and (2) an intervention (medical or nonmedical) that, if canceled, will generate the resources necessary to implement the new treatment, and whose cancellation will reduce community well-being by less than the incremental gain expected from the new treatment.13-15 Until both conditions are met researchers should not infer cost effectiveness or “value for the money” for particular therapies—a result prematurely suggested by van den Brink et al in their economic evaluation of PRT and rectal cancer.

In their recent response, the authors also state that “data on cost effectiveness are then one of many pieces of information... that might be weighed”. In other words, cost-effectiveness analysis is about efficiency only and does not involve equity considerations. However, assuming that efficiency and equity considerations are separable is wrong.16-19 For example, in the analysis presented by the authors they assumed that a QALY is a QALY regardless of who gains it or who loses it. This is an equity assumption. If this equity assumption does not reflect the one held by a decision maker, then the results of the analysis are of no use to the particular decision maker.

We do not negate the numerous useful insights presented by van den Brink et al in their paper, or the importance of PRT in the treatment paradigm for some patients undergoing rectal cancer surgery. But in the era of TME it is not yet decided which patients should receive radiotherapy, an observation driven home by the original results of the Dutch TME Trial. Moreover, we encourage researchers performing cost-effectiveness analyses to either consider the opportunity costs of implementing the interventions analyzed, or to avoid concluding that such interventions are cost effective.

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Cardiac Toxicity of Mediastinal Radiotherapy: Which Are the Critical Structures?

To the Editor: We read with great interest the recent article by Adams et al1 on late cardiovascular toxicity in patients treated with mediastinal radiotherapy for Hodgkin’s disease between 1970 and 1990, showing by echocardiography and ECG a high prevalence of significant valvular defects (42%), conduction defects (75%), and findings suggestive of restrictive cardiomyopathy (22%). All radiation treatments were performed as mantle technique with a median dose of 40 Gy, using equally weighted anterior and posterior 4- or 6-MV photon beams.

The present study, as have previous reports,2,3 raises the question of which cardiac structures are causative of the above abnormalities and may benefit from protection in future radiotherapy concepts. Such protection can be achieved by limiting the irradiated volume4 or technical advances in delivery of radiotherapy.5 Based on our experience from an ongoing analysis of late cardiac toxicity in Hodgkin’s disease survivors treated between 1978 and 1985,
we would like to comment on some details of former and current principles of radiotherapy planning and delivery that are of relevance for an association of radiation dose to particular cardiac structures and specific late effects.

The authors state that the actual dose to particular cardiac structures in their patient cohort is unknown. We think that it is difficult but not impossible to reconstruct the radiation dose received by specific cardiac structures during mediastinal radiotherapy in the 1970s and 1980s. Previous investigators of cardiac radiation damage have either estimated the heart portion exposed to radiotherapy from twodimensional simulation films and calculated the dose within this area at a defined depth or attempted three-dimensional dose reconstruction.6 As part of our ongoing study of cardiac toxicity, our group has reconstructed dose distributions of patients treated between 1978 and 1985 by matching simulation films of previously treated patients to digital radiographic reconstructions of computed tomography (CT) scans of current patients with comparable thoracic anatomy. Matching these two imaging modalities on the basis of heart contours using state-of-the-art radiotherapy treatment planning software permits calculation of radiation dose to previously contoured heart structures in the test patient. Additionally, the ability of cardiac magnetic resonance imaging (CMRI) to detect myocardial, valvular, and coronary disease,7 opens up the possibility to generate axial images of the heart anatomy and pathology in previously irradiated patients and reconstruct the radiotherapy technique directly in these magnetic resonance imaging (MRI) scans. Although the density information provided by CT is usually required for calculation of radiation dose distribution, use of an MRI study alone for radiotherapy planning is possible.8

