Surgery in metastatic prostate cancer: a pilot study

PRASANNA SOORIAKUMARAN

There is some evidence to suggest that radical treatment of the primary tumour in patients diagnosed with metastatic prostate cancer can reduce symptomatic progression and increase survival. In this article, the author describes a pilot study to investigate whether a large study looking at survival benefit in early metastatic disease is feasible in the UK and calls for recruits.

Prostate cancer is the most common cancer and the second most frequent cause of cancer death in Western men.1 Recent data from the STAMPEDE trial suggest a median survival of just 42 months in the control arm of metastatic men.2 Current standard care consists of androgen deprivation therapy (ADT) +/- chemotherapy based on the STAMPEDE and CHAARTED studies.2,3 However, there are emerging data suggesting that radical therapy directed at the prostate impacts survival, especially in those with limited metastatic burden, defined as 1–3 skeletal lesions without any visceral metastases (oligometastases).4,5 Many men also suffer symptomatic disease progression and eventually require palliative surgical intervention, which is less frequent in those treated with initial radical prostatectomy compared to systemic therapy alone.6,7

There are convincing data to support the concept of radical therapy in many metastatic cancers, including ovarian cancer, renal-cell carcinoma, glioblastoma, peritoneal carcinomatosis from gastrointestinal cancer, and colon cancer.4 Hence, there is a rationale to examine whether it has a role in prostate cancer. Further, there is a strong biological rationale for considering a radical approach to metastatic prostate cancer.4 The 'seed and soil' hypothesis postulates that a receptive micro-environment (the 'soil') allows disseminating malignant cells (the 'seed') to engraft into and form metastases, with soil development thought to be driven by factors secreted by the primary tumour. There is evidence that the primary tumour can seed to distant sites and that cancer cells at those end-sites can further seed the primary

Box 1. TRoMbone eligibility criteria

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<td>Willing and able to give informed consent</td>
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<td>Male, aged 18–74 years</td>
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<td>Synchronous oligometastatic prostate cancer (1–3 skeletal lesions on standard imaging)</td>
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<td>Locally resectable disease</td>
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<td>ECOG PS 0–1</td>
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<td>Suitable for radical prostatectomy and extended pelvic lymphadenectomy within three months of starting standard care</td>
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<td>Contraindications to radical prostatectomy and extended pelvic lymphadenectomy</td>
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<td>Visceral metastases</td>
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<td>Prior radiotherapy to the abdomen/pelvis or to skeletal metastases</td>
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<td>Any systemic therapy for prostate cancer for three or more months</td>
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<td>Participation in another prostate cancer clinical trial</td>
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BLOG
Blowing our TRoMbone
Read the accompanying blog and have your say at: www.trendsinmenshealth.com/blog

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lesion, leading to a vicious circle of metastasis; this ‘self-seeding’ phenomenon is dependent on the presence of an intact primary focus. Also, we know that disseminated tumour cells in men with clinically localised prostate cancer before prostatectomy confer a five-fold increased risk of future metastases, but the same burden of these cells detected after surgery does not increase that risk.6 Hence, the primary lesion might have a role in driving metastatic progression.

PROSPECTIVE STUDIES
Despite all the above, there are as yet no published prospective studies that directly evaluate the role of cytoreductive surgery in advanced prostate cancer. Recent observational cohort studies from the US SEER database and the Munich Cancer Registry found that men with metastatic prostate cancer treated with radical therapy had higher five-year survival than those treated with systemic therapy alone.9,10 We also recently showed that at least 1206 men in Sweden have been treated with initial radical therapy (surgery or radiotherapy) for likely metastatic or micro-metastatic prostate cancer from 1996–2010, and that men who underwent initial ADT without radical therapy were approximately three times more likely to die of prostate cancer than those that had radical therapy (in press).

So, the next question is which radical therapy modality should we interrogate in metastatic prostate cancer? There are no prospective data to inform this choice currently, so we have to extrapolate from the metachronous (recurrent) metastatic disease setting. A subgroup analysis of the SWOG 8894 trial on 1286 men with metastatic prostate cancer showed a reduced risk of death in those who had previously undergone radical prostatectomy compared to those who had not.11 Another study of 161 men who all received ADT for failure post-radical therapy showed that time to subsequent failure after ADT was longer in the surgical cohort than in the radiotherapy cohort.12 A report on 916 men with metastatic prostate cancer who originally received either radical prostatectomy or radiation for clinically localised disease also showed a substantial reduction in prostate cancer mortality rates for the surgically treated group.13 It may therefore be that surgery could be a good choice for the radical treatment modality to be used in prospective studies.

