our study, fluucytosine levels were not monitored, but patients had regular blood counts and electrolyte and creatinine measurements. We showed that in a resource-constrained setting, in combination with amphotericin B, fluucytosine can be used safely and increases both survival and fungal clearance. Patients receiving the combination treatment had similar rates of adverse events as those receiving amphotericin B monotherapy. Fluconazole combined with fluucytosine, recommended as second-line treatment by the WHO, is an attractive treatment for cryptococcal meningitis because of ease of administration. Fluconazole is cheaper than amphotericin B and has a favorable toxicity profile. However, amphotericin B–sparing combinations consistently show lower rates of yeast clearance from cerebrospinal fluid — early fungicidal activity — than those containing amphotericin B. Bicanic and colleagues found that early fungicidal activity was closely correlated with survival. Therefore, in addition to improving access to fluucytosine, it is imperative that stakeholders work to improve the availability of, and the capacity to safely administer, amphotericin B.

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Since publication of their article, the authors report no further potential conflict of interest.


DOI: 10.1056/NEJMc1305981

Ischemic Heart Disease after Breast Cancer Radiotherapy

TO THE EDITOR: In their analysis of ischemic heart disease in a Nordic cohort of survivors of breast cancer, Darby et al. (March 14 issue) observe a significant excess relative risk associated with radiotherapy, which is concordant with the risks seen in other radiotherapy-treated groups (Table 1). This finding suggests that the mean dose to the heart is the most relevant metric for predicting radiation-associated ischemic heart disease. The findings about the radiation risks also agree with those of a recent meta-analysis of low-to-moderate radiation exposure (Table 1), implying little sparing effect of low doses and protracted radiation exposures. The comprehensive analysis by Darby et al. of other risk factors for ischemic heart disease suggests minimal interaction with radiogenic risk, again consistent with (more limited) observations reviewed elsewhere.

All these findings suggest that there is excess ischemic heart disease associated with high (therapeutic) and low (diagnostic) doses of radiation. Although there has been concern about increased risks of cancer associated with computed tomographic (CT) angiograms and coronary-artery calcium scans, the evidence presented by Darby et al. and elsewhere strongly suggests that clinicians should also be concerned with cardiovascular morbidity and should limit the dose of radiation affecting the heart.

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No potential conflict of interest relevant to this letter was reported.

In their study on the risk of ischémie heart disease among women after radiotherapy for breast cancer, Darby et al. found that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray. In the definition of major coronary events, death from ischemic heart disease was included according to specific codes. However, the deaths of patients with valvular disease, specifically those with aortic valvular disease, cannot be excluded. It has been shown that valvular disease, especially aortic stenosis, is a well-recognized complication of radiation therapy.2-3

The following findings could support the role of valvular disease in deaths from ischemic causes. The percentage increase per gray in the rate of major coronary events and the percentage increase according to time since radiation exposure in the same events were similar among women with and those without risk factors for coronary artery disease. Thus, the effect of val-

| Table 1. Estimated Excess Relative Risk of Heart Disease in Groups Exposed to Radiation.∗ |
|--------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|
| Study                                             | Average Dose to Heart Sv (range) | Cohort          | End Point                        | Excess Relative Risk (95% CI)† |
| High-dose exposure                                |                                 |                 |                                |                                |
| Nordic breast cancer case–control study1          | 4.9 (0.03 to 27.72)              | 963 case patients and 1205 controls | Ischemic heart disease‡                | 0.074 (0.029 to 0.145)          |
| French–U.K. childhood cancer study2               | 11.1 (<1 to >15)§                | 4122 persons with survival at 5 yr | Death from any cardiovascular disease | 0.6 (0.2 to 2.5)                |
| U.S. Childhood Cancer Survivor Study3            | NA (<5 to >35)††                  | 14,358 patients | Myocardial infarction             | 0.04 (−0.02 to 0.10)¶            |
| Peptic ulcer study2                                | 1.01 (0.0 to 6.20)               | 3600 patients, with 76,571.7 person-yr of follow-up | Death from coronary heart disease‖ | 0.102 (0.039 to 0.174)          |
| Low- or moderate-dose exposure                     | <0.5 (0 to 5.92)                | 451,386 patients** | Ischemic heart disease or death from ischemic heart disease‡‡ | 0.10 (0.04 to 0.15)††            |

