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STAMPEDE: Is Radiation Therapy to the Primary a New Standard of Care in Men with Metastatic Prostate Cancer?

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Pre-clinical data suggests that radiotherapy (RT) to the primary can prevent further metastases, often termed as the "second wave". Additionally, progression of existing distant metastases can be tempered, possibly due to an immunologic effect from RT [1]. Retrospective data has demonstrated potential overall survival (OS) benefits from treatment of the primary in men with newly diagnosed metastatic (M1) prostate cancer [2,3]. However, these studies are subject to significant bias and require prospective randomized validation. Previous randomized trials, such PR07 may in fact in hindsight have supported these findings. Although, there was no documented overt M1 disease, the PR07 [4] study confirmed an improvement in OS in men with non-metastatic high risk prostate cancer when RT was added to androgen deprivation therapy (ADT). In PR07, a significant proportion of patients did not have cross-sectional imaging or bone scintigraphy to exclude distant metastases leading to the suggestion that RT may be beneficial in patients with advanced disease.

The first randomized trial to directly compare the addition of local therapy to the primary in M1 patients was the HORRAD trial [5]. This trial randomised 432 men with metastatic prostate cancer to ADT with or without prostate RT, and enrolled predominately high volume M1 patients. Overall there was no OS benefit from the addition of RT (hazard ratio [HR] 0.90, 95%CI 0.70–1.14). In an unplanned subset analysis within the HORRAD trial they showed a potential interaction of volume of disease (e.g. number of metastatic sites) and benefit of RT, with low volume patients trending towards a significant improvement in OS (HR 0.68, 95%CI 0.42–1.10). Given the non-significant results in all prespecified endpoints, and small sample size of this trial, especially in light of the very small subgroup analyses, the treatment of the primary in M1 patients remained experimental.

During the conduct and maturation of the HORRAD trial, the multi-arm, multi-stage, STAMPEDE trial added its newest arm, arm H, to assess the benefit of treating the primary with RT [6]. Arm H enrolled 2061 men, 1029 assigned to standard of care and 1032 to prostate RT, and tested the hypothesis that RT to the primary in the presence of metastases would improve OS. During the follow up of the STAMPEDE trial, the HORRAD results were reported, and in May 2018 the STAMPEDE investigators added the *a priori* hypothesis that RT to the primary will preferentially benefit low volume patients, using the CHAARTED definition of low volume, with a prespecified estimated HR of 0.70. Although when arm H first opened, the standard of care for metastatic prostate cancer was ADT alone, docetaxel was added as part of the standard of care to the trial in December 2015 [7], and was included as a stratification factor.

Due to the stratification factors and the randomization process in a large trial, all baseline characteristics were well balanced; most notably, volume of disease (low vs high), and use of docetaxel (18% in each arm). The primary endpoint was OS, and similar to the HORRAD trial there was no improvement in OS in unselected patients with M1 disease (HR 0.92, 95% CI 0.80–1.06; p=0.266). However, there was a significant improvement in the whole cohort in failure-free survival (FFS) (HR 0.76, 95% CI 0.68–0.84; p<0.0001), which is of potential value.

The prespecified subgroup analysis based on volume of disease met every criterion proposed for the reliability of subgroup analysis proposed by Sun et al [8]. In low volume patients there was not only a 17% absolute improvement in 3-year FFS (HR 0.59, 95%CI 0.49–0.72; p<0.0001), there was an 8% absolute benefit a 3-years in OS (HR 0.68, 95%CI 0.52–0.90; p=0.007). Furthermore, the interaction test for both OS and FFS based on volume of disease and treatment to the primary were highly

statistically significant, indicating that volume of disease can functionally serve as an imaging-based predictive biomarker of patients who preferentially benefit from RT to the primary.

Importantly, these patients have M1 disease and will not be cured by treatment of their primary, thus, minimizing toxicity is paramount. Given the slightly reduced doses of RT employed, there was no significant difference in grade ≥3 toxicity with the addition of RT (HR 1.01, 95%CI 0.87–1.16; p=0.941). In absolute terms, 6-months post-treatment there was only a 1% increase in grade ≥3 toxicity from the addition of RT, and by 2-years post-treatment there was 2% lower grade ≥3 toxicity in the RT arm. Furthermore, there was no significant difference in symptomatic local events, indicating that in hormone sensitive M1 patients, local symptomatic events are rare with ADT alone. Longer-term data will be important to determine the frequency of local symptoms (e.g. urinary obstruction, hematuria) without local therapy in patients who ultimately develop castrate-resistant disease.

Of note, two dose/fractionation schemes were allowed in the STAMPEDE trial arm H: 55 Gy in 20 fractions (daily), or 36 Gy in 6 fractions (weekly). The former is similar to the commonly-used hypofractionated regimen of 60 Gy in 20 fractions, while the latter regimen is similar to a commonly-used SBRT regimen (36.25 Gy in 5 fractions). This SBRT regimen, delivered every other day, is well-established as safe for localized prostate cancer, with minimal Grade 3 toxicity in the reported literature. It is important to note that dose escalation in localized prostate cancer has never shown OS benefits, and thus should only be done on trial in the M1 population given that these patients will not be cured by local therapy, and mitigating toxicity is critical. Although radiation oncologists could follow the STAMPEDE regimens exactly, it is likely that in the future more standardised schedules will be adopted, although 36Gy in weekly fractions of 6 Gy can be delivered with basic RT equipment in low- and middle-income countries.

