

Radiotherapy for newly diagnosed oligometastatic prostate cancer



The standard of care for metastatic prostate cancer is systemic therapy in the form of androgen deprivation therapy with or without novel antiandrogens or chemotherapy.¹ Administering local treatment to the primary tumour in the setting of metastatic prostate cancer has long been postulated to have a survival benefit on the basis of retrospective series.²⁻⁷ But such series can have selection bias in that patients undergoing local treatment can also have a low volume of metastatic disease (oligometastases), creating a major confounder in most analyses. To date randomised controlled trials investigating this subject have been sparse, and the value of local control in metastatic prostate cancer has been debated.

In *The Lancet*, Christopher Parker and colleagues⁸ present results of the STAMPEDE randomised controlled trial comparing standard of care (androgen deprivation therapy with or without docetaxel) with external-beam radiotherapy to the prostate. 2061 men with newly diagnosed metastatic prostate cancer who had received no previous treatment to the primary tumour were enrolled from 117 hospitals in Switzerland and the UK. Radiotherapy improved failure-free survival compared with standard of care alone (hazard ratio [HR] 0.76, 95% CI 0.68–0.84; $p < 0.0001$), but overall survival was not improved (0.92, 0.80–1.06; $p = 0.266$). However, in a prespecified analysis, men were stratified using the CHARTED⁹ definition for low or high metastatic burden. In patients with a low metastatic burden ($n = 819$), radiotherapy improved 3-year overall survival compared with standard of care (81% vs 73%; HR 0.68, 95% CI 0.52–0.90; $p = 0.007$), and failure free survival was also improved (0.59, 0.49–0.72; $p < 0.0001$). Patients with a high metastatic burden did not benefit from radiotherapy in terms of failure-free survival or overall survival. Parker and colleagues concluded that radiotherapy should be an option for men with newly diagnosed metastatic prostate cancer and a low metastatic burden.⁸

A relevant trial in this area of research is the HORRAD study.¹⁰ 432 men with metastatic prostate cancer were randomly allocated androgen deprivation therapy either alone or with radiotherapy. No difference in

overall survival was noted between the two treatment groups, but in the subgroup of men with low volume of metastatic disease ($n = 160$), radiotherapy showed some improvement in overall survival (HR 0.68, 95% CI 0.42–1.10), although the finding was not significant. The similar effect size for radiotherapy in men with low metastatic burden in the HORRAD and STAMPEDE trials, but the absence of statistical significance in HORRAD, suggests that HORRAD was underpowered from the standpoint of metastatic burden. We estimate that more than 250 men would have needed to be randomised to have an 80% probability of detecting a difference with an HR of 0.75. Taken together, both these trials build the case for local radiotherapy in selected men with newly diagnosed oligometastatic prostate cancer.

As with any trial, STAMPEDE does have several limitations. First, the main finding of improved survival with radiotherapy in the cohort with a low metastatic burden is based on a subgroup analysis and should be interpreted cautiously. Next, the analysis did not test various definitions of oligometastatic prostate cancer, leaving open the possibility for patients with (for instance) five bone metastases to potentially benefit from local therapy. Defining a metastatic volume threshold above which patients are unlikely to benefit from local therapy is an important area of further study. Also, metastatic deposits in STAMPEDE were identified using conventional imaging, and such a trial might hold less weight as more sensitive PET imaging becomes commonplace. The trial also did not comment on patients with non-regional (eg, retroperitoneal or thoracic or other) lymph-node-only metastases, a relatively common scenario. Do they benefit more from cytoreductive radiotherapy than the average oligometastatic patient with bone metastases? Moreover, the incidence of symptomatic local events was similar between control and radiotherapy groups, suggesting that radiotherapy might not add much local control benefit beyond androgen deprivation therapy with the dosage used in STAMPEDE—a counterintuitive finding. Furthermore, the total dose of radiation delivered in STAMPEDE (either 36 Gy in six fractions or 55 Gy in 20 fractions) was significantly lower than the



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Published Online
October 21, 2018
[http://dx.doi.org/10.1016/S0140-6736\(18\)32598-4](http://dx.doi.org/10.1016/S0140-6736(18)32598-4)
See Online/Articles
[http://dx.doi.org/10.1016/S0140-6736\(18\)32486-3](http://dx.doi.org/10.1016/S0140-6736(18)32486-3)

70 Gy or greater given for high-risk localised prostate cancer.¹¹ Thus, dose-optimisation studies are needed to reach a balance between local and oncological control and quality of life in the metastatic setting.

Based on the findings of STAMPEDE,⁸ radiotherapy could be considered for patients with newly diagnosed oligometastatic prostate cancer, but further studies are needed to delineate the clinical implementation of such treatment.

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We declare no competing interests.

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