have obscured a clinically relevant benefit. By further contrast with ATTRACTION-3, in KEYNOTE-181, high-level PD-L1 expression (ie, combined positive score ≥10) on tumour and immune cells predicted a significant improvement in overall survival with pembrolizumab compared with chemotherapy. In oesophageal cancer, as in other tumour types, the value of PD-L1 staining might be equally dependent on an antibody and testing compartment.[5]

Finally, although ATTRACTION-3 potentially sets a new standard for previously treated patients with oesophageal squamous cell carcinoma, the inclusion of few non-Asian participants might undermine the trial's global generalisability. The main drivers of non-endemic oesophageal squamous cell carcinoma pathogenesis (tobacco and alcohol) are similar in Asian and non-Asian countries, suggesting an underlying common biology. However, subgroup analysis of the more global KEYNOTE-181 trial suggests anti-PD-1 therapy is more effective in Asian patients with oesophageal squamous cell carcinoma than in non-Asian patients.[4] Determining whether tumour or host factors, including ethnicity or region of origin, have precedence in response to immune checkpoint blockade in oesophageal cancer will be crucial for future trial design and from a regulatory perspective. However, these issues should not detract from the large number of patients with oesophageal squamous cell carcinoma for whom the results of ATTRACTION-3 will provide renewed hope. In future, it is possible that perioperative immunotherapy or combinations of immunotherapy and chemotherapy or chemoradiation might ultimately improve long term survival in patients with early and locally advanced oesophageal squamous cell carcinoma.

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Quality of life considerations in the treatment of metastatic hormone-sensitive prostate cancer

Globally, the incidence and prevalence of prostate cancer are increasing, with more than 1·2 million men now estimated to be diagnosed every year.[1] Although in countries such as the USA and Australia, most men will be diagnosed with localised disease,[2] the burden of metastatic disease is still substantial and unevenly distributed.[3] Furthermore, men with advanced or metastatic disease experience poorer quality of life, and higher psychological morbidity and risk of suicide than men with localised disease.[4,5] Therefore, for these men, a consideration of the patient experience is crucial. In *The Lancet Oncology*, Neeraj Agarwal and colleagues[6] present patient-reported outcomes from the TITAN study, providing insight into the effects on quality of life when apalutamide is used as an adjunctive therapy to androgen deprivation in men with metastatic castration-sensitive prostate cancer. The question of treatment burden is important to men diagnosed with metastatic castration-sensitive prostate cancer, for whom overall survival, as well as radiographic progression-free survival and delay to cytotoxic therapy, are critical. But do treatments that improve these outcomes come at a cost of compromised quality of life?

In the TITAN study,[6] 1052 patients with metastatic castration-sensitive prostate cancer who were on continuous androgen deprivation therapy were randomly assigned to receive apalutamide (n=525) or a placebo (n=527). The previously reported primary


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endpoint results of the trial had shown that the addition of apalutamide to androgen deprivation therapy significantly improved both radiographic progression-free survival and overall survival. In the current paper, pain, fatigue, prostate cancer symptoms, and health-related quality of life were assessed in the two treatment groups. For pain and fatigue, patients were relatively asymptomatic at baseline and remained stable or improved over the duration of the trial. Overall health-related quality of life was preserved during treatment, and there were no between-group differences in any of the patient-reported outcomes. These results suggest that apalutamide is well tolerated in these patients, and therefore it seems to be a favourable option for patients from the points of view of both survival and quality of life. However, as noted by Agarwal and colleagues, other relevant patient outcomes, such as mood disturbance, insomnia, and cognitive deficits, were not assessed, meaning that the evaluation of quality of life was not extensive. A qualitative study component to allow for the patient voice would have added value. Additionally, further follow-up, including analysis of the trajectories for key patient-reported outcomes, would allow the identification of risk factors for a poorer response. This issue is an important consideration in light of research suggesting that background characteristics, such as low socioeconomic status and comorbidities, together with androgen deprivation therapy, predict poorer long-term quality of life.[7]

