

# Newer Radiotherapy Tx's Linked to Less CV Risk

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SAN ANTONIO — The considerable excess in cardiovascular mortality caused by older radiotherapy regimens for breast cancer appears to be greatly diminished with more modern ones, Sarah C. Darby, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This was the principal conclusion of her analysis of nearly 309,000 cases of early breast cancer enrolled in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry in 1973-2001.



A total of 37% of the SEER population received radiotherapy.

Heart disease was the leading cause of death in radiotherapy-treated patients; however, a straightforward comparison of cardiovascular mortality rates in women who did or did not get radiotherapy wouldn't be appropriate, since SEER participants were not randomized to this treatment.

A better comparison would take advantage of the fact that the heart is located slightly left of center in the body; thus, radiotherapy recipients with cancer of the left breast will get a higher radiation dose than those with right-sided cancer, ex-

plained Dr. Darby of the University of Oxford (England).

Sure enough, among SEER participants who received radiotherapy and subsequently died of heart disease, there was a highly significant 16% excess of cancers of the left breast. In the subset of radiotherapy-treated patients followed for 15 years or more, this excess risk climbed to 53%.

In contrast, among those patients who did not get radiotherapy, death due to heart disease was equally common in women with left- and right-sided breast cancer, the study found.

The key question is whether the excess cardiovascular risk associated with radiotherapy is a relic of outdated techniques or is still present with more recent regimens. A statistically significant downward trend in excess cardiovascular mortality in left-sided breast cancer patients was evident when SEER radiotherapy recipients were stratified by decade of cancer diagnosis. (See chart.)

However, it's too soon to say the hazard has gone away completely, since there are no 10-year follow-up data on the most recent radiotherapy group. And it's by no means clear that regimens just now being introduced—such as intensity-modulated radiation therapy—are going to be free from cardiovascular risk, she said at the meeting. ■

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DR. DARBY

## Heart Disease Deaths Declining Among Breast Ca Patients Treated With Radiotherapy

Year of Cancer Diagnosis	Ratio of Left- to Right-Sided Breast Cancer:	
	Patients who died in the first 9 years of follow-up	Patients who died in the 10th year or later
1973-1982	1.20	1.51
1983-1992	1.04	1.27
1993-2001	0.96	To be determined

Source: Dr. Darby

## Locally Recurrent Breast Ca Called 'Life-or-Death Problem'

SAN ANTONIO — The improved local control of breast cancer achieved via radiotherapy translates into a significant reduction in mortality due to the malignancy that becomes apparent only late, at 10 and 15 years' follow-up, Sir Richard Peto, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

That's the good news regarding radiotherapy from a new metaanalysis of the world's total randomized clinical trial experience in early breast cancer. The bad news: This reduction in breast cancer mortality is essentially canceled out—and in some subgroups outweighed—by a radiotherapy-induced excess in late deaths due to cardiovascular disease.

"The big thing about radiotherapy is it causes deaths from heart disease, not in the first decade after treatment, but in the second," said Dr. Peto, professor of medical statistics and epidemiology at the University of Oxford (England).

Still, the central point remains: Local control of breast cancer matters. And if preliminary evidence turns out to be correct in suggesting modern radiotherapy techniques achieve it with much less cardiotoxicity than the radiotherapy of the 1980s, then physicians can expect to see a continued further decline in overall mortality in breast cancer patients in the decade beginning in 2010, he said.

"Local recurrence is not a cosmetic problem, it's a life-or-death problem," he said. "Breast cancer is a disease where you've really got to think of what you're achieving on a time scale of decades, not years. The question is not 5-year survival, the question for a middle-aged woman is what is the 20-year survival?"

Dr. Peto presented a metaanalysis of data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) involving 24,000 women randomized to radiotherapy or no radiotherapy in 46 clinical trials that enrolled patients in the mid-1980s.

"With a quarter of a million woman-years of observation after year 5, we've got really clear results," he noted.

The 15-year rate of isolated local recurrence was 10% in women who received radiotherapy and 31% in those who did not. And 15-year mortality due to breast cancer was 44% in radiotherapy recipients, compared with 48% in controls. "It's a small but real benefit," Dr. Peto said.

Through stratification of trials based upon the magnitude of difference in local control, it became apparent that the greater the difference in local control in a given study, the bigger the long-term difference in breast cancer mortality, he said.

Looking more narrowly at the impact of radiotherapy after breast-conserving therapy in a series of randomized trials involving 6,097 women with node-negative disease, he found that the 10-year rate of isolated local recurrence was 10% in those who got radiotherapy, compared with 29% in controls. Ten-year breast cancer mortality was 17% in radiotherapy-treated women and 20% in controls.

The EBCTCG data show that in addition to the marked increase in late cardiovascular deaths associated with radiation therapy as practiced in the 1980s, treated women also face smaller but nonetheless significant increases in risk of death due to lung, esophageal, and contralateral breast cancer.

Nevertheless, he characterized the overall improvement in breast cancer outcomes since the 1980s as "a brilliant success." It's estimated that in 2010, mortality in middle age due to breast cancer in the United Kingdom will be just half of what it was in 1980, and a similar trend applies in the United States.

That's a success story unrivaled in oncology. Only the reduction in lung cancer deaths in recent decades even comes close—and that's not due to screening and treatment advances, but, rather, to smoking cessation efforts.

# Menstrual Timing of Breast Ca Surgery Doesn't Affect Prognosis

SAN ANTONIO — The timing of breast cancer surgery with respect to menstrual cycle phase failed to affect prognosis in two large multicenter prospective observational studies presented at the annual breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This has been a longstanding controversy. Since 1989, roughly two dozen surgical studies have examined the issue. Close to half have reported a survival advantage for breast cancer patients who undergo their surgery during the luteal phase of the menstrual cycle. The remaining studies concluded timing of surgery had no impact upon disease-free or overall survival.

But most prior studies involved a few hundred patients or less, many were single-center retrospective series, and nearly all relied upon patient recall of the last menstrual period, which has the potential for inaccuracy.

To shed light on the issue, investigators from the North Central Cancer Treatment Group conducted a study in which 842 patients undergoing breast cancer surgery at 103 sites were categorized as to menstrual cycle phase both by biochemical determination at time of surgery and by recall of last menstrual period, explained Clive S. Grant, M.D., professor of surgery at the Mayo Clinic, Rochester, Minn.

Five-year disease-free survival in 231 women operated on during the luteal phase was 81.9%, not significantly different than the 82.2% rate among 364 women in the follicular phase or the 79.1% rate in women in an indeterminate menstrual phase. Nor did overall survival differ between the groups.

Biochemical determination of menstrual phase based upon hormone levels at the time of surgery demonstrated that reliance upon last reported menstrual period would have resulted in misclassification of 29% of women, a finding that casts doubt upon the validity of much of the prior work in this area.

In a separate presentation, Richard Sainsbury, M.D., reported on 412 women followed for a median 59 months after undergoing breast cancer surgery in a multicenter study. The 3-year overall survival of 90.7% wasn't affected by timing of surgery in relation to menstrual cycle.

The initial data analysis relied upon patient report of last menstrual period. Hormone levels at the time of surgery were also measured, however, and in the near future the data will be reanalyzed using those measurements to categorize patient menstrual status, according to Dr. Sainsbury, professor of surgery at University of Leeds (England). ■