcinoma are the anaplastic features that portend an ominous prognosis whether or not small-cell morphology is present, and these often emerge during PCa progression. Anaplastic criteria have been developed to identify which patients may benefit most from chemotherapy, including exclusive visceral or predominantly lytic bone metastases, bulky tumor masses, low PSA levels relative to tumor burden, and/or short response to ADT [69]. Of the seven anaplastic criteria, Aparicio et al [69] found that bulky tumor mass was significantly associated with poor outcome, whereas neuroendocrine markers did not predict outcome or response to therapy. Much research is under way to characterize and identify the patients most likely to respond to chemotherapy and multimodal treatments.

Resectability is often a consideration when discussing local therapy in mPCa and deserves further mention. Oncologic and functional outcomes suggest the utility of RP in high-risk patients [70–72]. Moreover, these studies also address the concern regarding resectability and appropriate patient selection, which is imperative when selecting mPCa patients who might benefit from local therapy. As mentioned, a recent study found a survival benefit in mPCa patients who underwent local therapy; however, the study failed to identify which mPCa patients

may portend to improved survival benefit [60]. In an attempt to discern which mPCa patients might benefit the most from local therapy, Fossati et al [61] analyzed SEER-Medicare data for 8197 mPCa patients (M1a–c) during 2004–2011. The patients were categorized according to treatment type: local therapy versus nonlocal treatment (either ADT or observation) of the primary tumor. When compared with nonlocal therapy, local therapy of the primary tumor led to a higher CSM-free survival rate in patients with a predicted CSM risk $< 40\%$. Among mPCa patients, the potential benefit of local treatment of the primary tumor probably depends greatly on tumor characteristics, and proper patient selection will be essential.

3.5. Clinical trials evaluating local therapy in distant mPCa

The Systemic Therapy in Advancing or Metastatic Prostate Cancer (STAMPEDE) trial has been established to further evaluate multimodal therapy in the treatment of mPCa [73,74]. One arm of the trial will investigate RT treatment in patients with mPCa. As with all the existing arms in the STAMPEDE trial, these patients will be compared to the control arm receiving ADT alone (Fig. 1). A relative improvement of 25% in OS is the target. Accounting for co-recruitment to the other trial comparisons, ~1200 mPCa patients will be included in this comparison, with 600 of them allocated to the RT arm. Moreover, with a total of nine arms in the STAMPEDE trial, including the use of abiraterone, prednisone, and ADT, as well as another arm combining enzalutamide, abiraterone, and prednisone with ADT, optimal treatment options are likely to be further elucidated. A similarly designed prospective multicenter study in the Netherlands (HORRAD) randomizing patients with mPCa to hormonal therapy or hormonal therapy and RT has finished accrual (Fig. 2) [75].

While these studies have incorporated local therapy in the form of RT, several studies are now evaluating integration of surgery in the multimodal approach to mPCa. A UK-based trial, TRoMbone, is being established and aims

