Cardiac Risk from Radiation Exposure

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Cause-Specific Mortality in Long-Term Survivors of Breast Cancer Who Participated in Trials of Radiotherapy


Purpose: To examine long-term cause-specific mortality in patients irradiated for breast cancer as part of a randomized clinical trial.

Patients and Methods: We studied all available information from randomized trials initiated before 1975 in which radiotherapy was the randomized option and surgery was the same for both treatment arms. Eight such trials were identified.

Results: The increased all-cause mortality rate in 10-year survivors previously reported is no longer significant, although a numerical difference in favor of non-irradiated patients remains. This result was strongly influenced by the earliest trials, and more recent trials have found a nonsignificant net benefit in overall mortality associated with radiation therapy. An excess of cardiac deaths was apparent in both early and more recent trials ($P < .001$), but this was offset by a reduced number of deaths due to breast cancer, especially in more recent trials.

Conclusion: The reduction of breast cancer deaths suggests that radiation therapy may have a value beyond the clearly established improvements obtainable for local control. Use of techniques that minimize cardiac dose is important in reducing the risks of adjuvant radiotherapy, especially in good-prognosis patients.

Meta analysis of all randomized breast cancer trials initiated before 1975 in which radiotherapy was the randomized option and surgery was the same for both treatment arms.

- No chemo

Patients who underwent radical mastectomies and received postmastectomy radiation had poorer outcomes.

- 62% increase in cardiac deaths in women who received radiation
- “A divergence in favor of patients not given radiotherapy is apparent in the radical mastectomy trials after approximately 15 years”
Fig 4. SMRs (radiotherapy/no radiotherapy) and 95% CIs by trial for cardiac mortality (after 10 years).

Fig 5. SMRs (radiotherapy/no radiotherapy) and 95% CIs by trial for breast cancer mortality (after 10 years).
Takeaways

- Risk appeared to be related to the large doses and extensive fields
  - The three big studies showing the most dramatic cardiac impact utilized Cobalt 60 units which delivers large doses to the myocardium especially for those who underwent radical mast.
  - Several studies treated comprehensive nodes thus increasing exposure to the heart and coronary arteries.
Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer

Sharon H. Giordano, Yong-Fang Kuo, Jean L. Freeman, Thomas A. Buchholz, Gabriel N. Hortobagyi, and James S. Goodwin
Department of Breast Medical Oncology (SHG, GNH) and Department of Radiation Oncology (TAB), The University of Texas M. D. Anderson Cancer Center, Houston; Department of Medicine and Sealy Center on Aging, The University of Texas Medical Branch at Galveston, Galveston (Y-FK, JLF, JSG).
SEER data from 1973–2000

Women (n = 27,283) treated with adjuvant radiation for breast cancer diagnosed in 1973–1989 were included in the study.


13,998 women with left-sided and 13,285 with right-sided cancer

Giordano. JNCI 2005
No differences in age, race/ethnicity, disease stage, or follow-up time.

Dx in 1973–1979, there was a statistically significant difference in 15-year mortality from ischemic heart disease between patients with left-sided (13.1%, 95% confidence interval [CI] = 11.6 to 14.6) and those with right-sided (10.2%, 95% CI = 8.9 to 11.5) breast cancer (P = .02).

No such difference was found for women diagnosed in 1980–1984 or 1985–1989.

In the Cox model, the hazard ratio [HR] for ischemic heart disease mortality for women with left-sided versus women with right-sided disease was 1.50 (95% CI = 1.19 to 1.87) in 1979.

This declined by 6% with each succeeding year after 1979.
Not so fast…
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.
Population-based case-control study of major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease)

2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark

- 963 women had known major coronary events and 1205 served as controls.
Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast (P=0.002).

The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72).

Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9 to 14.5; P<0.001), with no apparent threshold.

Darby. NEJM 2013
The risk started to increase within the first 5 years after exposure and continued for at least 20 years.

The rate of major coronary events was higher among women with cardiac risk factors than among those without such risk factors.
The increase is proportional to the mean dose to the heart with no threshold in sight.

Begins within a few years after exposure and continues into the third decade after completing radiation therapy.

Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women.
KEEP CALM
WE GOT THIS
Ways to mitigate cardiac exposure @ FHCC

- Accelerated partial breast irradiation (APBI)
  - High dose rate Brachytherapy
  - External beam radiotherapy
- Deep Inspiration Breath Hold with daily Surface Guided Radiation therapy
- Prone technique
- Proton therapy
THE SAVI® BREAST BRACHYTHERAPY APPLICATOR:
Partial Breast Radiation Therapy for Early-Stage Breast Cancer

WHAT IS SAVI?
The Strut Adjusted Volume Implant (SAVI)® applicator delivers a form of accelerated partial breast radiation (APBI) known as breast brachytherapy, which delivers radiation from inside the breast. This allows physicians to precisely deliver treatment to the tumor cavity and surrounding tissue, and offers two key advantages: it spares healthy tissue from unnecessary radiation and reduces treatment time from 6 weeks to just 2-5 days.

HOW DOES IT WORK?
SAVI uses a bundle of catheters to deliver radiation. The catheters are expanded to fit the size and shape of the cavity, and a tiny radioactive seed travels through each catheter. This allows every catheter to deliver an individual dose of radiation, so physicians can customize treatment for every patient, regardless of the size, shape, or location of their tumor cavity.

BENEFITS OF SAVI BREAST BRACHYTHERAPY
- Customized radiation to individual patient
- Excellent local control of cancer
- Reduces toxicity from unnecessary radiation
- Treatment lasts just 2-5 days

RADIATION DELIVERY
Treatment is delivered twice a day for 2-5 days. Each treatment lasts approximately 10 minutes. The ends of the catheters are connected to a device—called an HDR afterloader—and a computerized system precisely delivers a tiny radioactive seed into each catheter. The seeds are completely removed after each treatment so radiation remains in the patient’s body between treatments. After the last treatment, the physician chooses the device and removes it through the same incision in which it was inserted.
DIBH with daily SGRT
DIBH with daily SGRT

**Left:** Axial image of a whole breast plan. **Right:** Coronal image of a whole breast plan.
Free breathing heart **orange**, Breath hold heart **pink**
DIBH with daily SGRT
DIBH with daily SGRT

- Patient treatment setup and real time monitoring with C-RAD
- Entire treatment completed 6.5 min
DIBH with daily SGRT

**Left:** Patient setup with SGRT. **Right:** Snippet from monitoring report. Shortly after the beam comes on at \( t = 3 \text{ min} \), sudden patient movement takes place. Once the predetermined motion threshold of 5 mm was reached the motion vector turns red and the beam automatically shuts off.
Prone
Prone

-4.48cm

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- Dmean < 150 cGy
- V1500cGy < 20 %
Protons (PBS)
Protons (PBS)

- Highly conformal targeting of dose to the high risk tissues with dramatic sparing of the organs at risk.
Protons (PBS)

Plan dose (RBE): Bilateral CW/Ax/SCV/Rt MC5040_JNK (PlanCT_7.27.2022)
Clinical: Monte Carlo v5.2
RBE scale factor: 1.1

CT: PlanCT_7.27.2022
PROCT01
Transversal: 4.00 cm
Slice 60/244

FHCC
conclusions

- We have learned from the past
  - Several modalities to mitigate cardiac exposure
  - APBI, DIBH with SGRT, prone and protons

- Post therapy surveillance?
  - No consensus at this time however consider long term surveillance if patient manifests with cardiac symptoms