Short communication

Radiation impact in breast cancer

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Introduction

Four questions were considered pivotal by the organizers of the Controversies in Breast Cancer 2009 meeting in Edinburgh, September 2009 with regards to the radiation (RT) effect in the adjuvant setting of early breast cancer: What are the data indicating that local radiotherapy is associated with long-term survival benefit? What must be irradiated to obtain a long-term effect? What is the mechanism of action whereby local RT can influence long-term outcome? Is the RT effect applicable to different subsets? Answers to these questions constitute the present contribution.

Data 1: why controversy?

Undoubtedly, until the 1997 publication of the British Columbia and Danish randomized trials [1,2], RT was viewed as a modality strictly affecting local control. Its widespread use since the 1950s was halted in the early 1980s, when it was felt that the newly emergent adjuvant chemotherapy [3,4] would be sufficient, particularly when data of significant cardiac toxicity due to RT became available at the same time [5]. These data have shown more than a 20% increase in cardiac mortality, with no identifiable systemic benefits in reduction of systemic events.

Table 1 – based on past analyses of Oxford-based Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses [6] – shows that trials which began with patients diagnosed before 1970 had cardiac mortality rates increased by 19 to 21% (hazard ratio (HR) = 1.19 to 1.21), according to the follow-up duration, whereas trials with patients diagnosed after 1993 had no increased risk (HR = 0.95 to 0.99).

What has changed in the past 25 years? Both the RT equipment and the three-dimensional computed tomography planning of RT fields today secure high-quality RT beams restricted and targeted directly to the tumor or lymph node bearing areas, with minimum scatter affecting the heart or lungs. The therapeutic ratio has therefore substantially increased, as reflected in the data. Another change, however, was the emergence of adjuvant chemotherapy.

Mechanism of radiation: chemotherapy impact on radiotherapy

In parallel with the substantial RT equipment improvement, data also indicate evidence for more RT-associated impact in the presence of rather than in the absence of adjuvant chemotherapy. The hypothesis of improved chemo-RT interaction first articulated in [1] indicated that, in the absence of adjuvant chemotherapy, whatever the RT impact, the patient may die from *systemic* micrometastases unaffected by loco-regional RT. On the other hand, if the systemic disease component is eliminated by adjuvant chemotherapy, then the residual disease at the loco-regional areas may be all that remains. This disease is the target for curative RT treatment.

Chemotherapy sensitivity: micrometastases versus macrometastases

The pivotal argument for this set of events comes from data showing systemic microscopic disease at a biologically younger age than the more bulky loco-regional disease – thus subject to less resistance, and therefore more curable by chemotherapy [7-9]. On the other hand, the more aged bulky loco-regional disease would contain a higher absolute number of chemotherapy-resistant mutants, and could be eliminated through a nonspecific higher loco-regional cell kill of radiotherapy [10,11].

Data 2: what is the actual radiation benefit?

The Oxford overview data [6] of RT-associated mortality show a reduction of hazards (hazard ratio = 0.83 to 0.70), indicating that the 17 to 30% of patients who are destined to die in the absence of radiotherapy will live as a result of RT preventing the systemic dissemination.

EBCTCG = Early Breast Cancer Trialists Collaborative Group; HR = hazard ratio; RT = radiation.

Table 1

Cardiac mortality in radiation trials before 1973 and after 1993

	Cardiac deaths[a]	Hazard ratio (95% confidence interval)
Diagnosed before 1973		
Follow up <5 years	230/180	1.19 (0.98 to 1.45)
Follow up >5 years	189/145	1.21 (0.97 to 1.50)
Diagnosed after 1993		
Follow up < 5 years	230/180	0.95 (0.79 to 1.14)
Follow up > 5 years	189/145	0.99 (0.73 to 1.50)

[a]Left-sided radiation versus right-sided radiation.

The first two trials that have shown significant systemic RT effect were the British Columbia and the Danish trials [1,2]. Their combined publication in 1997 in the *New England Journal of Medicine* was hailed as a milestone leading to an identifiable paradigm change: although a local modality, RT does have a profound systemic benefit, and should be uniformly introduced as part of guideline recommendations to patients with positive nodes, particularly those with four or more positive nodes involved. Data in both trials showed breast cancer mortality reduction, regardless of the number of lymph nodes involved (Tables 2 and 3).

