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Sorting out the Survival Impact of Radiation Therapy in Early-Stage Invasive Breast Cancer

Bruce G. Haffty, MD¹, Henry M. Kuerer, MD PhD², and Simon Powell, MD³

Bruce G. Haffty: hafftybg@cinj.rutgers.edu

¹Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

²Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

³Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Radiation plays a major role in the management of early-stage breast cancer. While its impact on local–regional control is clearly documented with both clinically and statistically significant gains, the impact of radiation on overall and disease-free survival in early-stage disease remains a matter of controversy and debate.^{1–4}

There are two major areas where the impact of radiation therapy on overall and disease-free survival has been extensively evaluated: 1. radiation to the whole breast following breast-conserving surgery (BCS + RT) and 2. comprehensive irradiation to the chest wall/breast and regional lymphatics after definitive surgery. In this commentary, we will review the evidence and controversies in these two major areas.^{1–3}

RADIATION TO THE BREAST AFTER BCS

Radiation therapy to the whole breast following breast-conserving surgery is widely embraced as an accepted standard of care for the majority of women with early-stage invasive breast cancer and ductal carcinoma in situ. A number of randomized trials have been conducted over the past 30 years which clearly demonstrate that BCS + RT provides high local control rates with disease-free and overall survival rates that are equivalent to mastectomy. Whether radiation following BCS can be eliminated has also been the subject of numerous randomized trials, all of which have clearly demonstrated that radiation improves local control significantly, even among relatively lower risk women, such as elderly patients with ER-positive invasive cancer.⁵ The majority of randomized trials have demonstrated that radiation therapy following BCS lowers the local relapse rates by at least half of the local relapse rate without radiation, and is associated with acceptable toxicity and morbidity.³ The impact of radiation following BCS on breast cancer mortality or overall survival, however, is not as evident.^{2,3,6}

One of the larger trials of low-risk women reported is NSABP-21. This trial randomized 1,009 women to tamoxifen alone, radiation and placebo, or radiation and tamoxifen. All patients had tumors that were less than 1 cm, negative margins, axillary dissection node negative, and estrogen receptor positive.⁷ The local relapse rate was 13.5 % with tamoxifen alone, 6.9 % with radiation and placebo, and 2.7 % with radiation and tamoxifen. This and a

number of other studies comparing local relapse rates with and without radiation therapy in favorable low-risk patients are summarized in Table 1.^{8–11}

Other studies of low-risk women with invasive as well as non-invasive breast cancers demonstrate similar reductions in local relapse with radiation therapy following breast-conserving surgery, compared to breast-conserving surgery alone. While in some cases of very low-risk patients, the absolute reduction in local relapse can be very low, and the relative benefit with respect to local relapse remains significant. Despite significant reductions in local relapse reported in all of the randomized trials comparing breast-conserving surgery to breast-conserving surgery and radiation, the impact on overall survival or distant metastasis has not been clearly demonstrated.

The observation that radiation to the breast after breast-conserving surgery may impact on breast cancer mortality, while not demonstrated clearly in any given randomized trial, was realized in larger pooled meta-analysis reported by Vinh-Hung in 2004 and the EBCTG in 2005.^{2,6} These meta-analyses of all randomized data reported not only a significant improvement in local relapse rates with radiation, but also a significant impact on breast cancer mortality.

In a more recent and detailed landmark meta-analysis of all randomized trials comparing BCS to BCS + RT in invasive breast cancer, Darby et al.³ reported not only significant reductions in local–regional control with RT following BCS, but also reported that RT reduced the breast cancer death rate by about one-sixth. Specifically, in this large meta-analysis of over 10,000 women in 17 randomized trials, comparing BCS to BCS + RT radiation therapy reduced the 15-year risk of breast cancer death from 51.3 to 42.8 %, representing approximately 1 breast cancer death avoided at 15 years for every 4 local relapses avoided at 10 years. Given the impact of radiation on both local control and breast cancer-specific survival, the standard of care for the majority of patients with invasive breast cancers undergoing BCS is the use of radiation following BCS. Given the potential impact not only on local relapse, but also on survival, the avoidance of radiation therapy must be approached cautiously outside the context of a clinical trial.

