Radiotherapy to the primary tumour for patients with metastatic prostate cancer: practice-changing results from STAMPEDE

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Background

STAMPEDE is a multi-arm multi-platform randomised control trial of treatment for locally advanced, recurrent or hormone-sensitive metastatic prostate cancer, which has energised the UK prostate cancer oncology community. Achieving rapid recruitment, it has generated results that have changed systemic therapy practice: Docetaxel has been added to lifelong androgen deprivation therapy as the standard of care (SoC) in this population, having demonstrated a clinically significant survival advantage [1], and abiraterone is currently being evaluated by NICE after showing a comparable survival benefit [2,3].

Retrospective series suggest that radiotherapy (RT) to the primary tumour may provide improved overall survival (OS) for men with metastatic cancer. This hypothesis has now been tested in Arm K of STAMPEDE [4,5]. Eligible patients had a diagnosis of metastatic prostate cancer requiring lifelong androgen deprivation, and no contraindication to RT. They were randomised 1:1 to either SoC or SoC plus external beam RT delivered to the prostate ± seminal vesicles. Protocol RT schedules were 55 Gy in 20 fractions over 4 weeks or 36 Gy in 6 weekly fractions of 6 Gy, chosen prior to randomisation according to centre or clinician preference. In line with results showing survival benefit for docetaxel treatment in this population, the study protocol was amended to permit this treatment which was given to approximately 15% of the trial population. Patients were stratified by hospital, age, PS, nodal involvement, aspirin/NSAID use and docetaxel use.

The primary outcome measure was overall survival (OS) and for interim analyses the primary activity outcome was failure free survival (FFS), defined as freedom from biochemical failure, local or distant progression or death from prostate cancer. Secondary outcomes were symptomatic local events, progression-free survival (PFS) equivalent to FFS but ignoring biochemical events, and metastatic progression-free survival (MPFS) defined as time to new metastases, progression of existing metastases or death.

The target sample size was 1250 patients, selected on the assumption of 1 and 3.5 year median FFS and OS respectively for the SoC control group, and 25% relative improvement in hazard ratios for failure and death for patients receiving SoC+RT. It was observed during recruitment that the two RT schedules were being used roughly equally, and therefore the sample size was increased to 1800 patients, to provide power to detect differences in FFS for each RT schedule-defined subgroup versus SoC alone.

Based on accumulating external results, and without reference to data from STAMPEDE, investigators concluded in May 2018 that any benefit from RT would be greater in patients with

lower metastatic burden, and that this potential benefit could be tested with reasonable power in the subgroup of STAMPEDE patients with lower burden.

Survival analysis used Cox proportional hazards and flexible parametric models, adjusted for stratification factors. For the subgroup analysis that tested the effects of prostate RT by baseline metastatic burden, high burden was defined according to the CHAARTED criteria as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both [6].

Results of the STAMPEDE radiotherapy comparison

Between January 2013 and September 2016, 2061 men newly diagnosed with metastatic prostate cancer were randomised from 117 sites, 1029 to SoC and 1032 to SoC+RT. The arms were well balanced with 40% and 54% of patients having lower and higher metastatic disease burden respectively, and 6% having unknown burden. Of the patients allocated to SoC+RT 88% received one of the protocol RT schedules, 6% an alternative schedule, and 6% declined treatment.

Across the whole patient group a significant improvement was seen in FFS (HR 0.76; 95% CI 0.68-0.84; p=3.4 10^{-7}) but not in OS (HR=0.92; 95 % CI 0.80-1.06; p=0.27) for patients treated using SoC+RT. In 819 men with lower metastatic disease burden, however, OS was significantly better for SoC+RT (HR=0.68; 95%CI 0.52-0.90; p=0.007) with 3-year survival rates of 73% for SoC versus 81% for SoC+RT. In 1120 men with a higher metastatic burden RT did not improve OS (HR=1.07; 95%CI 0.90-1.28; p=0.42) (Figure 1).

Both RT schedules were well tolerated, with no significant difference in rates or latencies of symptomatic local events between patients receiving SoC and SoC+RT.

Discussion

The STAMPEDE randomised comparison of over two thousand metastatic prostate cancer patients did not find a significant improvement in OS for SoC+RT in the whole patient group studied. However, a significant OS benefit was seen for patients with lower metastatic burden treated using SoC+RT (p=.007) in a subgroup analysis that met credibility criteria proposed by Sun *et al* [7]. An interaction test indicates that the observed effect was independent of other variables assessed. The HORRAD study of 432 men with metastatic prostate cancer randomised to receive androgen deprivation therapy (ADT) alone or with RT recently reported no significant improvement in OS for the ADT+RT arm when assessed across all patients, but a trend for improved OS in those patients with lower metastatic disease burden treated using ADT+RT (p=.063) [8]. This trend for improved survival in patients with lower metastatic burden receiving SoC+RT has now been confirmed in the larger STAMPEDE study.