The EBCTCG meta-analyses, originally not supporting the RT systemic impact, showed finally in their 2005 update a significant overall survival benefit of RT (HR = 0.83, range = 0.0002) (Tables 4 and 5) [6].

The benefit surprisingly is not restricted only to post-mastectomy radiotherapy, but there is a clear mortality reduction after breast-only irradiation following conservative surgery (partial mastectomy), with 19% reduction of odds of death (0.81, range = 0.0002) (Table 4, lower panel and Table 5).

When analyzing these data in more detail it is clear that the major benefit of RT stems from more recent studies that influenced the overall outcome of the Oxford overview. Specifically, the EBCTCG radiation meta-analyses between 1990, 2000 and 2005 showed a gradually escalating radiation benefit ratio: a 13% increased (overall) mortality in the 1990 overview (HR = 1.13), a 4% mortality increase in 2000 (HR = 1.04), but a significant 17% mortality reduction in 2005 (HR = 0.83). This compares with a 27 to 30% mortality reduction (HR = 0.73 to 0.70) from the most recent Danish and British Columbia trials.

Subsets: one to three versus four or more positive nodes? Are there other radiation-predictive markers?

Despite these data, controversy continues to exist as regards to the subsets of patients who would benefit from RT.

Table 2

Rates of breast cancer relapse and hazard ratios related to dose intensity of chemotherapy

Subset	Dose intensity of chemotherapy	No radiation (%)	Radiation (%)	Hazard ratio (DFS)
Arriagada and colleagues [20]				
Node-negative	0.0	59	47	0.70
Node-positive		82	67	0.65
Overgaard and colleagues [2]				
N1 to N3	0.4	53	37	0.61
$N4^+$		76	60	0.64
Ragaz and colleagues [1]				
N1 to N3	0.6	48	36	0.68
$N4^+$		83	62	0.55

Absolute and relative rates of breast cancer relapse (%) and hazard ratios related to the dose intensity of chemotherapy. N1 to N3, one to three axillary nodes involved; ($N4^+$), four or more axillary nodes involved. DFS, first event breast cancer recurrence (or any death).

Table 3

British Columbia Randomized Radiation trial, 2005 update

	Hazard ratio	95% confidence interval
DFS		
All patients	0.63	0.47 to 0.83
N1 to N3	0.64	0.42 to 0.97
$N4^+$	0.59	0.38 to 0.91
SysDFS		
All patients	0.66	0.49 to 0.88
N1 to N3	0.68	0.45 to 1.04
$N4^+$	0.63	0.41 to 0.97
Overall survival		
All patients	0.73	0.55 to 0.98
N1 to N3	0.76	0.50 to 1.15
$N4^+$	0.63	0.41 to 0.97

Cyclophosphamide methotrexate, 5-fluoracil + radiation versus cyclophosphamide methotrexate, 5-fluoracil alone, including all patients and involving patients with one to three axillary nodes involved (N1 to N3) and patients with four or more axillary nodes involved ($N4^+$). DFS, first event breast cancer recurrence (or any death); SysDFS, DFS with systemic recurrence as a first event. Adapted from Ragaz and colleagues [12].

Because the risk of loco-regional recurrence increases with the number of positive axillary lymph nodes, a widely adopted approach, historically, has been to accept RT only for patients with four or more positive axillary nodes. Although this

Table 4

Effect of radiation on local recurrences and breast cancer mortality in node-negative and node-positive disease

	Mastectomy + axillary clearance + radiation	Mastectomy + axillary clearance	Radiation gain (%)
Radiation after mastectomy and axillary clearance			
Isolated local recurrence (%)			
Node-negative	3.1	7.8	4.9
Node-positive	7.8	29.2	17.1
Breast cancer mortality (%)			
Node-negative	27.7	31.3	–3.6
Node-positive	54.7	60.1	5.4
Radiation after conservative surgery (lumpectomy, conservation)			
Isolated local recurrence%			
Node-negative	10.0	29.2	19.2
Node-positive	13.1	46.5	33.4
Breast cancer mortality (%)			
Node-negative	26.1	31.2	5.1
Node-positive	47.9	55.0	7.1

Adapted from Early Breast Cancer Trialists Collaborative Group [6].

