final efficacy of trastuzumab, we could consider that trastuzumab alone for some patients might provide enough efficacy, but for other patients concomitant administration with other anticancer agents might be necessary. Furthermore, use of HER2-targeting antibody–drug conjugates might be the best option for some patients. The complexity of identifying the optimum option in clinical practice seems to be a huge challenge.

Several new HER2-targeting antibody–drug conjugates with different linkers and payloads are in clinical development, with promising results. In *The Lancet Oncology*, Udai Banerji and colleagues report the results of a phase 1, first-in-human, dose-escalation and dose-expansion trial of trastuzumab duocarmazine (trastuzumab covalently bound to a linker drug containing duocarmycin).[7] After binding to HER2 and internalising, the linker is cleaved in the lysosome by proteases that release the active toxin. Such proteases can exert activity extracellularly through secretion from malignant cells. This extracellular cleavage of the linker drug might, therefore, induce a cell-killing effect that is not HER2-mediated. In Banerji and colleagues' study, trastuzumab duocarmazine showed impressive clinical antitumour effects in several types of cancers, including breast cancer with varying expression of HER2. For example, in the dose-expansion phase using the recommended phase 2 dose of 1·2 mg/kg, 16 (33%, 95% CI 20·4–48·4) of 48 assessable patients with HER2-positive breast cancer achieved an objective response (all partial responses), as did six (40%, 16·3–67·6) of 15 patients with low expression of HER2 and hormone receptor-negative breast cancer. The drug also showed an acceptable tolerability profile, with few grade 3–4 adverse events and no treatment-related deaths in the dose-expansion phase.

The encouraging results from this first-in-human study with this new drug help to support the notion that the family of antibody–drug conjugates could serve as new agents with many modalities of anticancer activity, allowing for multiple new strategies in the treatment of cancer.

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Underdiagnosis is the main challenge in breast cancer screening

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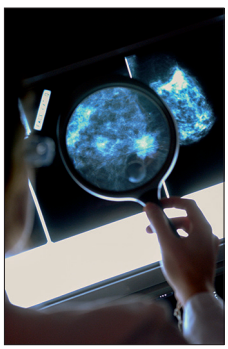
In *The Lancet Oncology*, Sepideh Saadatmand and colleagues[1] present the results of a multicentre, randomised, controlled trial that compared the performance of MRI plus mammography with that of mammography alone for breast cancer screening in women aged 30–55 years with familial risk of breast cancer, but without a documented mutation in a breast cancer susceptibility gene. Participants were randomly allocated to receive either annual MRI and clinical breast examination plus biennial mammography (MRI group) or annual mammography and clinical breast examination (mammography group). To my knowledge, this is the first study of MRI screening that used a randomised design. Therefore, this study not only allows for comparison of respective cancer detection rate and diagnostic accuracy, as did all previous studies[2–5] on the screening performance of MRI versus mammography, but also provides important outcome measures useful to evaluate the oncological implications of the respective screening methods. Although the study follow-up time was still too short to assess the impact of each screening

method on breast cancer mortality, such analyses will be possible and will be done a decade from now. For the time being, the authors report on tumour stage at diagnosis (eg, cancer size and lymph node status) as an established proxy for the effects of screening on breast cancer mortality and the need for adjuvant chemotherapy.

The results are compelling—Saadatmand and colleagues found that breast cancer detection almost tripled in the MRI group compared with the mammography group, similar to previous intraindividual comparison trials.[2–5] More importantly, they observed a significant tumour stage shift in the MRI group: cancers diagnosed in the MRI group were substantially smaller (median size 9 mm [5–14] *vs* 17 mm [13–22]; p=0·010), and less frequently node positive (four [17%] of 24 invasive cancers *vs* five [63%] of eight; p=0·023). Of note, when an improved, more sensitive screening method is first introduced, the results of the first (prevalence) screening round will always yield a mixture of old cancers (ie, pre-existing cancers that have gone undetected by the standard screening method and could have had time to cause metastases) and new cancers (ie, cancers that still are, and thus can be detected, at an early stage). To measure the effect of a new screening method on tumour stage at diagnosis, the results of subsequent (incident) screening rounds are more informative than those of the first round. Thus, at the incident screening rounds performed by Saadatmand and colleagues, the tumour stage shift between MRI and mammography screening becomes even more apparent, with two node-positive cancers (11%) of 18 invasive cancers in the MRI group compared with five (63%) of eight in the mammography group (p=0·014) and no interval cancers observed.