STAMPEDE recruited rapidly, and consequently median follow-up (37 months) is currently shorter than median survival (46 months). Longer-term analysis of STAMPEDE data may provide additional insights for population subsets. Palliative chemotherapy with docetaxel has become SoC for hormone-sensitive metastatic prostate cancer, with a survival benefit comparable to abiraterone therapy until disease progression. Patients receiving docetaxel in this study had the shortest follow-up, and although no significant difference in OS or FFS was seen for these patients, this may change

with longer follow-up. Improved systemic therapy, providing better control of metastases, may effectively move the border between low and high metastatic disease burden, enabling a greater number of patients to benefit from RT.

At the time of the study standard curative RT in the UK was 74 Gy in 37 fractions [9]. This schedule was felt to be burdensome for patients with metastatic disease, and given emerging evidence that the α/β ratio for prostate cancer was relatively low [10], RT schedules of 55Gy/20#/26 days and 36/6#/36 days were chosen for the trial. STAMPEDE has shown some evidence of heterogeneity in FFS by RT schedule (p=0.072): while a clear FFS benefit was seen for SoC+55Gy/20# compared to SoC alone (HR 0.69; 95% CI 0.59-0.8; $p < 10^{-6}$), for SoC+36Gy/6# the benefit did not reach significance (HR=0.85; 95% CI 0.73-0.99; p = 0.033). Longer-term analysis may shed more light on any difference in the effectiveness of the two RT schedules, potentially guiding identification of an optimised schedule, which future translational research might allow to be personalised.

Summary

In newly-diagnosed patients with prostate cancer and low-burden metastatic disease, OS was improved by adding prostate RT to SoC, and consequently SoC+RT should be considered the new standard of care for this population. The STAMPEDE authors suggest that RT might be given as 60 Gy in 20 fractions, the current standard UK external beam RT schedule for localised prostate cancer [11].

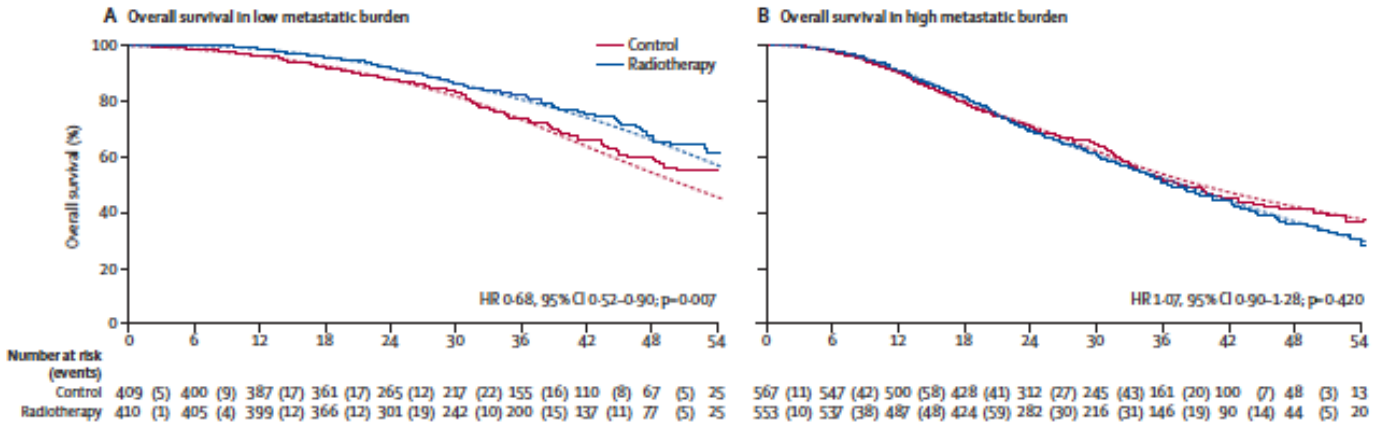

Figure 1. Kaplan-Meier curves and fitted survival models for STAMPEDE Arm K patients having lower and higher metastatic disease burdens (from Figure 4 of Parker *et al* [5] https://doi.org/10.1016/S0140-6736(18)32486-3, licensed under CC by https://creativecommons.org/licenses/by/4.0/)

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