* Adapted from Little et al.4 Moderate or high exposure was defined as a mean exposure of the heart to 0.5 Sv or more, and low or moderate exposure was defined as a mean exposure of the heart to less than 0.5 Sv. Unless otherwise specified, all end points are for morbidity. CI denotes confidence interval, and NA not available.† Values shown are for the excess relative risk per sievert of radiation exposure.‡ Ischemic heart disease was defined with the use of International Classification of Diseases, 10th Revision, codes I20–I25.§ The value represents the mean dose to the heart in 21 persons who died of cardiovascular disease.¶ The estimate was derived by fitting a linear model by weighted least squares, applied to the aggregate data provided in Table 4 of Mulrooney et al. We assumed average cardiac doses of 0 Gy, 2.5 Gy, 10 Gy, 25 Gy, and 40 Gy in the respective groups with the following specified ranges of cardiac doses: 0 Gy, more than 0 to less than 5 Gy, 5 Gy or more to less than 15 Gy, 15 Gy or more to less than 35 Gy, and 35 Gy or more.‖ Coronary heart disease was defined with the use of International Classification of Diseases, 8th Revision, codes 410–414.** The value for the meta-analysis excludes the numbers in three cohorts (Laurent et al., 2010; Muirhead et al., 2009; and Yamada et al., 2004) because of overlap with other studies.‡‡ The value was calculated with the use of a random-effects model; as calculated with the use of a fixed-effects model, the value was 0.10 (0.05 to 0.15).
vular disease on the rate of death from ischemic causes needs to be further analyzed in the study by Darby et al.

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No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1304601

TO THE EDITOR: Darby et al. assess rates of cardiovascular events and death in a large, well-studied cohort. However, we question the individual estimates of dose, because their virtual simulation and planning reconstructed “each radiotherapy regimen on the CT scan of a woman with typical anatomy” with the use of the calculations of a single case as the reference.1

Table 1 shows the results of a study comparing dosimetry of CT-based simulation in the supine and prone positions for 400 patients with breast cancer. Considerable anatomical variability is reflected by the volume range of the organs at risk included in the treatment fields of breast radiotherapy.3 The in-field volume receives the full dose and is an excellent surrogate for normal tissue exposure to breast radiotherapy.3 The prone position enabled lower mean doses to the heart and lung, as compared with the supine position.3 In the same group of patients, we found that the prone position limits the mean dose to the heart to approximately 1 Gy for patients with left-sided breast cancer and 0.6 Gy for those with right-sided breast cancer.3 Individual CT-derived dose distributions are warranted in order to prove associations with cardiovascular events.4

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DOI: 10.1056/NEJMc1304601

| Table 1. Volume Results for In-Field Heart and Lung in 400 Patients with Breast Cancer, According to Position for Radiotherapy.* |
|---|---|---|
| In-Field Organ | Supine Position | Prone Position |
| | Mean (95% CI) | Range | Mean (95% CI) | Range |
| cubic centimeters of in-field volume |
| Left-sided breast cancer | | | | |
| Heart | 8.75 (6.53–10.97) | 0–134.75 | 1.25 (0.66–1.84) | 0–41.02 |
| Lung | 98.58 (88.77–108.39) | 0–334.57 | 8.73 (5.42–11.74) | 0–228.27 |
| Right-sided breast cancer | | | | |
| Heart | 0 | NA | 0 | NA |
| Lung | 121.38 (110.44–132.32) | 0–464.77 | 16.78 (13.14–20.41) | 0–201.05 |

* A total of 200 patients with cancer of the left breast and 200 with cancer of the right breast participated in a prospective clinical trial that received approval from an institutional review board; each patient underwent CT-based simulation in both the supine and prone positions. The prone position resulted in a reduced mean dose of radiation to the heart and lung.6 The 95% confidence interval (CI) was calculated on the basis of paired t-statistics. NA denotes not applicable.
TO THE EDITOR: Darby et al. describe the risk of coronary events among patients with breast cancer treated with radiation between 1958 and 2001. The modern reality is that radiation-delivery techniques have improved substantially. Currently, with the use of breath hold for patients with more than 10 cm³ of cardiac volume treated (15% of the breast-cancer population), the mean dose to the heart can be reduced considerably from 3.2 Gy to 1.3 Gy. The remaining 85% of patients receive even lower cardiac doses. Figure 2 of the article indicated that even with a mean heart dose of 3 Gy, the increase in heart disease caused by radiation would be 0.9 percentage points; for women with cardiac risk factors, the risk increased by only 1.7 percentage points.

