Cumulative burden of disease: a relevant measure of the late side-effects of cancer treatment

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Children, teenagers, and young adults diagnosed with Hodgkin's lymphoma a decade ago had an excellent prognosis, with 10-year overall survival above 90%.¹ For those diagnosed today, outcomes should be even better through efforts to prevent side-effects by reducing treatment as far as possible without compromising cure. In *The Lancet Oncology*, a report by Nickhill Bhakta and colleagues² from the St Jude Lifetime Cohort Study (SJLIFE) shows that, in 10-year survivors of Hodgkin's lymphoma diagnosed between 1961 and 2004 who reached at least 18 years of age, treatment-related cardiovascular morbidity ranged from subclinical to life-threatening, with new manifestations continuing to appear during several decades of follow-up. In 670 participants from SJLIFE, at 50 years of age, the cumulative incidence of survivors experiencing at least one grade 3–5 cardiovascular condition was 45.5% (95% CI 36.6–54.3), compared with 15.7% (7.0–24.4) in age and sex frequency-matched community controls. These risks are known to depend on the treatments given (chemotherapy or radiotherapy) and are also strongly affected by age, sex, lifestyle factors (eg, smoking and exercise), and other cardiovascular risk factors (eg, hypertension and diabetes). The strengths of SJLIFE are the large size of the cohort for a relatively rare disease such as Hodgkin's lymphoma and the long-term prospective follow-up in the St Jude Long-term Follow-up Study, with direct clinical assessment possible for many patients.

Bhakta and colleagues² propose a novel method for quantifying the total cardiovascular burden of young survivors of Hodgkin's lymphoma treated in the past by considering all the cardiovascular conditions observed so far in the patient's lifetime. Their approach might be relevant not just for this example but also for many other cancer diagnoses and late side-effects. Furthermore, assessment of the continuing cumulative burden of treatment-related morbidity is relevant not only from a clinical viewpoint but also from a health economics perspective. A patient experiencing an asymptomatic grade 2 condition as a first cardiovascular event, followed years later by grade 3 cardiomyopathy, will see their life expectancy and quality affected much more by the latter than the former.

In addition to providing a useful measure of the consequences so far of treatments given in the past, the information contained in cohorts with long-

term follow-up remains the best available evidence that we have on which to base predictions of the future risks of late side-effects from presently used treatment strategies. Inevitably, the treatments received by the individuals in such cohorts are outdated. For example, in the St Jude Cohort, patients received old-fashioned radiotherapy, using high prescribed doses and large radiation fields, resulting in substantial doses to the heart. However, nowadays patients with Hodgkin's lymphoma receive mediastinal irradiation only if there is evidence of mediastinal disease and, even then, average heart doses would be about 7 Gy as opposed to doses of above 15 Gy for most of the St Jude cohort patients.^{3 and 4} Similar considerations apply to cardiotoxic chemotherapy agents. Although doxorubicin remains in common use, the number of cycles and cumulative dose are now adapted to fit the patient's disease risk profile and response to treatment, which is often assessed using functional imaging.⁵

To assist with predicting future risk from contemporary radiotherapy regimens with the generally lower cardiac doses used today, the radiation dose–response relationships for different heart diseases that have recently been derived might be helpful.^{6, 7 and 8} However, these dose–response relationships are based just on the first cardiovascular event and they vary both in slope and shape between different heart diseases (valvular heart disease, ischaemic heart disease, and heart failure). Further work would therefore be needed to derive an appropriate dose relationship for the cumulative burden of all cardiac morbidity for use in a prediction model. If these challenges can be overcome, the cumulative burden method could provide a valuable way of predicting the future risks of late effects when comparing treatment strategies to decide the best risk–benefit balance for today's patients with cancer. Predictions based on the cumulative disease burden might also provide an appropriate method for assessing the socioeconomic cost of progressive chronic heart conditions when evaluating the potential effect of using novel, and hopefully less toxic, cancer treatments. However, some of the new treatments proposed are expensive. For example, proton radiotherapy has been suggested as an alternative to standard photon-based radiotherapy for some patients because it promises to reduce the exposure of healthy tissue and hence the risk of late side-effects, including cardiovascular disease and second malignancies. As of today, proton radiotherapy is still substantially more expensive than photon-based radiotherapy and access remains limited either by the number of proton treatment facilities in the patient's country or by reimbursement issues.⁹ Similarly, new systemic treatments, such as brentuximab vedotin and immune checkpoint inhibitors, which can be used to reduce the need for radiotherapy, are prohibitively expensive for many health-care systems. Prioritising access to these treatments requires reliable clinical data on their effectiveness and relevant predictions of the future risks they might present (or avoid) to quantify the impact for each individual patient.

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