Radiotherapy Issues After Neoadjuvant Chemotherapy

Kimberley S. Mak, Jay R. Harris

Affiliations of authors: Harvard Radiation Oncology Program, Boston, MA (KSM); Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA (JRH)

Correspondence to: Jay R. Harris, MD, Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, 450 Brookline Avenue, Boston, MA 02115 (e-mail: jharris@core.harvard.edu).

Abstract

Radiotherapy (RT) is standard following neoadjuvant chemotherapy (NCT) and breast-conserving surgery. NCT leads to pathologic down-staging, allowing some patients to undergo breast-conserving therapy (BCT) instead of mastectomy. BCT can also be considered in select stage III patients who respond well to NCT. Clearly-negative surgical margins should be obtained in all patients undergoing BCT. RT is used selectively following NCT and mastectomy. Indications for RT have not been fully established; retrospective data and results from National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 currently form the basis for recommending RT. Patients with locally advanced breast cancer should receive postmastectomy RT (PMRT). Patients with residual nodal involvement require PMRT. Stage I-II patients with a pathologic complete response do not require PMRT. Patients without residual nodal involvement, but with residual breast involvement represent an intermediate-risk group. NCT also provides down-staging in the axilla. The role of axillary RT in the setting of NCT is under investigation in ongoing randomized trials.

The use of neoadjuvant chemotherapy (NCT) in breast cancer has the advantage of targeting both systemic and local-regional sites of disease. NCT leads to pathologic down-staging, allowing some patients who would have originally required mastectomy to undergo breast-conserving therapy (BCT), and sparing some patients axillary lymph node dissection. The main practical benefit to NCT may be an enhanced ability to tailor and limit subsequent local-regional treatment. Although indications for radiotherapy (RT) following initial breast-conserving surgery (BCS) (1) or mastectomy (2–4) are reasonably well-established, the role for RT after NCT and surgery is still being defined. Ideally, patients who do not need RT can be identified, sparing them the side effects and inconvenience of treatment, and decreasing health-care costs without loss of local-regional disease control.

RT Following NCT and BCS

RT is standard following NCT and BCS, even with a pathologic complete response (pCR). Patients older than 70 years with an estrogen receptor-positive cancer can be spared RT after BCS, but such patients are not generally candidates for NCT. Clinical trials are required to identify patients with a pCR who can be spared RT after NCT and BCS. Advances in treating HER2-positive cancers may one day make such patients candidates for omitting RT.

Risk Factors for Local-Regional Recurrence Following NCT and Mastectomy

As there are no randomized trials addressing the role of RT following NCT and mastectomy, there is limited data guiding recommendations for postmastectomy RT (PMRT). A recent systematic review identified 24 studies addressing the role of PMRT following NCT in stage II-III breast cancer. Twenty-three studies were single institution retrospective series, with the only clinical trial data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 (S). Retrospective data from MD Anderson Cancer Center (MDACC) and the prospective NSABP B-18 and B-27 currently form the primary basis for RT recommendations. One retrospective series from MDACC found a 27% 10-year actuarial rate of local-regional recurrence (LRR) in 150 patients treated with NCT and mastectomy without PMRT (6). Clinical stage IIIB or greater, pathologic involvement of 4 or more lymph nodes, and no tamoxifen use independently
predicted for LRR. Another study compared 542 patients treated with NCT, mastectomy, and PMRT to 134 patients who did not receive PMRT (7,8). Ten-year LRR rates were lower with PMRT (11% vs 22%, \[P < .001\]). Notably, patients with clinical stage III–IV disease and a pCR had a 10-year LRR rate of 33% without PMRT, compared with 3% in similar patients who received PMRT (\[P = .006\]).

