might not have decreased as it has in childhood cancer. Alternatively, reducing the incidence of subsequent primary neoplasms in survivors of AYA cancer might require a stronger focus on lifestyle factors.

Although this study represents a substantial contribution, several limitations merit note. Late effects are most closely associated with the types and doses of therapy received. Unfortunately, the investigators did not have access to treatment data, relying instead on diagnosis as proxy. However, a patient with Hodgkin lymphoma might receive only two cycles of chemotherapy or might undergo six cycles and radiotherapy, with consequently vastly different risks for subsequent primary neoplasm. Without treatment data, the clinician is still left uncertain on how to counsel an individual patient on his or her personalised risk, or what screening to recommend. AYA-specific risk prediction models that include treatment exposure are urgently needed.

Finally, description of risk is only a first step towards the ultimate goal of improving the quantity and quality of life for survivors of AYA cancer. Studies that identify effective interventions for this population, whether in the prevention, screening, or treatment of late effects, are crucial. Determining what health-care delivery models maximise uptake of such interventions in a population known to face substantial barriers to access will also be necessary.

For decades, paediatricians have insisted that children are "not just little adults". We must now be equally emphatic in declaring that when it comes to the late effects of cancer and cancer therapy, AYAs are "not just big children", but instead deserve recognition as their own unique group.

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I declare no competing interests.

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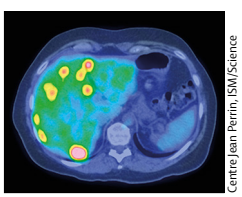
PET oestrogen receptor imaging: ready for the clinic?

Oestrogen signalling is a key component of normal mammary gland physiology and mediates breast cancer pathogenesis in most breast cancers.[1] Drugs targeting oestrogen-mediated growth in breast cancer, termed endocrine therapy, provide a key therapeutic strategy. The presence or absence of oestrogen receptors is a predictor of breast cancer response to endocrine therapy; documenting oestrogen receptor expression from a biopsy sample before initiating therapy is a well established clinical standard.[1] Although primary breast tumour biopsy is well developed, safe, and effective, tissue sampling and assays pose challenges in the metastatic setting. These challenges spurred investigators to develop non-invasive approaches for oestrogen receptor assay, including PET molecular imaging methods,[2,3] investigated by Sun Young Chae and colleagues in this issue of *The Lancet Oncology*.[4]

Among several early candidates for PET oestrogen receptor imaging probes, 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) emerged as the most successful agent.[2,3,5] ^{18}F-FES is a synthetic oestrogen labelled with the positron-emitting isotope ^{18}F and closely mimics oestradiol's binding affinities for oestrogen receptors and sex hormone-binding globulin.[2] ^{18}F-FES PET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imaging uses ligand quantities of less than 5 μg, leading to peak concentrations of 1 nM or higher, which are important to visualise regional binding of oestrogen receptors and to avoid physiological effects.[2,3] Previous studies[6,7] have shown that ^{18}F-FES PET can be done safely and with acceptable levels of radiation exposure, and that its uptake correlates with oestrogen receptor in-vitro expression, assayed by both radioligand binding-based assays and immunohistochemistry. Other early studies[8,9] showed that ^{18}F-FES uptake predicts response to endocrine therapy in the metastatic setting.

The small, often retrospective nature of previously published ^{18}F-FES PET studies does not meet the level of evidence needed to support clinical use. Chae and colleagues[4] take an important step in addressing this need in a prospectively designed and properly powered study of ^{18}F-FES PET diagnostic accuracy for oestrogen receptor expression compared with immunohistochemistry of tissue biopsy. Their study of 93 patients, of whom 85 (91%) completed ^{18}F-FES PET and had interpretable tissue oestrogen receptor assays, represents the largest study published so far comparing imaging to pathology in this setting. The results of the study support earlier evidence that show an association between ^{18}F-FES uptake and oestrogen receptor expression by Allred score, and it provides new data showing high inter-rates agreement (0·90 [95% CI 0·78–1·0]) between the qualitative interpretation of ^{18}F-FES PET and oestrogen receptor expression when analysed by experienced PET readers. The study also supports ^{18}F-FES safety and the ability to image oestrogen receptor expression at premenopausal circulating oestradiol concentrations.

Some limitations of the study by Chae and colleagues[4] include the use of Allred score for determining oestrogen receptor positivity rather than the 1% expression threshold recommended in American Society of Clinical Oncology—College of American Pathologists guidelines.[1] Moreover, some patients were exposed to aromatase inhibitors before ^{18}F-FES PET, and had low ^{18}F-FES PET uptake despite positive oestrogen receptor expression on biopsy for these patients. Although other studies have compared quantitative measures of ^{18}F-FES uptake to tissue assay, the present study's[4] primary aim uses the qualitative presence or absence of ^{18}F-FES uptake as the primary imaging measure; however, this measure has also been shown to be predictive of metastatic breast cancer response in some previous studies.[8,10] Overall, this well designed and carefully constructed study provides good evidence to support the use of ^{18}F-FES PET to measure oestrogen receptor expression in breast cancer.