WHO TO STUDY
So, if we accept that surgery to the primary lesion should be investigated in metastatic prostate cancer, the next question is which men should be included. Do we really think that the benefit for surgery might be seen in men with a superscan of metastatic burden, or, perhaps more likely, will any benefit be confined to those with limited systemic disease? The recent landmark CHAARTED study demonstrated that men presenting with oligometastatic prostate cancer (≤3 skeletal lesions) have improved overall survival (and are probably less chemo-responsive) compared to those with polymetastatic disease (>3 skeletal deposits),3 and thus oligometastatic disease might represent a transitory disease phenotype. Furthermore, all the above observational data in support of radical prostatectomy for metastatic disease are heavily confounded by selection bias, with those undergoing radical treatment likely having fewer skeletal metastases than those undergoing ADT alone; a subgroup analysis of the SEER data supports this contention.14 Hence, if there is a true survival benefit for radical therapy, it is likely to be confined to cases with a lower metastatic burden. Thus, if we are to interrogate the question of radical therapy for metastatic cancer, then it makes sense to limit the cohort to oligometastatic men, at least in initial studies.

THE TRO MbONE STUDY
TRO Mbone, Testing Radical prostatectomy in men with prostate cancer and oligometastases to the bone, has been set up as a randomised, controlled feasibility study. TRO Mbone aims to randomise 50 men to standard care (ADT with/without docetaxel) versus standard care plus radical prostatectomy with extended pelvic lymphadenectomy. All modalities of surgery (open, laparoscopic and robotic) are allowed and a quality assurance program is built in, mandating only one surgeon per centre perform these cases, evidence of >100 cases performed prior to the study, and a median lymph node yield >10 nodes using a standardised dissection.

Men who are stage M1b with one to three skeletal metastases, age <75, ECOG PS 0–1, and with locally resectable disease will be eligible for TRO Mbone. The choice of staging modality will be as per standard clinical care, with more sophisticated imaging such as PSMA- or choline-PET allowed but not required for eligibility.

Three centres will run TRO Mbone: Oxford (Freddie Hamdy), the Royal Surrey County Hospital (Christopher Eden), and University College London Hospital (John Kelly, Prasanna Sooriakumaran). The study will be managed by the Surgical Intervention Trials Unit (SITU) at the University of Oxford (Operational Lead Surjeet Singh). The eligibility criteria are shown in Box 1.

CHALLENGES
TRO Mbone has two main challenges: the ability to identify eligible patients and the ability to randomise these men to the study treatments. The current AJCC TNM staging system of prostate cancer groups all skeletal-metastatic patients together as M1b, and there are no official statistics as to numbers presenting with newly diagnosed oligometastatic prostate cancer. Our prospective audit demonstrated that roughly 20% of newly diagnosed skeletal-metastatic patients present with oligometastases. None of the current randomised trials are recording number of skeletal metastases and
thus, while our proposal represents a novel opportunity to evaluate response specifically in the oligometastatic population, it will require a change in imaging reporting practice to identify these patients. Teams across the country routinely comment on the presence of metastatic disease without defining the extent of the metastatic burden, and hence for TRoMbone to succeed, we need to start separating metastatic disease into oligo- and poly-subgroups.

The original power calculation based on a survival primary endpoint required over 400 subjects, and thus we developed an international study of which TRoMbone was planned as the UK arm. The international study has opened in Germany, Sweden and Austria and, despite being able to identify large numbers of eligible patients, is recruiting slowly due to a lack of equipoise and acceptance of uncertainty as to the relative benefits of the treatment options. This ability to randomise represents the second major challenge to TRoMbone’s success.

CALL FOR PATIENTS
TRoMbone has been accepted onto the National Institute of Health Research Portfolio and thus has access to Clinical Research Network support. It has ethical and other regulatory approvals, and opened to recruitment in February 2017. We have 12 months to recruit the 50 patients needed; if we miss this target, it is highly unlikely to proceed to a full study. We are, therefore, asking the UK urological community to refer eligible patients to one of the three sites. Centres that demonstrate the ability to identify and refer eligible patients will be taken forward in the full grant application if we are successful in demonstrating feasibility. Patients can start systemic therapy as part of normal care prior to referral, so there is no delay in their treatment and no increased risk of breaching cancer waiting time targets. Those randomised to surgery will have their operations at the referral centres, as well as a single follow-up visit before discharge back to the local referring unit. Participants randomised to systemic therapy alone will require just one follow-up visit with the referral centre. Hence, the extra travel burden on study patients from local centres is minimal (Figure 1).

TRoMbone represents a great opportunity for the urological community in the UK to conduct a study with global impact and the potential to transform the management of early, lethal prostate cancer. We hope
you can be a part of it and that, together, we can make it a success. Please contact either myself (prasanna.sooriakumaran@nds.ox.ac.uk) or the study co-ordinator (Neelam Hassanali; trombone@nds.ox.ac.uk) if you have any queries about potential participants.

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REFERENCES