hormone receptor-positive cancer, the survival curves flatten out. Thus, compared with patients with hormone receptor-positive breast cancer, those with hormone receptor-negative disease might actually have fewer breast cancer cells persistent in their marrow that can be affected by bisphosphonate or denosumab therapy.

This study of denosumab, in addition to many randomised controlled trials of bisphosphonates, indicates that adjuvant dosing with these therapies is generally safe, leads to a substantial reduction in skeletal events and an improvement in disease-free survival, and should be part of almost all adjuvant regimens for postmenopausal hormone receptor-positive breast cancer.

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I declare no competing interests.

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Hypofractionated radiotherapy after mastectomy: a new frontier

Hypofractionation is an elegant approach that promises to help to contain the costs of cancer care and mitigate financial toxicity. For selected patients with breast cancer, considerable evidence from large randomised trials with long follow-up, primarily in the setting of breast conservation, supports the equivalent efficacy and toxicity of shorter courses of hypofractionated whole-breast radiotherapy (such as 42·5 Gy in 16 fractions[1] or 40 Gy in 15 fractions[2]) than conventional courses, which required 5 or more weeks of daily treatments. The transformative impact of hypofractionation in the setting of breast conservation[3] has also motivated investigation of hypofractionation after mastectomy.[4] In *The Lancet Oncology*, Shu-Lian Wang and colleagues[5] report the 5-year outcomes of a randomised, non-inferiority, open-label, phase 3 trial in China that compared postmastectomy hypofractionated radiotherapy (43·5 Gy in 15 fractions over 3 weeks) with conventional treatment (50 Gy in 25 fractions over 5 weeks).

One reason that trials are needed specifically in patients who have undergone mastectomy relates to the more advanced stage of patients typically treated with postmastectomy radiotherapy. In the trial by Wang and colleagues, eligibility criteria included at least four positive lymph nodes or T3–4 tumours. Although the radiobiological properties of the individual cells causing these tumours might not necessarily be expected to diverge from those in patients with earlier stages of the disease, who constituted the bulk of patients enrolled in clinical trials establishing hypofractionation after breast-conserving surgery, the number of tumour clonogens remaining after surgery and systemic therapy in the breast or regional nodal basins might be higher in patients such as those enrolled in the trial by Wang and colleagues than in those with early-stage disease. In this context, the fact that no difference in 5-year cumulative incidence of locoregional recurrence was observed is reassuring (8·3% [90% CI 5·8–10·7] in the hypofractionated radiotherapy group *vs* 8·1% [90% CI 5·4–10·6] in the conventional fractionated radiotherapy group; absolute difference 0·2%, 90% CI –3·0 to 2·6; hazard ratio 1·10, 90% CI 0·72 to 1·69; p<0·0001 for non-inferiority). Nevertheless, the 8% incidence of locoregional recurrence at 5 years is already substantial, presumably because of the inclusion of patients with high-risk breast cancer. Therefore, further follow-up will be

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Published Online
January 30, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30062-2

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essential to confirm long-term equivalence of disease control in this setting, in which patients derive not only a substantial reduction in locoregional recurrence, but also a meaningful survival benefit from adjuvant radiotherapy.[6]

Another important consideration is toxicity, with particular concerns that a higher dose per treatment fraction might be problematic in the setting of regional nodal irradiation.[7] Patient-reported and physician-assessed normal tissue effects on the arm and shoulder were reported among 864 patients who received regional nodal irradiation in the British START trials.[8] Although patients receiving a 42·9 Gy schedule as compared with 50 Gy in the START pilot trial did have a higher occurence of physician-assessed shoulder stiffness (hazard ratio 3·07, 95% CI 1·62–5·83), no such difference was observed for the hypofractionated schedules used in the subsequent START-A and START-B trials.[8] In the study by Wang and colleagues, no brachial plexopathy was observed, and frequencies of lymphoedema and shoulder dysfunction were also reassuringly low, with less than 1% frequency of grade 2 toxicity for both events and no significant difference between treatment groups. However, toxicity assessments reported in this study were limited to measurements on the Common Terminology Criteria for Adverse Events and the Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer late radiation morbidity scales; assessment of patient-reported outcomes or with more sensitive approaches such as plethysmography or perometry to evaluate oedema or robot-assisted measures of shoulder function merit consideration in future trials. Moreover, trends that did not achieve statistical significance for a possible increase in lung toxicity in patients receiving hypofractionation in the study by Wang and colleagues merit further follow-up and evaluation in additional trials.

