The need for better treatments for metastatic prostate cancer

Around 7,000 men in the UK are diagnosed with metastatic prostate cancer each year, and about 200,000 diagnosed worldwide. While there have been improvements in treatment for these men in recent years, many still die within 5 years of diagnosis, so better treatment options are needed.

The current standard of care for men with metastatic prostate cancer is long-term hormone therapy plus treatment with either the chemotherapy drug docetaxel or additional hormone therapy with abiraterone.

Radiotherapy is currently used for treating localised or locally-advanced prostate cancer. We know that it improves survival for these men. It is not generally used in metastatic prostate cancer, as it was thought to be shutting the stable door after the horse had bolted.

This briefing paper explores the evidence around the use of prostate radiotherapy for men with metastatic prostate cancer, drawing on recently published data from the STAMPEDE and HORRAD trials.

What evidence is there on prostate radiotherapy for metastatic disease?

Some retrospective analyses have suggested there may be an association between radiotherapy to the primary tumour and improved survival among men with metastatic prostate cancer. The HORRAD trial found no overall survival benefit from adding radiotherapy to hormone therapy for men with metastatic prostate cancer, but raised the possibility that survival might be improved in the subgroup of patients with low metastatic burden disease.

The STAMPEDE trial tested whether adding radiotherapy to the prostate to long-term hormone therapy in men with newly diagnosed metastatic disease could improve survival.

Key points

- Around 7,000 men in the UK are diagnosed with metastatic prostate cancer each year, and many of these men die within 5 years of diagnosis, so we need better treatments.
- Currently, men whose disease has already spread at the time of diagnosis have drug treatment only
- STAMPEDE tested whether adding radiotherapy to the prostate to long-term hormone therapy in men with newly diagnosed disease that had spread beyond the prostate could improve survival
- Overall, radiotherapy did not improve survival for all men whose disease had spread beyond the prostate.
- For the subgroup of men with ‘low burden’ disease (disease that had spread to lymph glands or to nearby bone, and has not spread to other internal organs), radiotherapy significantly improved survival, with 81% of men alive after three years, compared to 73% in the group receiving drug therapy alone.
- Radiotherapy to the prostate should now be a standard of care for men with prostate cancer who have a lower metastatic burden, but not for men with a higher metastatic burden
- Radiotherapy to the prostate is also likely to be beneficial to patients who have pelvic node positive disease
- Radiotherapy is relatively low-cost, has modest toxicity and widely available in most parts of the world
Does prostate radiotherapy improve overall survival?
There was no evidence that radiotherapy improved overall survival in the group as a whole. 65% of men were alive after 3 years in the radiotherapy group, compared to 62% in the standard of care group. This difference was not statistically significant.

From a pre-planned subgroup analysis, there was evidence that radiotherapy improved overall survival for men with low metastatic burden (oligometastatic) disease. In the subgroup of men with low metastatic burden, 81% of men were alive after three years in the radiotherapy group, compared to 73% in the standard-of-care group. This difference was statistically significant.

There was no evidence of a treatment effect in men with higher metastatic burden disease.

Does prostate radiotherapy improve failure-free survival?
Overall, STAMPEDE found strong evidence of improvement in failure-free survival in men in the radiotherapy group. In the radiotherapy group, three year failure-free survival was 32%, compared to 23% in the standard-of-care group. This difference was statistically significant.

There was evidence that the improvement was greater among men with low metastatic burden disease than high metastatic burden disease.

Does radiotherapy increase side-effects?
The proportion of patients reporting at least one severe side-effect (grade 3+) was similar in both groups (39% for the standard of care plus radiotherapy group, compared to 38% for the standard-of-care group). Most side-effects were those associated with long-term hormone therapy. 5% of patients allocated to the radiotherapy group reported having bladder side-effects of grade 3+, and 1% for bowel side-effects. There were few severe late side-effects associated with radiotherapy in either the radiotherapy or standard-of-care groups.

What is low metastatic burden prostate cancer?
Low metastatic burden prostate cancer is prostate cancer that has spread either to lymph glands outside the pelvis and/or to bones in the pelvis and spine, and has not spread to other internal organs. It is sometimes referred to as 'low volume metastatic' or oligometastatic disease.

Baseline bone and CT scans were read to classify whether a patient had lower metastatic burden or higher metastatic burden disease.

About the radiotherapy comparison in STAMPEDE
1029 men who were randomised to receive standard of care (hormone therapy with or without docetaxel) were compared to 1032 men who were randomised to receive radiotherapy plus standard of care (hormone therapy with or without docetaxel).