There are, however, subsets of patients who are at so low a risk of recurrence, that while the relative reduction in local relapse may still be significant with the use of RT after BCS, the absolute benefit is so small that the impact on breast cancer mortality is clinically not meaningful. A common and clinically relevant example of this is in women over age 70 with hormone receptor-positive tumors, where observation following BCS is considered an acceptable standard of care. In a recent update of the CALGB trial randomizing women with ER+ tumors over age 70 to RT versus No RT, with over 12 years of follow-up, the tamoxifen and RT group had a local–regional relapse free rate of 98 % compared to a local–regional relapse rate of 90 % with Tam alone.⁵ Despite this 8 % difference in local–regional control, there were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or overall survival. The authors appropriately concluded that TAM alone following BCS remains a reasonable option for breast cancer patients over age 70 with early-stage estrogen-positive invasive breast cancer. In the original Canadian study of women over age 50 with receptor-positive tumors treated by radiation or

observation, Fyles reported with 5.6 years follow-up a 7.7 % rate of local relapse with observation and tamoxifen compared to a 0.6 % rate of local relapse with tamoxifen and radiation.¹⁰

Given the level I evidence that whole-breast radiation therapy lowers the local–regional relapse rate following BCS significantly, whole breast radiation remains the standard of care for the vast majority of early-stage breast cancer following BCS. Even in women over age 70 with low co-morbidities and a long life expectancy, most physicians discuss the benefits of radiation in significantly lowering the local relapse rate, particularly in those patients who may not be compliant with hormonal therapy. The avoidance of radiation therapy in women under age 70 has raised concerns given the demonstrated benefit not only in local–regional control, but also the potential benefit in distant metastasis and breast cancer-specific survival. As noted above, despite the fact that no individual trial randomizing radiation to no radiation revealed a significant impact on breast cancer-specific survival, the meta-analysis of all 17 trials resulted in an 8 % reduction in breast cancer mortality with the use of radiation following BCS.³ This significant reduction in breast cancer mortality appropriately raises concerns regarding not only the avoidance of radiation, but also the use of alternative approaches such as partial breast irradiation, in women with early-stage invasive breast cancer and the current lack of long-term survival data utilizing this technique. Given the concerns, many clinicians and patients would only consider the avoidance of radiation or the use of partial breast irradiation in the context of a clinical trial.

As noted above, the observation that whole breast irradiation could potentially impact on breast cancer mortality was not brought out in any individual randomized trial, but was demonstrated in meta-analysis reported by Vinh-Hung in 2004, Lancet in 2005, and more recently with more detailed data and longer follow-up in the 2011 article by Darby.^{2,3,6} While the impact of whole breast irradiation on local–regional relapse is highly significant both clinically and statistically, the impact of whole breast irradiation on breast cancer mortality remains questionable in a large segment of the population evaluated in those randomized trials. Darby et al. divided the pathologic node-negative patients enrolled in the randomized trials into 3 groups: those with large reductions (>20 %) in first relapse with radiation, those with intermediate reductions (10–19 %) with radiation, and those with small reductions (<10 %) with radiation. Although those with the large reduction of >20 % had a significant 7.8 % reduction in breast cancer mortality with confidence intervals ranging from +3.1 to +12.5 % in breast cancer mortality which was significant, the reduction in breast cancer mortality in the intermediate group was only 1.1 % with confidence intervals from –2 to +4.2 %, and the reduction in breast cancer mortality in the low-risk group was only 0.1 % with confidence intervals from –7.5 to +7.7 %.³ These data suggest that for the low-and intermediate-risk groups, radiation had no impact on breast cancer mortality.

Although the reduction in breast cancer mortality was highly significant in those patients where the absolute reduction in the first breast cancer event with radiation was >20 %, the impact on mortality was neither clinically nor statistically significant in those patients where the absolute reduction in the first event with radiation was <20 %. It should be noted that of the 7,287 node-negative women in the meta-analysis, 5,363 or 73 % were in the low- or intermediate- risk groups. Not surprisingly, the relatively small number of patients with

node-positive disease in this meta-analysis ($n = 1,050$) had a highly significant reduction in both local relapse of 21.2 % and a statistically significant reduction in mortality of 8.5 % (CI 1.5–15.2).

Overall, these data suggest that while radiation to the whole breast has both a clinically and statistically significant impact on local relapse in nearly all patients with breast cancer, the impact on breast cancer mortality is only apparent when the group receiving BCS + RT has an absolute risk reduction of 20 % or greater. In the current era of breast cancer screening, appropriate surgical and pathologic processing and analysis, and the widespread use of systemic therapy, the vast majority of node-negative women treated with BCS + RT would fall into the lower or intermediate-risk group. Whether in the current era of lower local relapse rates, the reduction in local relapse rates with radiation therapy translates into a proportional reduction in breast cancer mortality remains to be determined.