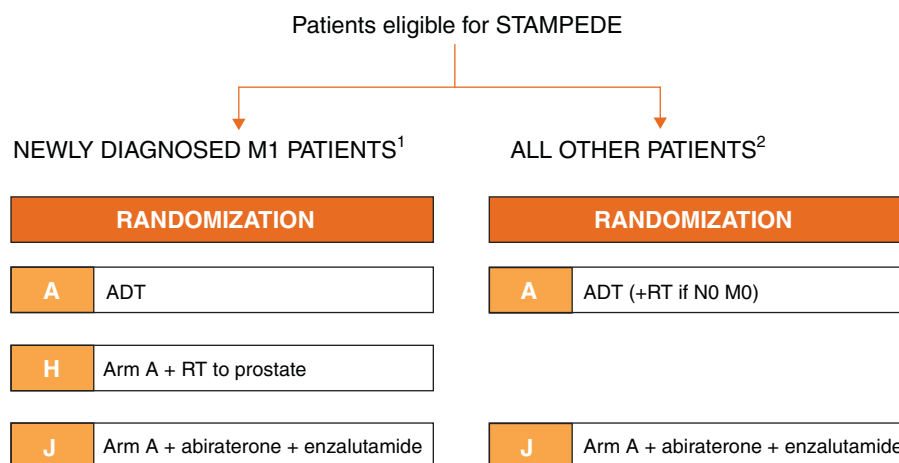


Fig. 1 – Study design for the STAMPEDE trial (protocol version 12.0 with inclusion of enzalutamide + abiraterone comparison). Source: STAMPEDE trial. Protocol version 12.0. http://www.stampedetrial.org/PDF/STAMPEDE_Protocol_v12.0_clean.pdf

¹ Except for patients with a contraindication to radiation therapy (RT).

² All suitable patients with newly diagnosed, locally advanced disease should also have RT to the prostate.

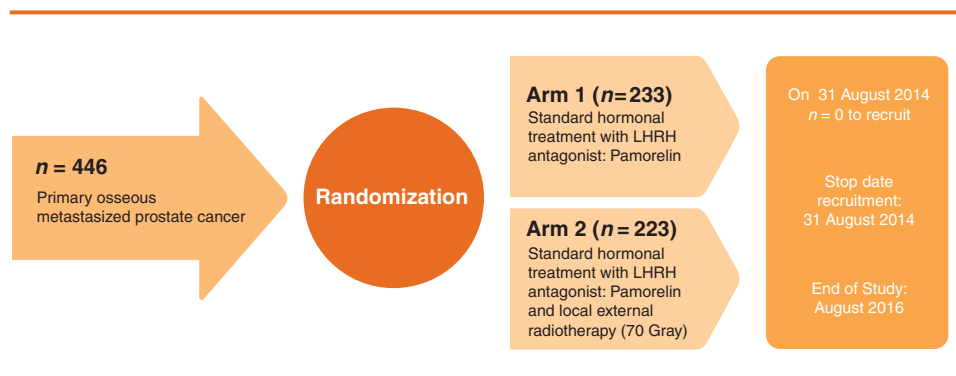


Fig. 2 – Study design for the HORRAD trial. Source: European Urological Association. HORRAD study facts and figures. http://www.uroweb.org/fileadmin/documents/2014_FactsHORRAD_Facts__Figure_update_06-Sep-2014.pdf. LHRH = luteinizing hormone–releasing hormone.

to randomize men with oligometastatic disease to RP plus treatment as usual versus treatment as usual alone, and will investigate 5-yr OS as its endpoint (P. Sooriakumaran, personal communication). It is premised on data from CHARTED supporting different prognoses in oligo- versus poly-metastatic disease, and thus the “control” exerted by the primary tumor in metastatic disease may be greater for lower-burden disease.

A multicenter, randomized phase 3 trial of best systemic therapy or best systemic therapy plus definitive local therapy (radiation or surgery) of the primary tumor in mPCa (ClinicalTrials.gov NCT01751438) is under way in North America to evaluate whether treatment with systemic therapy in combination with local therapy in distant metastatic disease (M1) is more effective than systemic therapy alone [76].

While systemic therapy in mPCa is the current standard of care for castrate-sensitive PCa [4,5], recent findings suggest that a combination of chemotherapy and ADT may improve survival in select patients [6]. However, both

TRoMbone and the North American trial are designed to allow for changes in standard systemic treatments over time to prevent them from becoming obsolete as standards evolve. In the North American trial, best systemic therapy allows for initiation of therapy as seen fit by the treating physician. Randomization will correct for any discrepancy in systemic treatments. The primary endpoint of this trial is PFS, defined as the time from the start of systemic therapy to the date of disease progression or death, whichever occurs first. Progression is defined according to Prostate Cancer Working Group 2 [77]. Early progressors (within 6 mo) are not randomized to the treatment arm but undergo end-of-study evaluation to gather data on this poor-prognosis group (Fig. 3). The trial is not limited to oligometastatic disease and is also open to patients with all volumes of mPCa without evidence of progression at 6 mo. Data from this trial should provide further insight into which patients may benefit from local therapy in addition to systemic treatment and should provide for a better-informed phase 3 trial evaluating this treatment paradigm.

