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Words of Wisdom

Re: Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE)
Parker CC, James ND, Brawley CD, et al

Lancet 2018;392:2353–66

Experts' summary:
Parker et al. analysed the impact of radiotherapy (RT) to the primary tumour in men with de novo metastatic castrate-sensitive prostate cancer (mCSPC) enrolled in the STAMPEDE trial, and report results for a prespecified subgroup analysis by metastatic disease burden (MB), defined according to previously published CHAARTED definitions [1]. A total of 2061 men were randomised between 2013 and 2016, and RT consisted of either six consecutive weekly fractions of 6 Gy (total 36 Gy) or 20 daily fractions of 2.75 Gy over a period of 4 wk (total 55 Gy). After median follow-up of 37 mo the primary endpoint of overall survival (OS) did not differ between the RT and control groups (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.80–1.06; $p = 0.266$), with 3-yr OS of 65% in the RT group and 62% in the control group. While prostate RT did not improve OS for unselected patients, a significant benefit was observed in the subgroup with low MB ($n = 819$; HR 0.68, 95% CI 0.52–0.90; $p = 0.0098$), with 3-yr OS 73% in the control group and 81% in the RT group and a 3.6-mo benefit for RT. RT was well tolerated, with an adverse event rate of $<10\%$.

Experts' comments:
Treatment of the primary tumour in men with mCSPC is an area of controversy. Local therapy may reduce the risk of morbidity from local progression, and hypothetically may improve survival by altering local and possibly systemic progression when used in combination with life-prolonging systemic therapy [2,3]. The STAMPEDE trial has shaped the treatment landscape for mCSPC by providing practise-changing results for combination systemic therapies [4], and now provides insights into the role of local RT in this disease. While OS was not better among unselected men with mCSPC, the subgroup analysis for low- versus high-volume disease raises hope that prostate RT should now be considered a new standard of care for oligometastatic disease. While these results are encouraging, various factors must be considered before they change clinical practise.

First, this study reports outcomes from a prespecified subgroup analysis without stratification by MB before randomisation and consequently does not meet the Sun criteria for subgroup analyses [5]. Secondly, the subgroup analysis is premature, with an event rate of only 25% in the low-MB subgroup. Considering that only 26 deaths separate the two groups, another 5 yr of follow-up or 1200 more patients would be needed for appropriate power with OS as the primary endpoint. Third, these STAMPEDE data are not fully corroborated by confirmatory studies. The HORRAD trial similarly found no OS benefit for RT (HR 0.90, 95% CI 0.70–1.14) in a cohort of 432 unselected men with metastatic PC, and a subgroup analysis in those with fewer than five bone metastases found a trend favouring RT that did not reach statistical significance (HR 0.68, 95% CI 0.42–1.10) [6]. Fourth, and as frequently seen with phase 3 data, the standard of care for treatment of de novo metastatic PC has changed significantly in recent years to include androgen deprivation combined with docetaxel [1], abiraterone [4], and/or metastasis-directed therapy [7]. Hence, results from STAMPEDE and HORRAD must be extrapolated with caution in the contemporary era of these new treatments, in particular with increasing use of more sensitive imaging of oligometastatic CSPC. Finally, the RT dose is low, even palliative, with no difference in local control (42% vs 45%), leaving open the question of whether definitive local therapy with RT or surgery confers better disease control. While STAMPEDE supports the notion that local therapy may improve outcomes, it does not provide insights into the benefit of radical prostatectomy or RT in this clinical scenario.

Because of the above issues, this trial does not provide level 1 evidence for prostate RT as a new standard of care for patients with oligometastatic CSPC. It is our opinion that efficacy benefits need to be verified in another prospective trial before treatment of the primary with RT can be considered the standard of care. Several randomised trials are currently recruiting (eg, g-RAMPP [NCT02454543], PEACE-1 [NCT01957436], and SWOG S1802 [NCT03678025]). These trials need to be supported, as they will address the issue of definitive local treatment in the context of abiraterone combination regimens, and incorporate advances in radiographic (^{68}Ga PSMA-PET-CT) and genomic (with metastatic tissue or liquid biopsies [8]) biomarkers that will further evolve patient selection.

Conflicts of interest: The authors have nothing to disclose.

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Re: Long-term Rate of Mesh Sling Removal Following Midurethral Mesh Sling Insertion Among Women With Stress Urinary Incontinence

Gurol-Urganci I, Geary RS, Mamza JB, et al

JAMA 2018;320:1659-69

Experts' summary:

Stress urinary incontinence (SUI) is a highly prevalent condition with a significant effect on quality of life for nearly one-third of adult women. A midurethral sling (MUS) remains the most common surgical treatment for SUI. This study examines long-term mesh removal rates following MUS insertion using a national population-based retrospective cohort. Conducted in England, the study included Hospital Episode Statistics (HES) data, which capture records for all inpatient admissions to National Health Service (NHS) hospitals. The authors found that of the 95 057 women who had an MUS inserted between 2006 and 2015, nearly two-thirds were retropubic cases (the remainder were obturator). The rate of sling removal was 3.3% at 9 yr, and was lower in the transobturator than in the retropubic group. The rate of reoperation for SUI was 4.5% at 9 yr, and the rate of any reoperation (removal + reoperation for SUI) was 6.9% at 9 yr.

Experts' comments:

The authors address an important question on a scale much larger than in prior studies. With access to data for inpatient admissions at all NHS hospitals in England, they were able to capture a large portion of the national population to give clinicians a sense of what happens in the long term after mesh slings are placed in women for SUI. Their reported reoperation rates are low, with a mesh removal rate at 1 yr of only 1.4%, which increased to only 3.3% at 9 yr. When the rates of mesh removal are combined with reoperation for SUI, they increased to only 2.6% at 1 yr and 6.9% at 9 yr. These reoperation rates are lower than those previously reported by Funk et al. [1] in a study of more than 150 000 women in the USA, in which the 9-yr cumulative incidence of repeat surgery following any SUI surgery 14.5%, with a sling-specific reoperation rate of 13%. The reoperation rates for MUS published in this new study are lower than those previously reported by Funk et al for several SUI procedures, including bulking agents, needle suspensions, Burch, and MUS.

This study is retrospective and unfortunately there is no information provided regarding overall complications following MUS, as only reoperations are identified. Therefore, patients requiring treatment for de novo overactive bladder, dyspareunia, mesh extrusion/erosion, and other complications that were not managed via surgical excision were not identified in the study. Furthermore, other details regarding mesh excision (total vs partial vs incision alone), while differentiated, are not clearly defined.

Despite some of these significant limitations, the authors provide important information for clinicians and their patients considering surgery for SUI (overall favorable reoperation rates following MUS) on a very contentious topic at a very critical juncture.

Conflicts of interest: The authors have nothing to disclose.

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