Despite accurate randomisation, the number of invasive cancers remained three times higher in the MRI group (24 in the MRI group and eight in the mammography group) until the end of the study period, suggesting that potentially 16 women in the mammography group will have undetected invasive breast cancer. This excess incidence of cancers in the MRI group could considered overdetection of inconsequential disease. It is possible, however, that the excess cancer detection in the MRI group does not correspond to overdetection, but reflects successful early diagnosis of prognostically significant cancer. This interpretation is more plausible because of the younger age of women included in this study; because of the higher incidence of larger, node-positive tumours observed in the mammography group; and because of the further reduction of node-positive tumours observed in incident versus prevalence screening rounds in the MRI group. The cancers detectable by MRI might not represent self-limiting, overdetected disease, but will grow and cause lymph node metastases long before they become detectable on mammography or become clinically obvious as interval cancers.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Rather than overdiagnosis, the higher cancer incidence in the MRI group is attributable to the fact that it is impossible for a less sensitive screening programme (mammography) to catch up with a more sensitive screening programme (MRI). Each successive year, new cancers develop and enter the sojourn phase; the greater sensitivity and greater lead time of MRI will always contribute to a higher incidence of breast cancer in the MRI group until screening is discontinued and sufficient long-term clinical follow-up is available. This follow-up will have to be longer than the 5 years covered by Saadatmand and colleagues, since the MRI-detectable cancers in the mammography group that were undetectable by mammography did not progress to become clinically apparent as interval cancers in that time. This observation suggests that breast cancers can remain undetected by mammography and remain clinically silent for possibly many years, and yet could be clinically relevant cancers that cause metastases during this clinically silent phase.[6]

In view of the devastating consequences of a late diagnosis of cancer, avoiding underdiagnosis should be deemed more important than avoiding overdiagnosis. We can alleviate much of the adverse consequences of overdiagnosis by providing patient information and appropriate selection of management.[7] However, we cannot make up for the lethal consequences of underdiagnosis. Taken together with the fact that breast cancer continues to represent a major cause of cancer-related deaths in women (regardless of whether they participate in mammography screening), the burden of proof should be reversed. Rather than assuming that most additional cancers detected in the MRI group reflect overdiagnosis

until proven otherwise, we should assume that not detecting these cancers by mammographic screening leads to harm.

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Nanoparticle augmentation of radiotherapy in sarcoma

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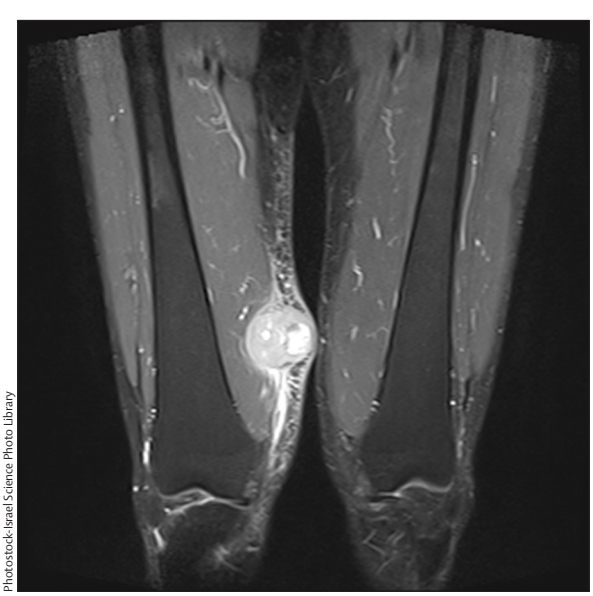
Soft-tissue sarcomas represent a heterogeneous group of mesenchymal tumours that have classically been defined by their tissue of origin. In the past few years, high-throughput efforts have characterised the genomic and epigenomic landscape of these malignancies, uncovering molecular mechanisms that underlie diverse biological properties and clinical behaviours.[1] However, despite this more comprehensive understanding, surgical resection remains the cornerstone of treatment for nearly all subtypes of extremity soft-tissue sarcoma. Whereas limb-sparing surgery alone has been associated with unacceptable levels of local recurrence,[2] surgery plus neoadjuvant or adjuvant radiotherapy has become the dominant approach for improving local control, largely obviating the need for amputation when gross negative resection margins can be achieved.[3] With the utility of radiotherapy well established, more recent efforts have focused on augmentation strategies to achieve optimal oncological outcomes in soft-tissue sarcoma of the extremities.



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In *The Lancet Oncology*, in a non-blinded, multicentre, randomised, controlled, phase 2–3 trial (Act.In.Sarc), Sylvie Bonvalot and colleagues tested a first-in-class nanoparticle, NBTXR3, as a radiotherapy enhancer for patients with non-metastatic, locally advanced soft-tissue sarcoma of the extremity or trunk wall.[4] NBTXR3 comprises a negatively charged phosphate coating, which permits uptake by tumour cells, and a core of inert, crystalline hafnium oxide (HfO_2), which is activated by external-beam radiotherapy to generate oxygen free radicals and augment the cell destruction induced by radiotherapy alone.[4] Previously, radioenhancement with NBTXR3 was shown by means of in-vitro cell line models and in-vivo tumour xenografts;[5] in their previous phase 1 trial, Bonvalot and colleagues showed its clinical activity in human patients,[6] providing equipoise for this subsequent randomised phase 2–3 trial.

Patients in this study were randomly assigned to receive either preoperative external-beam radiotherapy alone or following the administration of intratumoral NBTXR3. Patients in both groups received either intensity-modulated radiotherapy or 3D conformal radiotherapy to a dose of 50 Gy, followed