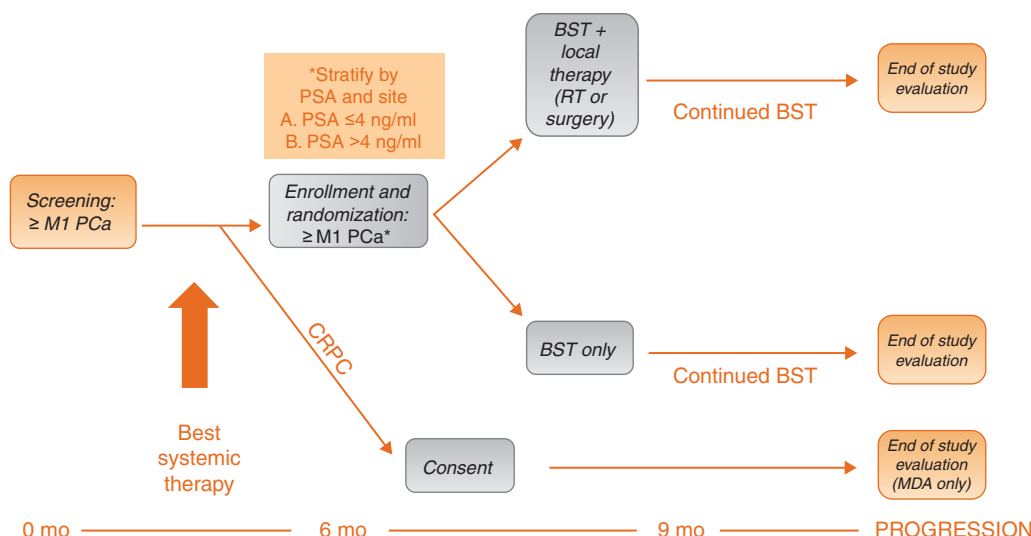


Fig. 3 – Study design for NCT01751438. BST = best systemic therapy; PCa = prostate cancer; PSA = prostate-specific antigen.

4. Conclusions

There is increasing clinical, molecular, and genetic evidence that local therapy of the primary tumor may impact outcomes in patients presenting with de novo mPCa. There are prospective data demonstrating improved outcomes for multimodal treatment of locally advanced PCa, and retrospective data suggesting improved survival and decreased symptomatic local progression in patients with occult nodal metastasis at the time of PLND who go on to RP. Emerging data on the origin of metastatic disease and preliminary studies examining tumor debulking in mPCa have shown promise. At present, these data are hypothesis-generating and provide a rationale for prospective RCT, but should not direct current management. Treatment paradigms are dynamic as new systemic therapies become increasingly available for hormone-sensitive mPCa. Whether a new standard approach to mPCa treatment will include integration of local therapy will only be determined by completion of ongoing clinical trials with demonstration of an impact on symptomatic tumor progression or tumor biology.

Author contributions: Brian F. Chapin 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: Bayne, Williams, Chapin.

Acquisition of data: Bayne, Williams, Chapin.

Analysis and interpretation of data: Bayne, Williams, Cooperberg, Gleave, Montorsi, Novara, Smaldone, Sooriakumaran, Wiklund, Chapin.

Drafting of the manuscript: Bayne, Williams, Chapin.

Critical revision of the manuscript for important intellectual content: Bayne, Williams, Cooperberg, Gleave, Montorsi, Novara, Smaldone, Sooriakumaran, Wiklund, Chapin.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: Bayne, Williams, Chapin.

Supervision: Chapin.

Other: None.

Financial disclosures: Brian F. Chapin certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Brian F. Chapin is primary investigator for NCT01751438. Prasanna Sooriakumaran will be chief investigator for TRoMbone. There are no other conflicts of interest to disclose.

Funding/Support and role of the sponsor: None.

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