Current evidence indicates that in terms of survival, the optimal management of metastatic castration-sensitive prostate cancer is a combination of standard androgen deprivation therapy with luteinising hormone-releasing hormone agonists or antagonists together with a newer-generation antiandrogen. In the study by Agarwal and colleagues, the agent used in addition to androgen deprivation therapy is apalutamide, and similar improvements in survival have been seen with both abiraterone and enzalutamide.[8,9] However, additional research is needed to evaluate the toxicities of these treatments; although no obvious changes in patient-recorded outcome measures were found between androgen deprivation therapy plus apalutamide versus androgen deprivation therapy alone, other studies have reported different results with related agents. For example, in the LATITUDE study,[8] the investigators reported a higher frequency of hypokalaemia in the abiraterone group with standard androgen deprivation therapy group as compared with the group receiving standard androgen deprivation therapy alone, and a 7% increased risk of serious adverse events. In the ENZAMET study,[9] worsening fatigue was reported in the enzalutamide with standard androgen deprivation therapy group as compared with the group receiving standard androgen deprivation therapy alone, as well as an increased risk of seizures. Although these studies did not analyse patient-reported outcomes specifically, they did identify that additional risks can occur with combination therapies.

In conclusion, Agarwal and colleagues have provided an additional treatment option for men with metastatic castration-sensitive prostate cancer, that seems to prolong survival with low morbidity costs, and also defers cytotoxic therapy, allowing the patient to avoid high-toxicity approaches at least temporarily. Adjunctive approaches, such as tailored exercise programmes and psychosocial therapies, could provide further improvements to quality of life in this context.[10] We note that the use of the term castration in this field has been criticised by patients as being emasculating, and we suggest that clinicians and researchers work to develop a shared language around these treatment modalities. Effective clinician communication and values-based support for men making treatment decisions will become even more crucial as the treatment approaches become more complex. The development of prostate cancer survivorship care that is men-centred and holistic must keep pace with medical advances,[10] and including quality-of-life considerations in clinical research is a valuable starting point.

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Stereotactic beam radiotherapy for prostate cancer: is less, more?

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In *The Lancet Oncology*, Douglas Brand and colleagues[1] report an important trial, in which the authors aimed to investigate the fractionation sensitivity of radiotherapy in the curative treatment of low-risk and intermediate-risk prostate cancer. Participants received either conventionally fractionated or moderately hypofractionated radiotherapy, or ultra-hypofractionation (stereotactic body radiotherapy) in five fractions, delivered either daily or every other day. Acute toxicity might be worse when treatments are delivered in few large fractions and an overall treatment time as short as 1–2 weeks, compared with protracted schedules delivered in 6–8 weeks. In this trial, however, stereotactic body radiotherapy was equally well tolerated as conventionally fractionated or moderately hypofractionated radiotherapy. This is an important issue, because stereotactic body radiotherapy is much more patient-friendly in terms of convenience and less costly than are more protracted fractionation schedules. Although the study limits its focus to early tolerance (up to 12 weeks after radiotherapy), this study is the first that was designed to use contemporary radiotherapy delivery techniques—ie, linac-based volumetric modulated arc radiotherapy or CyberKnife.

Dose constraints to the organs at risk (eg, rectal wall, bladder wall, and urethra) were well established, aiming to limit toxicity to acceptable levels. The proportions of patients in the stereotactic body radiotherapy group who had physician-reported moderate (grade 2) gastrointestinal and genitourinary acute toxicity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), were 62 (15%) of 415 patients and 121 (29%), respectively, compared with the proportions in the conventionally fractionated or moderately hypofractionated group (33 [8%] of 432 patients and 96 [22%], respectively).

The proportion of moderate gastrointestinal toxicity was higher than those reported by some phase 2 trials using similar stereotactic body radiotherapy scenarios, with proportions ranging from 2% to 8%.[2–4] To reduce the dose to the rectal wall, the use of gadgets such as endorectal balloons or spacers implanted between the rectum and the prostate have been recommended.[5,6] Because both procedures are invasive or, at least, uncomfortable, an alternative could be to reduce the dose constraints applied to the rectal wall while keeping the dose prescription to the target unchanged. This method might lead to an optimisation of the final treatment plan by substantially reducing the intermediate and low doses to the rectal wall.[7] Nowadays, dose distribution optimisation can be substantially and easily improved with software for multicriteria optimisation planning, based on Pareto surface.[8]

Because the prostatic urethra inside the target volume always gets the full prescribed dose, the proportion of patients with moderate genitourinary acute toxic effects was similar to that which has