All the men taking part in this comparison of STAMPEDE:
• had prostate cancer that was newly diagnosed as metastatic
• were starting long-term hormone therapy for the first time
• had not previously received radical treatment
• were fit enough to have radiotherapy
• had no clinically-significant cardiovascular history

Men taking part in STAMPEDE:
• had an average age of 68
• had a median pre-hormone therapy PSA of 97
• 42% had lower metastatic burden disease
• 18% received docetaxel in addition to hormone therapy as part of the standard of care

Patients have been followed up for an average of 37 months. The primary outcome was overall survival.
Can we believe the sub-group results in men with low metastatic burden disease?

The overall survival results among men with low metastatic burden disease are statistically significant; the 95% confidence interval excludes 1.0, and the effect size we saw was large. If there was really no benefit for radiotherapy in this sub-group, the odds of us observing the effect size we did would be approximately 1 in 150. This means we can be confident that radiotherapy did improve overall survival among men with low metastatic burden disease. We also found evidence of heterogeneity of treatment effect by metastatic burden (p=0.01). Putting all this together means we have very good evidence that the survival benefit of radiotherapy is both real and confined to the low metastatic burden disease group.

How does radiotherapy fit with other treatment options for men with metastatic prostate cancer?

There is convincing evidence from RCTs and systematic reviews that separately adding radiotherapy, abiraterone and docetaxel to long-term hormone therapy improves survival. We do not know for sure how these three treatments compare, because this has not been specifically tested. Each of them seems to have a similar survival benefit, although radiotherapy results released from STAMPEDE are from a different (narrower) group of men than the results on docetaxel or abiraterone from STAMPEDE, and the benefit was seen in only a sub-group (those with low metastatic burden).

Radiotherapy has a different mechanism of action to either docetaxel or abiraterone, so there may potentially be an additive effect by treating the prostate with radiotherapy in addition to giving a systemic therapy such as docetaxel or abiraterone. Radiotherapy can be scheduled either after docetaxel or alongside abiraterone. It is likely that, in practice, suitable men would receive prostate radiotherapy in addition to, not instead of docetaxel or abiraterone. 18% of the men in who received radiotherapy also received hormone therapy + docetaxel and the effects of radiotherapy appear similar in those receiving and not receiving docetaxel.

Which radiotherapy schedule should be used?

48% of men were planned for 36Gy/6f, and 52% for 55Gy/20f. While there was some suggestion that the effect on failure-free survival was greater among men who had 55Gy/20f compared to men who had 36Gy/6f, there is not enough evidence to be certain. Since the STAMPEDE protocol was developed, results from trials of hypofractionated radiotherapy have shown good results, meaning practice in earlier stage prostate cancer has changed. Given that the trial has proven the principle that local radiotherapy improves survival, and that standard radical radiotherapy for localised prostate cancer is now 60Gy in 20 fractions over four weeks, we believe that this schedule may now also be used for men with a lower metastatic burden. With contemporary techniques for target delineation and treatment delivery, this schedule is very well tolerated.

Criteria for assessing the credibility of sub-group effects

Sun et al. propose a number of criteria for assessing the credibility of sub-group effects. The results from STAMPEDE meet these criteria:

- Low/high metastatic burden status was determined from scans taken before randomisation
- The hypothesis was specified in advance of the analysis
- Only a small number of hypothesised effects were tested (metastatic burden, and radiotherapy schedule)
- The interaction test suggests a low likelihood that the apparent subgroup effect could be explained by chance (one in a hundred)
- The subgroup effect was independent of other assessed variables
- The direction of the sub-group effect was correctly pre-specified (those with low burden disease would benefit more from radiotherapy)
- The interaction is consistent with other related outcomes (failure-free survival and prostate cancer specific survival) and the results from a separate trial (HORRAD)
- It also is biologically plausible that the effect of local radiotherapy would be smaller in patients with greater burden of metastatic disease.

The size of the subgroup effect is also large. It is therefore credible that radiotherapy improves the survival of men with low metastatic burden disease.
Recommendations

1. Radiotherapy to the prostate should now be a standard of care for men with prostate cancer who have low metastatic burden disease, but not for men with high metastatic burden disease.

2. Radiotherapy to the prostate is also likely to be beneficial for patients who have pelvic node positive disease.

3. Radiotherapy to the primary tumour may also be beneficial for other types of metastatic cancer with low burden disease; research is needed to test this.

What implications do these results have for other patients?

Radiotherapy improves survival of men with locally advanced disease, and we now know it helps men with low metastatic burden disease. We think these latest results mean patients who have pelvic node positive disease (which falls between the definitions of locally-advanced and low metastatic burden disease) should also receive radiotherapy.

The benefits of radiotherapy to the primary tumour for patients with metastatic disease have not been well studied in other cancer types. The results from STAMPEDE suggest it may be worth testing whether patients with other types of cancer with low metastatic burden might benefit from local therapy (radiotherapy).

Further information


Boevé LMS, Hulshof MCCM, Vis AN, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. European Urology. 2018.

Animated abstract of the STAMPEDE results:
https://vimeo.com/294574932

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