It is important to reassure women with breast cancer that with the use of current technologies, the cardiac dose can be decreased considerably, and cardiac risk factors can be better managed. The recent meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group observed an improvement of 3% in overall survival for patients undergoing breast radiotherapy, under-scoring that the risk–benefit ratio remains in favor of radiation treatment.

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No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMcc1304601

TO THE EDITOR: Darby et al. discuss cardiac toxic effects that were seen within 4 years after radiotherapy for early breast cancer. From 2000 through 2012, in the Targeted Intraoperative Radiotherapy Alone (TARGIT-A) randomized trial, investigators evaluated 3451 patients with breast cancer who were 45 years of age or older and who had unifocal invasive ductal carcinoma with a diameter of 3.5 cm or less. The study showed that a single dose of targeted intraoperative radiotherapy as part of a risk-adapted strategy given at the time of lumpectomy and focused to the tumor bed, which completely excluded the heart and other organs, achieved ipsilateral breast-tumor control that was noninferior to external-beam radiotherapy to the whole breast. The planned analysis of survival, which included 36 deaths from breast cancer and 52 deaths not related to breast cancer, showed a significantly lower rate of death from causes not related to breast cancer with targeted intraoperative radiotherapy, as compared with external-beam radiotherapy (hazard ratio, 0.47; 95% confidence interval [CI], 0.26 to 0.84; P<0.009). This reduction in deaths with targeted intraoperative radiotherapy was driven by fewer deaths from cardiovascular causes and other cancers. This level-one evidence suggests that for patients who have tumors with a good prognosis, it is important to ensure that our treatments do not increase the risk of death not caused by breast cancer. Targeted intraoperative radiotherapy appears to achieve this while maintaining cancer control. In addition, it has been shown to have a beneficial effect on the wound microenvironment, and perhaps this effect could spill over, causing favorable systemic effects.

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Drs. Vaidya, Bulsara, and Wenz report receiving reimbursement from Carl Zeiss for travel expenses to attend conferences and steering committee meetings, and Dr. Vaidya reports receiving honoraria from Carl Zeiss. No other potential conflict of interest relevant to this letter was reported.


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DOI: 10.1056/NEJMc1304601

THE AUTHORS REPLY: We agree with Little et al. that clinicians should be aware of the risk of cardiovascular morbidity and limit the dose to the heart when performing radiotherapy for breast cancer. As pointed out by Liu et al., many radiotherapy centers already do this by means of techniques such as breath hold, by treating patients in the prone position (as indicated by Formenti et al.), or by intraoperative radiotherapy (as indicated by Vaidya et al.). We agree with Liu et al. that a comparison of benefits and risks is important in radiotherapy for breast cancer. As discussed in our article, the results of our study provide reassurance for the majority of patients that their absolute risk of heart disease from radiotherapy is likely to be small, as compared with the probable absolute benefit from radiotherapy.1 Our results can also be used to identify the minority of patients for whom the benefits of radiotherapy do not clearly outweigh the risks.

In the cohort study2 preceding our case–control study, we compared patients who underwent radiotherapy for the treatment of cancer of the left breast with those treated for cancer of the right breast, and we found an increased risk of aortic valvular disease among those with cancer of the left breast, with an incidence-rate ratio of 1.70 (95% CI, 1.14 to 2.53; P = 0.009). Valvular disease was not a case-defining event in our case–control study, but in response to Toutouzas et al., we note that the study of valvular disease will require further work.

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Since publication of their article, the authors report no further potential conflict of interest.


DOI: 10.1056/NEJMc1304601

Omalizumab for Chronic Urticaria

TO THE EDITOR: Maurer et al. (March 7 issue) report the results of a phase 3 trial of omalizumab for the treatment of urticaria. Figure 1 of their article shows that withdrawals from the study because of “disease progression” occurred only in patients who received omalizumab; there were no withdrawals due to disease progression in the placebo group. Furthermore, the percentage of patients who withdrew due to disease progression correlated with the dose of omalizumab (1% in the 75-mg group, 4% in the 150-mg group, and 8% in the 300-mg group); this suggests that omalizumab may itself, paradoxically, contribute to urticaria.

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