These data have significant implications regarding the risk on the avoidance of radiation in the current era. Most importantly, the absolute risk of local relapse in the majority of patients treated currently is less than 20 %, and therefore the absolute risk reduction with radiation therapy to the whole breast is even less. Many patients who included in the meta-analysis discussed above were treated in an earlier era, where the tumors were generally larger, often diagnosed by clinical palpation, attentions to margin status were not as refined, and systemic therapy was not universally employed. Currently, a majority of patients are diagnosed with screening mammography resulting in smaller tumors, attention to margin status is routine, and systemic therapy is almost always employed. These factors have resulted in a significant shift to a more favorable risk profile of early-stage breast cancers and significantly lower local relapse rates. Several more recent single-arm studies of observation in favorable breast cancers have reported local relapse rates under 10 %, particularly in those patients with hormone receptor-positive tumors (luminal A) treated with hormonal therapy.¹¹

There is no question that regardless of the risk associated with observation after breast-conserving therapy, radiation therapy administered to the breast will significantly lower that risk by at least half, and the absolute individual benefit to the patient is dependent on her particular tumor biology and the use of systemic adjuvant therapy. Clearly, these patients can benefit from a significant improvement in local control with breast irradiation, but avoidance of radiation is unlikely to impact on breast cancer or overall mortality.

IMPLICATIONS FOR FUTURE TRIALS

These data have significant implications going forward with clinical trials addressing the question of avoidance of radiation. While we continue to advocate for the routine use of whole breast irradiation following breast-conserving surgery in the majority of women with early-stage invasive breast cancer, prospective clinical trials addressing the issue of avoidance of radiation in favorable subsets of patients is a reasonable approach to help address this issue. In favorable patients, such as those with luminal A tumors, where available data suggest that local recurrence rates are likely to be less than 10 % over 10 years following BCS and hormonal therapy alone, prospective trials addressing the issue of

avoidance of radiation are unlikely to impact on breast cancer mortality or overall survival. These patients are, however, highly likely to benefit from a significant improvement in local relapse with the use of radiation therapy, and therefore we feel that avoidance of radiation or the selective use of partial breast radiation is most appropriately offered in the context of a clinical trial, where the risks, benefits, and available treatment options are clearly outlined and articulated.

IMPACT OF COMPREHENSIVE REGIONAL NODAL IRRADIATION TO THE CHEST WALL/BREAST AND REGIONAL LYMPHATICS

The role of comprehensive nodal irradiation to the chest wall and regional nodes following mastectomy (PMRT) or to the breast and regional nodes following lumpectomy is clearly embraced for women with more advanced disease and 4 or more involved lymph nodes. For patients with early stage, but node-positive disease (i.e., high-risk node negative or patients with 1–3 positive nodes), the role of comprehensive nodal irradiation and postmastectomy radiation is not as clear and remains controversial. An RTOG trial addressing PMRT in women with 1–3 nodes failed its accrual goals. Other ongoing trials and recently reported but not fully published trials (MA.20 and EORTC) demonstrated a benefit and further analysis, and details from these studies will likely help clarify which subsets of patients derive the greatest benefit.^{12,13}

A meta-analysis of all postmastectomy trials was published by the EBCTCG in 2005 demonstrating a disease-free and overall survival benefit to PMRT.² It should be noted, however, from the meta-analysis published in 2005, that the impact on survival was not realized in those trials where the improvement in local control was less than 10 %. As noted in Table 2, in the subgroups of patients where the improvement in local control was 10–20 % and >20 %, there appeared to be a significant impact on breast cancer mortality. However, in the subset of patients where there was less than a 10 % improvement, there was no evidence for an impact on breast cancer mortality.²

Recently updated by Darby et al. in 2013, focusing on patients with 1–3 nodes, there remained a statistically significant benefit in patients with 1–3 nodes, and the benefit persisted in subset analysis of those trials which employed systemic therapy and was independent of whether there was 1, 2, or 3 nodes involved.¹