Secondly, it should be noted that a large proportion of Hodgkin’s disease patients treated worldwide in the 1970s and 1980s were irradiated with less sophisticated techniques than employed at the Harvard Joint Cancer for Radiation Therapy during this period, as described by Adams et al. The anterior/posterior opposing-beam mantle technique has evolved from techniques using an anterior mediastinal field only, with or without boost dose to the posterior mediastinum, often using lower energies with resulting overdosage near the surface, corresponding to anterior portions of the heart. In our patient series, three-dimensional dose reconstruction of anterior mantle field technique using cobalt-60 (mean energy, 1.25 MV) typically resulted in relative maximum doses in the anterior heart region of 150% (without boost) and 120% (with boost). Related to a median prescribed mediastinal dose of 40 Gy, this corresponds to 60 Gy and 48 Gy, respectively, in the anterior cardiac structures, in particular the right atrium, the right ventricle, and the right coronary artery. In a recent review, radiation tolerance doses for several late effects including pericarditis, cardiomyopathy, coronary artery disease, and valvular disease have been estimated to be between 30 and 40 Gy.9 In fact, a high risk of complications (eg, severe constrictive pericarditis) has been observed with such anterior mantle field technique.10 Not only the treatment of the mediastinum through an anterior beam only but also the treatment with opposing photon beams of 4 to 6 MV energy, as described in the present report, can result in significant overdosage of the anterior heart structures, depending on the anterior-posterior diameter of the patient. Computer-calculated doses in the anterior cardiac region were described as being 2.5% to 6% higher than the manually calculated dose used for treatment prescription.11 Interestingly, the group of Adams et al identified an RSR pattern in the right precordial lead as the most common conduction defect, occurring in 60% of patients, and concluded that the most anterior structures of the intracardiac conduction system were at most risk for fibrosis from mediastinal radiotherapy, a finding that may be explained by the presence of radiation dose peaks in this area.

In summary, we would like to encourage attempts to link toxicity data to the anatomic radiation dose distribution within the heart and draw attention to a possible overdosage to anterior heart structures even with current mediastinal irradiation techniques.

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In Reply: We appreciate the comments by Vordermark et al in reply to our article “Cardiovascular Status in Long-Term Survivors of Hodgkin’s Disease Treated With Chest Radiotherapy.”

We agree that it would be ideal to have dosimetry calculated for specific cardiac structures to quantify their region-specific dosage so that the sensitivity of various tissues can be estimated. The data are not available to address this retrospectively.

There are two implications of data concerning cardiac abnormalities in patients after radiotherapy. First is the issue related to what abnormalities are likely to be present in patients treated in the past, when the clinician generally will not have access to the sort of site-specific dosing that can be calculated today, and which of those cardiac abnormalities persist on long-term follow-up. The published data are useful in addressing this issue, and in fact a review such as ours is probably the only way to address this issue. Second is the issue of determining the site-specific radiosensitivity of cardiac structures to allow assessment of risk in current patients and to optimize protocols moving forward. Our data set is not helpful in the latter regard, and it is probably unlikely that many retrospective reviews will contain the data to accurately address this issue while also addressing cardiac issues in detail. Both sets of issues are important but are really quite different and almost certainly must be addressed by different study designs.

Our experience suggests it may not be possible to shoehorn both types of study designs to address the latter issues, as is suggested by Vordermark et al. We have had great difficulty in retrospectively producing dosimetry calculations while performing at least two projects. Problems we have run into include missing data on height and weight at treatment and missing scout films. Many institutions in the United States also have a policy of disposing of medical records and films after a certain time period has elapsed without a patient visit; thus our concern about the feasibility of combining both factors into studies of previously treated patients.

We appreciate the comments by Vordermark et al on linking toxicity data to anatomic radiation doses distribution and the possible overdosage to anterior heart structures, even with current mediastinal irradiation techniques.

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The Impact of Hormone Replacement Therapy on the Incidence of Breast Cancer in Norway

To the Editor: In a letter to the Editor of the Journal of Clinical Oncology, Hemminki et al analyzed the effects of