reduces the relative risk of radiation-related second malignant neoplasia compared with photon radiotherapy and surgery in patients with localised prostate cancer. The authors used retrospective cancer registry data for the photon radiotherapy and surgery groups and encountered the analysis challenges previously outlined in this Comment, including, but not limited to, relatively short follow-up, incomplete or no data on important confounding factors (such as alcohol or tobacco use), relevant comorbidities, and specific details about radiotherapy dose, volume, and radiation technique. Propensity score matching was used to minimise the effect of known confounding factors when comparing the carbon ion radiotherapy cohort with the photon radiotherapy and surgery groups, but this analysis further reduced the already modest numbers of patients for this type of analysis and power to identify differences between cohorts. In fact, their calculated hazard ratio of 1·18 (95% CI 1·02–1·36) for photon radiotherapy compared with surgery is actually more favourable than that reported by either Wang and colleagues[5] or Krasnow and colleagues,[6] and possibly reflects the shorter median follow-up. Notwithstanding these concerns, Mohamad and colleagues' study is noteworthy as one of the very few investigations that exceeds studies of dose modelling to support the use of particle beam therapy to decrease the risk of radiation-related second malignant neoplasia.

The most important contribution of this paper is probably an increasing awareness of radiation-related second malignant neoplasia following prostate radiotherapy. The published literature confirms that the overall risk of photon radiotherapy is small but not inconsequential for patients younger than 65 years. Carbon ion radiotherapy appears to reduce this risk, but limited access to these facilities makes it impractical for most patients. Although Mohamed and colleagues did not address it, scarce data suggests that more widely available proton therapy might provide the same advantage as carbon ions for radiation-related second malignant neoplasia and should be investigated further.[8,9] Moreover, their report should not encourage a general move from photon radiotherapy for those who choose radiotherapy for their prostate cancer. Ready access, favourable economics, and abundant level 1 evidence of safety and efficacy weigh heavily in its favour. Nonetheless, the risk of radiation-related second malignant neoplasia should be a part of patient discussion, especially for younger patients with treatment options beyond photon radiotherapy.

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Importance of early treatment in metastatic prostate cancer: a question of life or death

Patients diagnosed with metastatic prostate cancer have become less common with the widespread use of prostate-specific antigen tests and improved awareness of prostate cancer. Although screening remains controversial, patients who walk into our clinics with newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) remain the most challenging to treat group of patients with prostate cancer. These patients generally have a poor prognosis and overall survival times are still only around 3 years, despite substantial

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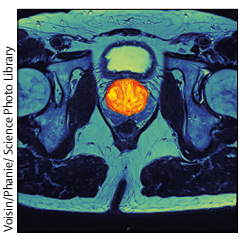
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improvements during the past 15 years.[1] Why these patients do so poorly compared with those who progress from a localised state to a metastatic state is unclear, but it is probably related to a different underlying biology or simply that the large tumour burden that developed over time has allowed intrinsically resistant clones to form.

The high-risk patients that were enrolled and studied in the LATITUDE study,[2] the final analysis of which is reported by Karim Fizazi and colleagues in *The Lancet Oncology*, clearly show the value of early aggressive therapy in managing aggressive and rapidly lethal prostate cancer.[3] Looking at the results, I was struck by several important findings. First, the median overall survival in patients treated initially with placebos and androgen deprivation therapy (ADT) was only about 3 years. This survival result is striking because it is similar to that in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone[4] or enzalutamide[5] in phase 3 trials. This observation suggests that patients with either localised or metastatic prostate cancer at the time of diagnosis had the time to progress from diagnosis to mCRPC, with a median of ten bone metastases and a prostate-specific antigen concentration of more than 40 ng/mL, yet still survived for almost 3 years receiving abiraterone or enzalutamide treatment. By contrast, patients who started on ADT alone in LATITUDE lived only 3 years from diagnosis to death even though, in theory, they had access to several life-prolonging therapies when they became castration resistant. Looking closely at the data, we realise that the patients in LATITUDE actually became castration resistant in only 7 months on ADT alone.[3] Unfortunately, patients only started subsequent therapy 14 months later and ended up dying less than 1 year after that. This probably reflects real-world situations, and probably contributes to the striking difference in survival seen between the two treatment groups in LATITUDE. With abiraterone acetate plus prednisone and ADT in patients with high-risk metastatic prostate cancer, survival was 53·3 months (95% CI 48·2–not reached) versus the 36·5 months (33·5–40·0) in the control group (hazard ratio 0·66 [95% CI 0·56–0·78]; p<0·0001). Clearly, patients with high-risk metastatic prostate cancer are likely to progress quickly and die from, rather than with, prostate cancer. Timing of treatment appears to be crucial. Effective therapies such as abiraterone[2,3,6] or docetaxel[7,8] in high-risk newly diagnosed metastatic prostate cancer are optimally used immediately. Early use maximises the effect before castration resistance sets in and, importantly, avoids the delays that probably render these therapies less effective. This situation is evident in LATITUDE, where almost half the patients never received life-prolonging therapy after ADT before dying from the disease. The median secondary progression-free survival of 30·1 months (95% CI 26·2–33·4) in the placebo group suggests that patients who did receive subsequent therapy (median time to subsequent therapy 21·2 months [18·6–23·5]) did not respond for very long given the short time (about 9 months) between these events. The question that remains in the mCSPC setting is whether patients are better managed with chemotherapy or abiraterone plus ADT. Results suggest similar overall survival benefits.[9] For individual patients, decisions will be made on balancing the choice of docetaxel for six cycles (18 weeks) then a break from therapy until castration-resistant prostate cancer sets in versus continuous abiraterone and prednisone until resistance occurs. On a biological level, it would be ideal to be able to establish which patients would benefit most from docetaxel over abiraterone. For now, the best appraoch remains unknown but at least patients and physicians have options. Unfortunately, the outlook is poor for these high-risk patients with either approach, so ongoing research is assessing the upfront combination of docetaxel plus a new-generation hormonal therapy. If timing is truly important, a combination approach would avoid delays in introducing effective subsequent therapies and should hopefully show further improvements in patient outcomes.