Table 5

Breast cancer mortality reduction by radiation after conservative surgery (lumpectomy, conservation)

	Hazard ratio	Two-tailed *P* value
Radiotherapy only to conserved breast	0.84	0.004
Radiotherapy only to conserved breast and other sites (lymph nodes)	0.83	0.0002

Breast alone versus breast plus lymph nodes. Adapted from Early Breast Cancer Trialists Collaborative Group [6].

approach seems logical, it is not supported by the available data.

In the studies of Ragaz and colleagues and of Overgaard and colleagues, as published in the original 1997 *New England Journal of Medicine* analyses [1,2], while patients with four or more positive nodes involved had a higher percentage of absolute relapses, the proportion of events reduced with the loco-regional RT and the hazards reflecting mortality reduction are similar in patients with one to three positive nodes versus four or more positive lymph nodes (Tables 2 and 3). The 2005 *Journal of the National Cancer Institute* update of the British Columbia trial (Table 3) confirmed these earlier data [12]; a recent analysis from the Danish trials also showed that the survival benefits were similar in both nodal groups [13].

Classifying patients into groups with one to three positive nodes versus four or more positive nodes emerged as an artificial distinction originating from early trials of systemic therapy in the 1970s, where it was considered that benefit of any adjuvant therapy may be restricted only in those patients with four or more positive lymph nodes, as toxicity for lower-risk cases may be prohibitive. Later chemotherapy studies, as seen from the recent EBCTCG meta-analyses [14], demonstrated the benefit of adjuvant systemic therapy to be of similar magnitude in patients with one to three involved nodes and in those with the four or more, or even zero, involved nodes [15]. The same trend is followed with RT, and the recent *Journal of Clinical Oncology* editorial on the subject concurs, indicating that 'It is time that we dispense with the artificial partitioning of patients into groups with one to three versus four or more positive nodes' [15].

In light of the above, the focus is on other RT predictive markers – clinical, pathological or molecular biological – which may allow a more accurate identification of cohorts who will derive more substantial RT benefit, from those who derive less or none. This distinction will allow therapeutic policies when fewer patients will be irradiated and when more

benefit will be seen in those irradiated, at a much lower overall cost. What are those subsets other than nodal status?

The first subset concerns estrogen receptor status, lymphovascular space invasion and young age. Cheng and colleagues developed a clinical model to predict loco-regional recurrence rates and the impact of RT on survival. In addition to axillary nodal status, negative estrogen-receptor status, lymphovascular space invasion, and younger age at diagnosis were also all found to be significant [16].

Another subset is the proportion of nodes involved. Truong and colleagues showed from the British Columbia dataset that not only the absolute number, but also the proportion of nodes involved (that is, the percentage involvement rather than the absolute number) does play a role [17].

Also, extensive nodal involvement/extracapsular spread should be considered. Ragaz and colleagues showed that patients with extensive lymph node replacement and/or extracapsular spread have significantly higher recurrences, and display also more benefit from radiation [18].

Finally, there is rising evidence that molecular prognostic factors based on cDNA microarrays will provide more RT predictive markers – as in the Genome Health ONCOTYPE gene 21 or the Dutch Mamma Print assays for chemotherapy [19].

Conclusion: new paradigms of radiation therapy in breast cancer

The present review provides evidence of loco-regional RT offering additional benefits over the adjuvant chemo-hormonal therapy after surgery, with the following evolving paradigms affecting therapeutic guidelines.

First, adjuvant chemotherapy for breast cancer may eradicate more effectively the systemic micro-metastases than the loco-regional ones, and will need RT to finish the job.

RT, although a local modality, does have a strong systemic effect, significantly reducing the rate of systemic recurrences and thus improving overall survival – both in the setting of post mastectomy and after conservation.

While absolute recurrence rates vary with the nodal status, the reduction of events after RT is constant and comparable among patients with one to three positive nodes or patients with four or more positive axillary nodes involved.

Clinical parameters other than nodal status (that is, one to three positive nodes vs. four or more positive nodes involved) – such as the percentage of nodes involved, the extent of nodal involvement/extracapsular spread, the invasion of vascular channels, estrogen receptor-negative status, HER-2/Neu-positive status, or RT molecular biological predictive factors – all constitute interactively indications for RT, with more research into RT predictive markers essential.

Finally, RT may be required for most high-risk patients because presently available chemotherapy, hormonal or biological combinations cannot provide the optimum curative approach for most patients with early breast cancer.

Competing interests

The author declares that they have no competing interests.

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