These data should be compared to other recently approved standards of care for the management of M1 patients [9, 10]. Abiraterone is commonly used in the USA with standard ADT. Based on recent data presented at ESMO, low risk M1 patients derived a 4% absolute OS benefit at 3 years, a 14% increased grade ≥3 toxicity, treatment often for years until progression, and in the USA would cost >$300,000. This is in contrast to an 8% OS benefit from as few as 6 treatments of RT, no increase in grade ≥3 toxicity, and a cost of <$20,000.

So to answer the question, is RT to the primary a new standard of care? Yes -- for low volume patients that have no contraindications to RT. In these patients, RT to the primary provides no increase in grade 3 toxicity, a large FFS, and an impressive OS benefit within the first 3-years post-treatment. For men with high volume disease, RT to the primary does not appear to improve OS; longer-term data from STAMPEDE will be helpful to understand whether prostate RT will ultimately reduce long-term local symptoms due to progression of castrate resistant disease in the prostate.

How does one factor in other ongoing standards of care, such as abiraterone, or treatment of metastatic sites with metastasis-directed therapy? First, given the comparable, if not superior benefit of RT to the primary, it is reasonable to offer this in low volume patients without the use of abiraterone. This is logical, given that abiraterone benefits both low and high volume patients similarly, whereas delayed use of RT to the primary may miss the window of benefit where treatment of the primary improves OS. The alternative option is to give RT and abiraterone together, which is being tested in localized and recurrent prostate cancer in multiple clinical trials. The

addition of abiraterone to RT in clinical N1 patients improves DMFS in STAMPEDE, a known surrogate of OS, with no concerning safety interaction. Fortunately, the benefit of abiraterone to RT is being tested in the M1 population in the PEACE I trial (NCT01957436), and thus we will have level 1 evidence to support this combination in the next few years.

Some colleagues suggest that the STAMPEDE results simply point to the benefits of "local treatment" in newly diagnosed metastatic prostate cancer, which raises the question, can radical prostatectomy (RP) provide comparable results? This remains an experimental and unanswered question, and should not be performed outside of a clinical trial. It is unknown if the very low toxicity observed in STAMPEDE from the addition of RT will be mirrored with RP, especially if post-operative RT is allowed. It is known from ProtecT that multiple quality of life domains in the first 5-years post-treatment favour treatment with RT [11], and that post-operative RT can increase toxicity. Furthermore, it is known that stage of disease is associated with increased side effects post-RP and incidence of positive margins. Clinicians are beholden to consider the long-term effects of treatment in a population who have a finite life expectancy.

RT and surgery are also biologically different treatments. It is unknown if the proven synergy of RT with ADT will exist with RP. In fact, in localized prostate cancer that synergy has not been demonstrated when adding ADT to RP. There may be an underlying biological rationale as to why RT combined with ADT is effective. Regardless, multiple exciting trials are testing the benefit of RP in M1 patients, including SWOG 1802 (NCT03678025), TRoMbone (ISRCTN15704862), and others. The largest of these trials is the SWOG 1802 trial, which allows for significant diversity and heterogeneity of treatment. Either RP or RT is allowed to the primary, adjuvant RT is allowed post-RP, use of metastasis-directed therapy, and various systemic therapies, including standard ADT, abiraterone, and docetaxel are all allowed. Men with both low and high volume disease are included. Thus, there is concern if the overall trial is negative, like HORRAD and STAMPEDE for OS, that these numerous subgroups will be adequately powered to detect a difference. Given the broad support from leaders across radiation oncology, medical oncology, and urology for lack of equipoise in randomizing low volume patients to potentially no treatment of the primary, it will be interesting the types of patients accrued to the SWOG trial given the results from STAMPEDE.

Finally, the benefit of treating metastatic sites has recently gained much attention from trials suggesting a potential OS benefit, such as SABR-COMET. As treatment of the primary with RT is now considered by many as a new standard of care, the next arm of STAMPEDE being planned is to deliver standard of care (systemic therapy and RT to the primary) and randomize patients to metastasis-directed therapy (estimated sample size approximately 2000 patients).

One of the strengths of STAMPEDE is that the OS effect of RT is seen in patients staged with fairly basic imaging of Technetium$^{99}$ bone scintigraphy and computerised tomography cross sectional imaging. This can be done throughout the world, even in countries with limited resources. As imaging continues to evolve and more patients are found to have small volume oligometastatic disease at the time of diagnosis, local therapy with RT does not lose its impact on OS.

STAMPEDE has confirmed that once again RT provides the most cost-effective and least toxic method of delivering life prolonging therapy in metastatic prostate cancer. Questions remain about sequencing and alternative treatments, and we encourage the participation in clinical trials. For now,

our diverse international group agrees that RT to the primary in low volume metastatic patients should be considered a new standard of care.

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