Although the reductions in local–regional relapse and breast cancer mortality reported in the meta-analysis by Darby et al. are impressive, patients in the meta-analysis with 1–3 nodes randomized to no PMRT had relatively high rates of local–regional recurrence (21 %) and overall recurrence (45 %) compared to current reports.¹ Given that the reported trials in this meta-analysis are predominantly older studies from a completely different era, the applicability to modern patients has been questioned. Today, there is earlier detection of disease, improvements in surgical approaches, more detailed pathologic processing with serial sectioning often detecting nodal micrometastasis, and more effective systemic therapy; therefore, the absolute reduction in both local–regional recurrence and breast cancer mortality associated with PMRT in the current era of patients with 1–3 involved nodes would be expected to be substantially less than that reported in this meta-analysis. In fact,

recent contemporary series of patients treated with mastectomy with 1–3 nodes without PMRT at MDACC, MSKCC, and Cleveland Clinic all report local–regional relapse rates of less than 10 % at 5 years follow-up.^{14–16} While radiation therapy would likely still impact on the local–regional relapse rates in these patients, its impact on breast cancer mortality is less evident and requires further study and subset analysis.

On the other hand, improvements in radiation therapy techniques, with CT-based planning, lower doses to the non-target cardiac and pulmonary structures, and more accuracy and precision in delivering radiation to the target chest wall and regional lymphatics, are likely to improve the treatment effect, reduce potential toxicities, and improve the therapeutic gain. Therefore, while the absolute reduction in local–regional relapse rates associated with PMRT in patients with 1–3 nodes is likely to be smaller than that reported in the meta-analysis, the relative benefit and risk/benefit ratio of PMRT may persist among higher risk patients (example, large T2, extensive lymphovascular invasion, etc.) with 1–3 involved lymph nodes.

These results are also consistent with recent reports from the Canadian MA.20 trial¹² and the EORTC 22922/10925 trial.¹³ Patients with 1–3 involved lymph nodes, predominantly treated with breast-conserving surgery, comprised a majority of patients in these trials, in which patients were randomized to radiation directed to the breast/chest wall alone or radiation delivered to the breast/chest wall and regional lymphatics. Both of these randomized trials also demonstrated in addition to improved local–regional relapse, reduced distant metastasis, and reduced breast cancer mortality in the cohort of patients randomized to regional nodal irradiation. The full publications of the MA.20 and EORTC trials in the near future will hopefully provide clinicians with further insight and details regarding the benefits of regional nodal irradiation in these patients.

Appropriately, clinicians and patients are still likely to be selective in the use of PMRT and regional nodal irradiation, utilizing the full spectrum of available clinical data and literature, including age, co-morbidities, histology, grade, receptor status, primary tumor size, extent of nodal involvement, and other factors in the ultimate decision of whether to do PMRT in patients with low nodal burdens. The currently available randomized data, however, provide a high level of evidence that PMRT and regional nodal irradiation following lumpectomy are associated with a clinically significant benefit in the majority of patients with positive nodes, including patients with 1–3 nodes. Given these data, it is important to consider and discuss the potential benefits and risks of comprehensive nodal irradiation and PMRT in all patients with node-positive disease. As we move forward in the genomic era, it is likely that genomic and molecular tumor subtyping will help better select patients where omission of radiotherapy may be safe. Furthermore, randomized trials are underway with the NRG designed to address the interrelationship of preoperative systemic therapy response in documented node-positive cancer and the need for PMRT and comprehensive nodal irradiation.¹⁷

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Local relapse rates in “low risk” ER + patients treated with breast-conserving surgery with or without radiation

TABLE 1

Study	Number patients/ follow-up	Local relapse observation/ hormonal TX (%)	Local relapse radiation/ hormonal TX (%)	Age (years)	Other
NSABP-21 (6)	1,009/8 years	16.9	2.8	80 % >50	<1 cm pN0
GBSG-V 8	361/5.9 years	7.5	5	45-75	pT1/N0
Uppsala 9	381/20 years	25.8	11.5	<80	pT1/N0
CALGB 4	636/10 years	10	2	>70	T1/Clinical N0
Canadian 10	769/5.6 years	7.7	0.6	>50	T1/T2 Clinical N0
PRIME II 11	1,326/5 years	4.1	1.3	>65	

TABLE 2

Impact of improvement in local control on breast cancer mortality

Improvement local regional control	Breast cancer mortality (%)	
	15-year risk (active vs control)	15-year absolute reduction (SE)
<10 % (mean 1 %)	41.3 vs 42.3	1.0 (0.9)
10–20 % (mean 17 %)	44.0 vs 48.5	4.5 (0.8)
>20 % (mean 26 %)	47.4 vs 53.4	6.0 (1.6)