What is next? The most clinically compelling application for ^{18}F-FES PET is to guide treatment selection for metastatic breast cancer, in which imaging can assess the level and heterogeneity of oestrogen receptor expression across the full burden of disease.[2,3,8,9] Notably, in the study by Chae and colleagues, only a small fraction of patients had metastatic oestrogen receptor expression differing from primary tumour expression (four [8%] of 51 patients with biopsy samples), similar to previous ^{18}F-FES PET studies[10] of newly metastatic breast cancer. However, other studies in heavily pretreated patients identified higher fractions of differences (as high as 0·4),[8] supporting the benefit of imaging in this population. Moving ^{18}F-FES PET to the clinic as a predictive assay requires the same level of evidence provided by Chae and colleagues' study—prospectively designed and properly powered studies establishing predictive accuracy in metastatic disease. One such trial, the ongoing ECOG-ACRIN EAI142 trial (NCT02398773) tests ^{18}F-FES uptake (both qualitative and prospectively defined quantitative measures) as a predictor of progression-free survival in first-line therapy for metastatic oestrogen receptor-positive breast cancer. Other multicentre trials are testing ^{18}F-FES PET predictive accuracy in Europe, including IMPACT (NCT01832051). Results from these studies, along with those of Chae and colleagues,[4] can provide the definitive evidence for the analytic validity, safety, and predictive accuracy of ^{18}F-FES PET in metastatic breast cancer needed to support regulatory approvals and payer coverage for this clinically valuable imaging approach.

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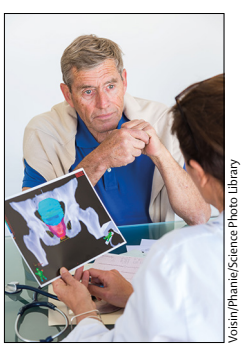
Effective and well tolerated: where do these drugs fit now?

In *The Lancet Oncology*, Bertrand Tombal and colleagues[1] describe the health-related quality of life (HRQOL) reported by participants in the PROSPER study, the main endpoints of which were published by Hussain and colleagues in 2018.[2] The trial identified a significant improvement in metastasis-free survival for men with non-metastatic, but castrate-resistant, prostate cancer who received enzalutamide in addition to standard androgen deprivation therapy, compared with those who received placebo. However, particularly for interventions designed to improve survival rather than achieve cure, there is a major trade-off that patients have to consider. What is the balance between improved survival versus extra toxicity or loss of HRQOL that the additional therapy can cause?

It is reassuring that the findings of Tombal and colleagues show no major detriment to HRQOL for men in the active treatment group. Although side-effects of androgen deprivation therapy can be severe for some individuals, this study—similar to our trial[3] investigating the effects of androgen deprivation therapy on HRQOL in men with non-curable prostate cancer—shows that castration status in the presence of relapsed or metastatic disease is compatible with a similar HRQOL to that of the equivalent general population. Whether this finding relates to psychological benefits of active intervention or good symptom control, which counterbalance any physical or psychological detriment of advanced disease, is a moot point. In the study by Tombal and colleagues, high HRQOL was maintained for roughly 2 years, which might well be attributed to slowing progression to bulky disease. Regarding specific HRQOL domains, enzalutamide increased time to deterioration in the pain severity composite index (from the Brief Pain Inventory Short Form) and in urinary symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire PR25). The Functional Assessment of Cancer therapy–Prostate (FACT-P) scale also showed longer time to deterioration in emotional wellbeing, the prostate cancer subscale, and the FACT-P total score. A longer time to deterioration of symptoms, associated with a delay in development of local or metastatic disease, is an important contributor to maintaining better functional status and overall HRQOL.

Although all men continued taking standard androgen deprivation therapy in this study, the addition of enzalutamide led to increased hormone-therapy related symptoms, which is possibly consistent with the different anti-androgen mechanism of the drug. However, the difference was not clinically significant between the groups in PROSPER. Although the incidence of grade 3 adverse events reported in PROSPER[2] was relatively high (31% enzalutamide *vs* 23% placebo), this did not appear to translate to a detriment in HRQOL.

The crucial question now is at which stage and in what sequence this drug, and others in its class (such as apalutamide, which has very similar outcomes in this patient cohort,[4] and darolutamide [NCT02200614, which is still active]) should be used most appropriately. Patients with castration-resistant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