Techniques used for postmastectomy radiotherapy often increase the dose of radiation to the skin compared with adjuvant whole-breast radiotherapy after breast-conserving surgery, and most patients in the trial by Wang and colleagues received electron radiation with bolus. The only significant difference observed was reduced severity of acute skin toxicity in patients treated with hypofractionation, which is reassuringly consistent with observations in the setting of breast conservation that acute dermatitis seems to be less severe with hypofractionation than with conventional radiotherapy.[9]

Finally, differences in techniques between patients treated on the trial done in China and those treated in other regions of the world justify additional research. For example, in Wang and colleagues' study, most patients received two-dimensional radiotherapy rather than three-dimensional radiotherapy or intensity-modulated radiotherapy. Moreover, treatment did not include the internal mammary region (or axilla), and only 55% of patients with HER2-positive cancers were treated with trastuzumab, with meaningful implications for the ability to extrapolate the findings of the current study to patients treated differently, particularly with regard to cardiac outcomes. Breast reconstruction was an exclusion criterion for the trial, and further research in that setting is important, in view of the known effect of radiotherapy on breast reconstruction outcomes[10] and the consequences for quality of life among survivors.

Trials specifically focused on reconstruction outcomes after moderate hypofractionation are underway in the USA (Alliance 221505 [NCT03414970] and FABREC [NCT03422003]). Together with other ongoing trials,[8] this research will hopefully advance our understanding in the near future, and one day, hypofractionated regional nodal irradiation might be considered a standard approach worldwide. For now, we owe our gratitude to Wang and colleagues for their illuminating work in an area of great ongoing interest and investigation.

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RJ reports grants from the US National Institutes of Health, Doris Duke Charitable Foundation, Komen Foundation, the Greenwall Foundation, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium; personal fees from Vizient (consulting) and Amgen (consulting); and stock options in Equity Quotient.

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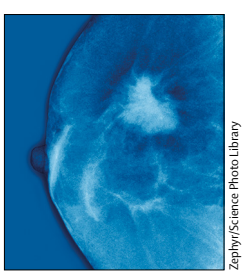
Endpoint selection in HER2-positive early breast cancer



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Published **Online** January 29, 2019 http://dx.doi.org/10.1016/S1470-2045(18)30779-4

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Compared with definitive endpoints such as overall survival, the use of intermediate endpoints such as disease-free survival improves the efficiency of trial design, resulting in studies requiring smaller sample sizes and shorter follow-up. In oncology, the validation of intermediate endpoints as adequate surrogates of definitive outcomes is challenging.[1] In early-stage breast cancer, evidence supporting the surrogacy of intermediate endpoints and definitive outcomes such as overall survival is scarce. Disease-free survival is a composite endpoint typically comprising locoregional and distant recurrences as well as new contralateral breast cancers, second cancers, and death from any cause. Disease-free survival has been used frequently as a primary endpoint in trials of early-stage breast cancer despite scarce data supporting its adequacy as a surrogate for overall survival.

In an Article in *The Lancet Oncology*, Everardo Saad and colleagues[2] aimed to validate disease-free survival as a surrogate for overall survival in patients with HER2-positive, early-stage breast cancer using individual patient data from several large randomised trials of HER2-targeted therapy. After a systematic review, they identified eight trials on this topic with available data (21 480 patients, 3233 deaths, and 5371 disease-free survival events). The availability of individual patient data allowed the investigators to explore both trial-level and patient-level surrogacy of disease-free survival. Results showed that disease-free survival correlated strongly with overall survival at the trial level (R_2=0·75) and also predicted for the net benefit of treatment at the patient level (r_s=0·90). The inclusion of both trial-level and patient level correlation is a major strength of the analysis and provides robust support for the adequate surrogacy of disease-free survival and overall survival in HER2-positive, early-stage breast cancer. However, before disease-free survival is embraced as the optimal primary endpoint in this setting, several limitations of the analysis need to be considered.

The surrogacy of disease-free survival was less strong among studies with small numbers of events. This aspect is concerning, because during the past decade the frequency of events in clinical trials has fallen substantially in HER2-positive, early-stage breast cancer. For example, the 3-year disease-free survival in the trastuzumab group of the 2005 combined analysis of the National Surgical Adjuvant Breast and Bowel Project B-31 and North Central Cancer Treatment Group N9831 trials was 87·1%.[3] By contrast, in the 2017 report of the APHINITY trial, the proportion of patients in the trastuzumab-only group with events was almost halved, with a 3-year invasive disease-free survival of 93·2%.[4] In a lower-risk cohort of predominantly lymph node-negative, HER2-positive breast cancer, the 7-year disease-free survival was 93·3%.[5] Whether disease-free survival will retain robust surrogacy in a more contemporary setting with low event frequencies is uncertain.

Another important consideration is that despite a strong estimate for treatment-level association between disease-free survival and overall survival, the confidence intervals for estimates were wide. Whereas subgroup data defined by lymph node status and hormone receptor status yielded similar results, there was a weaker association in hormone receptor-positive disease than in hormone receptor-negative disease, which is unsurprising. Among HER2-positive breast cancers, there is a well-established difference in the timing of disease-free survival events between