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Intermediate efficacy end points to assess modern therapies

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Abstract

A retrospective, single institution study of 450 men with biochemical recurrence after radical prostatectomy included 140 men with androgen deprivation therapy deferred until metastatic disease onset. Metastasis-free survival was an independent predictor of overall survival. This research highlights the need to develop appropriate intermediate end points to expedite prostate cancer treatment.

Effective clinical trial design in men with nonmetastatic prostate cancer (nmPC) has been hampered by this patient population's heterogeneity and prolonged survival times, which often defer definitive overall survival end points by a decade. The availability of newer therapies, including nontoxic hormonal and immunotherapeutic agents, has raised hopes for delaying metastatic disease in patients with nmPC. An intriguing study by Schweizer *et al.*¹ provides evidence that, in patients with nmPC, metastasis-free survival (MFS) independently predicts overall survival, thereby raising the possibility that MFS could be used as an intermediate clinical trial end point for patients with nmPC. This retrospective study of men treated between 1981 and 2010 at a single institution evaluated 450 men with biochemical recurrence after radical prostatectomy. In the 140 men who developed metastatic prostate cancer, androgen deprivation therapy was deferred until the onset of metastatic disease. Using Cox regression models, MFS was an independent predictor of overall survival.

The analysis by Schweizer *et al.*¹ was hindered in ways that are inherent to retrospective analyses covering several decades. Firstly, patients treated between 1981 and 2010 would have had access to a range of different therapies and supportive measures that could have influenced overall survival and, consequently, the outcomes of this retrospective analysis. For example, patients treated with bisphosphonates in this study had substantially improved overall survival compared with patients who did not receive these drugs. As such, bisphosphonates (which have not conveyed an independent overall survival benefit in previous randomized placebo-controlled studies) probably serve, to some extent, as a surrogate for therapeutic development with the passage of time. Patients in this study who received bisphosphonates probably also received other agents with potential overall survival benefits—agents that would not have been available to patients in prior decades. Another point to consider is that all patients in the study were treated with radical prostatectomy,

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Competing interests

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with no further therapy until metastatic disease developed. It is not known how treatment with radiation, adjuvant hormonal therapies, or novel treatments for nmPC might have influenced the link between MFS and overall survival. Furthermore, as the authors acknowledge, patients with aggressive disease features, such as rapidly rising PSA, were probably imaged or treated early, leading to ascertainment bias and producing a longer MFS than would be expected in the general nmPC population.

Up until now, overall survival benefit has been the gold standard clinical end point for approval of therapeutic agents in prostate cancer. Although there is increased interest in delaying metastatic disease, denosumab—a receptor activator of nuclear factor κ B (RANK) ligand inhibitor—presents a cautionary tale. Denosumab is designed to inhibit osteoclast formation, function, and survival, with the aim being to increase bone density and delay the morbidity associated with osseous metastasis. This agent is FDA-approved to delay skeletal-related events in metastatic prostate cancer and increase bone density in patients receiving androgen deprivation therapy. In a randomized phase III study of more than 1,400 men with nmPC, denosumab delayed metastasis by 4.2 months (HR 0.85; $P = 0.028$).² Yet in the absence of mature data assessing survival, the FDA ultimately ruled that the benefits of denosumab were not substantial enough to warrant its indication for nmPC as a means to delay metastatic disease. Although this decision was partially based on the risks of osteonecrosis in these patients, a clear benchmark or precedent for a risk:benefit ratio acceptable to the FDA in nmPC remains undefined.

Nonetheless, Schweizer *et al.*¹ raise important issues that need to be addressed. Establishing reliable clinical trial end points for men with nmPC would improve access to therapies that could delay the potential morbidity of metastatic disease, while also ensuring that treatments have a meaningful clinical benefit and not merely a presumed clinical benefit extrapolated from studies of metastatic disease. For example, although studies to evaluate the use of docetaxel in the adjuvant setting are ongoing, the efficacy of this treatment prior to metastatic disease is not known.^{3,4}

In addition to the association of MFS with overall survival, univariate analyses by Schweizer *et al.*¹ found similar associations between overall survival and PSA doubling time, number of metastases, and pain with metastasis (the latter two were also significant in a multivariate analysis). These parameters reflect tumour volume or momentum (how quickly a tumour reaches a clinically significant volume). A prior retrospective analysis of patients treated at the same institution as the Schweizer study cohort revealed associations between changes in PSA kinetics after therapy and subsequent MFS.⁵ The multiple methods currently available for evaluating PSA kinetics, beyond rudimentary PSA doubling-time calculators, might increase the utility of PSA measurement.⁶ Using PSA kinetics—and abandoning older PSA progression criteria that evaluate PSA changes based on percentages alone—could enable patients with progressive nmPC to receive secondary therapies before they develop metastases, or prevent the premature discontinuation of treatments that might slow the rate of increase of PSA.⁷ The use of PSA kinetics would also take into account the fact that immunotherapies, such as sipuleucel-T and PSA-TRICOM, can provide clinical benefits without inducing absolute PSA declines, with no significant accompanying toxicity.⁸ For example, PSA kinetics evaluated at 3 months or beyond might reveal an absolute increase in the PSA value, but they might also demonstrate a slowing of the PSA kinetics, perhaps indicating a decrease in tumour growth-rate. Ultimately, randomized studies are needed to prospectively evaluate the association between changes in PSA kinetics and harder clinical outcomes, such as MFS, overall survival, and the development of symptomatic disease.

PSA kinetics assessment is just one tool for assessing clinical benefit in men with nmPC. Modern imaging technologies have greatly improved the detection of metastases to bone, an important development given that the vast majority of patients with nmPC will ultimately develop osseous metastatic disease. In preliminary studies, a sodium fluoride (NaF) PET scan has been shown to detect occult osseous lesions in men with nmPC and biochemical recurrence.⁹ Such imaging studies could be used to determine clinical benefit that could serve as an intermediate end point in nmPC clinical trials. However, such trials would ultimately require confirmed correlations between changes in novel imaging results and MFS or overall survival. Although NaF PET imaging has been approved for the evaluation of metastatic prostate cancer, care should be taken not to overinterpret findings or to use a positive NaF PET result to automatically trigger aggressive, toxic therapies, such as chemotherapy, until more is known about how the lead time for this imaging modality compares with conventional imaging techniques.

Recent and ongoing studies of modern therapies present many opportunities for evaluating PSA kinetics, and possibly NaF PET imaging, as indicators of MFS and predictors of overall survival. Trials of enzalutamide (NCT01664923), abiraterone (NCT00473512, NCT01751451, and NCT01314118), and sipuleucel-T¹⁰ in men with nmPC have been completed or are ongoing. Data gleaned from these studies could further support the use of PSA kinetics, NaF PET imaging, or conventional MFS as intermediate clinical trial end points.

In recent years, therapy for prostate cancer has advanced significantly, giving patients with metastatic disease many promising treatment options. The challenge ahead is to develop intermediate clinical trial end points, beyond conventional measures of MFS and overall

survival, enabling practitioners to deploy these new therapies earlier in the disease process. Clinical benefit might be even greater in patients with nmPC, whose tumour burden is smaller than those with metastatic disease. Now that the pieces are in place to help patients with nmPC, we must agree on the rules of the game as we move forward, and acknowledge that the game is indeed changing.

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