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Editorial

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Radical Prostatectomy in Low-volume Metastatic Prostate Cancer? The Need for New Evidence

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There is a comfortable nihilism that has long governed the management of metastatic prostate cancer (mPC): once the disease has spread, the primary tumour is considered irrelevant. Treat the systemic disease, palliate the local symptoms, and accept that the prostate—however bulky or biologically active—is merely a bystander with no impact on further disease evolution. For surgery specifically, this view remained largely unchallenged because of inherent biases and a long absence of prospective randomised data. The role of prostate radiotherapy has, by contrast, been investigated in randomised trials for over a decade.

The scientific rationale for cytoreduction rests on three pillars. First, experimental and clinical data suggest that the primary tumour acts as an ongoing source of metastatic seeding and a reservoir releasing circulating tumour cells conditioned by the prostate microenvironment for enhanced metastatic fitness [1]. Second, local disease burden carries real morbidity; obstructive uropathy, local pelvic extension, haematuria, and recurrent urinary retention are not trivial consequences for patients with metastatic disease, who may live for many years, and the need for palliative transurethral resection, percutaneous nephrostomy, or suprapubic catheterisation represents a significant failure of systemic treatment. Third, local therapy may carry antitumour immunomodulatory effects that augment systemic treatment responses [2].

Radical surgery in men with mPC is feasible and safe at experienced centres [3], and the TRoMbone feasibility randomised controlled trial confirmed that randomisation is achievable [4]. Two phase 3 randomised controlled trials have investigated external beam radiotherapy in this setting: STAMPEDE and HORRAD. Both showed improved progression-free but not overall survival (OS), apart from an OS benefit in the STAMPEDE pre-specified subgroup analysis of men with low-volume mPC [5,6]. On this basis, prostate radiotherapy with androgen deprivation therapy (ADT) is now a strong European Association of Urology guideline recommendation for men whose first presentation is low-volume M1 disease by CHAARTED criteria. The PEACE-1 trial, however, did not reproduce this survival advantage when an androgen receptor pathway inhibitor (ARPI) was added [7]. Whether the STAMPEDE benefit persists in the contemporary ARPI era therefore remains an open question, and one with direct relevance to any surgical trial in this space.

The results of two randomised trials published in this month's issue of *European Urology* sharpen the debate but do not resolve it.

Chapin and colleagues report the mature outcomes of an MD Anderson-led phase 2 trial: 119 men with metastatic disease at presentation, selected for best systemic therapy (BST) response, randomised to continued BST alone or BST plus definitive local therapy (three-quarters by radical prostatectomy) [8]. The trial was negative for progression-free survival (PFS; hazard ratio [HR] = 0.89, p = 0.6) and OS (HR = 1.07, p = 0.8). Several limitations qualify this conclusion. It was powered for feasibility, not survival. The PFS endpoint relied on bone scintigraphy, an imperfect comparator to contemporary prostate-specific membrane antigen positron emission tomography (PSMA-PET). Most patients received ADT alone rather than ARPI-inclusive BST, reflecting the 2013–2018 enrolment window. Response to initial ADT does not define low-volume disease, and three patients in the BST-alone arm required palliative local intervention during follow-up—a signal of local morbidity not captured by aggregate survival curves. The iden-

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Table 1 Selected ongoing phase 3 randomised trials of local therapy of the primary tumour in metastatic hormone-sensitive prostate cancer.

Trial	Country/ sponsor	Population	Intervention vs control	Primary endpoint	Target sample	Status
SWOG-1802 (NCT03678025)	USA/ SWOG	De novo mHSPC responding to SST; MDT to up to 4 sites permitted	SST + definitive treatment of primary (RP or RT) vs SST alone	Overall survival	1273	Active
PRESIDENT (ISRCTN15704862)	UK/NIHR	De novo low-volume mHSPC; PSMA-PET staging	Best oncological care + RP vs best oncological care alone	Coprimary: oncological response; HRQoL	749	Opening
SIMCAP (NCT03456843)	USA/ academic	De novo oligometastatic prostate cancer	BST + cytoreductive RP vs BST alone	Failure-free survival	190	Active
IP2-ATLANTA (NCT03763253)	UK/ academic	De novo mHSPC; low- and high-volume	SOC vs SOC + minimally invasive ablative therapy vs SOC + RP or RT (± MDT)	Radiographic PFS	918	Active

BST = best systemic therapy; HRQoL = health-related quality of life; MDT = metastasis-directed therapy; mHSPC = metastatic hormone-sensitive prostate cancer; PFS = progression-free survival; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiotherapy; SOC = standard of care; SST = standard systemic therapy.
Sample sizes and endpoints are summarised from registry entries and published protocols; readers are referred to individual trial registrations for full details.

tification of the aggressive variant prostate cancer molecular signature (aberrant p53, RB1, and PTEN by immunohistochemistry) as a biomarker of worse PFS (HR = 1.74, $p = 0.04$) is nonetheless a useful tool for future trials.

In the RAMPP trial, Graefen and colleagues report a more favourable result. Among 132 men with low-volume mPC, surgery plus BST reduced 5-yr cancer-specific mortality compared with BST alone: 13% versus 23% (HR = 0.39, $p = 0.045$) [9]. The effect size is striking but must be interpreted cautiously. RAMPP was stopped early at 26% of planned accrual; like the Chapin trial, its systemic therapy regimens largely predate ARPI-inclusive standards; and the majority of patients had bone scintigraphy rather than PSMA-PET. Clinical progression was not improved, and men in the surgical arm received salvage therapies earlier than the BST-only group—raising the possibility that the additional interventions, rather than surgery itself, drove the cancer-specific mortality benefit. In total, 42 % of operated patients experienced adverse events and 14% experienced Clavien-Dindo grade 3 complications or higher. Neither trial reported patient-reported outcomes—a critical omission given the surgical morbidity at stake.

Further research is therefore imperative to determine whether surgery adds value to current multimodality care for low-volume metastatic hormone-sensitive prostate cancer. Several phase 3 randomised trials are underway internationally to address this question (Table 1). Informed by TRoMbone, the UK National Institute for Health and Care Research-funded PRESIDENT trial (PRostatEctomy Surgery In Disseminated low-volume mPC with Endpoint assessment using nuclear imaging Technology with PSMA-PET computed tomography) will contribute UK-led data alongside SWOG-1802, SIMCAP, IP2-ATLANTA, and other studies summarised in Table 1.

PRESIDENT will recruit 749 men with newly diagnosed low-volume mPC across at least 25 sites, with a target of at least 30% participation from the Black community, randomising patients to current best oncological care with or without surgery; staging is by PSMA-PET, coprimary endpoints are oncological response and quality of life, and the trial includes comprehensive biobanking and an allied translational research programme [10].

Surgery combined with systemic therapy transformed outcomes in breast and colon cancer. Chemoradiotherapy redefined cervical and rectal cancer. The two trials reported in this issue of European Urology do not provide definitive evidence for or against cytoreductive surgery in mPC. The assumption that intensified systemic therapy alone will always be sufficient continues to warrant challenge, and SWOG-1802, PRESIDENT, and the other ongoing phase 3 surgical trials in Table 1 will be awaited eagerly. In the meantime, clinicians should exercise caution before offering surgery to men with low-volume mPC outside a randomised trial.

Conflicts of interest: PS is Chief Investigator of the PRESIDENT trial (Department of Health & Social Care NIHR portfolio study; UK). RJB and FCH are Coinvestigators on the PRESIDENT trial. PS and FCH were the lead and senior investigators, respectively, on the TRoMbone trial. No other conflicts of interest.

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