In the meantime, what can clinicians do? First, in these high-risk patients, the addition of either abiraterone or docetaxel to the ADT standard of care should always be considered. If docetaxel is the first or only option in this setting, patients should be monitored closely for a suboptimal response after 6–8 months (prostate-specific antigen nadir >0·2 ng/mL). Since these patients will probably have earlier progression and mortality, immediate therapy could be considered or patients should at least be monitored closely. Once patients progress to mCRPC, early introduction of an approved mCRPC therapy, such as abiraterone or enzalutamide, is warranted. Effective therapies that significantly improve the outcome of patients with metastatic prostate cancer are now available in both the castration-sensitive and castration-resistant settings. Therefore, if an average patient

diagnosed with mCRPC or mCSPC has not received at least one life-prolonging therapy in addition to ADT, that should now be considered suboptimal care. Importantly, the LATITUDE trial further highlights the importance of early introduction of life-prolonging drugs in addition to ADT in patients with lethal prostate cancer. Patients' survival and quality of life depend on these concepts.

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Conclusions from quality of life studies in patients with resected high-risk melanoma: one part of the full story

In *The Lancet Oncology*, Dirk Schadendorf and colleagues[1] report the health-related quality-of-life outcomes from the COMBI-AD trial using the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) instrument. In the COMBI-AD trial, patients with resected stage III melanoma, with *BRAF*^{V600E} or *BRAF*^{V600K} mutations, were randomly assigned to receive adjuvant dabrafenib and trametinib or matching placebos. The authors report no difference in health-related quality of life during the 12 months of treatment, and conclude that the risk–benefit profile of this adjuvant therapy is therefore favourable. There is an implication that the high proportion of patients with pyrexia (273 [63%] of 435 patients) and fatigue (204 [47%]), as well as the 114 [26%] patients who discontinued trial therapy because of adverse events,[2] are not factors associated with the outcome. For an individual patient, the conclusions from this trial are just one part of the full story.

There are two additional adjuvant therapy trials, in a similar patient population, that report no difference in health-related quality of life despite a high incidence of severe adverse events, including deaths.[3,4] These trials investigated the role of adjuvant immunotherapy. One assessed adjuvant ipilimumab compared with placebo[3] and the other compared ipilimumab with nivolumab.[4] These three adjuvant therapy trials are likely to affect the future treatment of this patient group. As adjuvant trials, they all assessed patients who were disease-free, but who had been exposed to potentially morbid adverse reactions that could also affect quality of life. It is important to consider that there seems to be no difference when comparing health-related quality-of-life outcomes in these randomised trials, and how this message can be conveyed to patients.

Limitations in health-related quality-of-life assessments can include several factors. The EQ-5D questionnaire, which is validated to assess patients with cancer,[5] does not have symptom specificity that might be relevant to the assessments in COMBI-AD, with respect to fatigue and pyrexia. The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–30 (EORTC QLQ-30) instrument was used in the other two adjuvant therapy trials, but has not been specifically validated to assess immunotherapy and does not address endocrinopathies or dermatological immune-related adverse events, both of which are very relevant to those trials.[3,4,6]

All of the trials previously described were done with a protocol of timed assessments, including health-related


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