A subsequent series of 226 patients at MDACC who achieved pCR after NCT and mastectomy found that stage I-II patients who received PMRT had a 0% 10-year LRR rate, vs 33% for stage III patients who did not receive PMRT. This rate decreased to 7.3% in patients who received PMRT (\[P = .040\]) (9). Another series of 132 patients with clinical stage I-II disease treated with NCT and mastectomy without PMRT identified T3N0 stage, 4 or more positive nodes, young age, and no tamoxifen use as predictors for LRR (10). The 5-year LRR rate for 42 patients with clinical T1-T2 disease and 1–3 positive lymph nodes was only 5%.

Taken together, these studies demonstrate that patients with locally advanced or T3N0 disease have a substantial risk of LRR after NCT and mastectomy without PMRT even with a pCR. These data suggest that early-stage disease and 3 or less involved nodes have a low risk of LRR; however, RT was used selectively at MDACC and these results may be subject to potential selection bias.

Analyses from the randomized trials NSABP B-18 and B-27 (11) provide additional important data, given prospective data collection with quality control, larger patient numbers, longer follow-up, and uniformly mandated omission of PMRT after mastectomy and regional nodal RT after BCT. Most of the patients in NSABP B-18 and B-27 had stage II disease; 1071 were treated with mastectomy and 1890 with BCT. In the combined analysis of both trials with 10 years of follow-up, residual pathologic disease in the lymph nodes (hazard ratio [HR] = 4.48) and breast (HR = 2.21) were significant predictors for LRR (11). To a lesser extent, initial clinical nodal status (HR = 1.53) and initial tumor size (HR = 1.58) predicted for LRR. Importantly, lymphovascular invasion, histologic subtype (estrogen receptor, PR, and HER2/neu status), and partial response to chemotherapy were not assessed. These data indicate that LRR risk following NCT and mastectomy depend on both initial clinical and final pathologic staging (Table 1).

**Recommendations for RT Following NCT and Mastectomy**

Patients with stage III or T3N0 breast cancer who undergo NCT and mastectomy should receive PMRT given a high risk of LRR, even if patients have a pCR. In contrast, PMRT for stage I-II patients is determined on a case-by-case basis. Based on the NSABP results, PMRT is indicated for patients who have residual nodal disease, whereas patients with residual breast disease but no residual nodal disease represent an intermediate-risk group, and we recommend a tailored decision based on multiple factors including younger age, extensive residual invasive disease, lymphovascular invasion, estrogen receptor-negative disease, close/positive margins, and poor response to chemotherapy. The available data indicates that stage I-II patients with a pCR do not require PMRT.

**Identifying Patients Who Could Undergo BCT Instead of Mastectomy**

An important benefit of NCT is the potential for patients to undergo BCS rather than mastectomy. Prospective and randomized trials found that NCT was associated with higher rates of BCT than adjuvant chemotherapy, ranging widely from 13% to 83% (12-17).

A retrospective series from MDACC included 340 patients with T1-4, N0-3 M0 breast cancer treated with NCT followed by BCS and RT. Five-year in-breast recurrence rate was 5% and LRR rate was 9% (12). On multivariate analysis, clinical N2-N3 stage, lymphovascular invasion, residual tumor size, and multifocal disease were associated with LRR. The authors concluded that selected patients with T3-4 disease could be managed with BCT. Many institutions including ours, however, favor mastectomy and PMRT in patients with locally advanced disease even with an excellent clinical and pathologic response.

NSABP B-18 and B-27 provide long-term data on risk factors for LRR following NCT and BCT. On multivariate analysis, age less than 50 years (HR = 1.41, \[P = .025\]), clinically node-positive status (HR = 1.70, \[P < .001\]), and pathologic residual nodal disease (HR = 2.25, \[P < .010\]) predicted 10-year LRR (11). Ten-year in-breast recurrence rates of greater than 10% were only seen in patients aged 50 years or younger, who were clinically node-positive and had residual nodal involvement. No information was provided on the influence of estrogen receptor status.

BCS and RT are a reasonable option for patients with early-stage breast cancer down-staged with NCT. Careful selection of patients with clear-negative margins at BCS is important given the frequent finding of multifocal residual disease.

**Table 1.** LRR rates after NCT and mastectomy in NSABP B-18 and B-27

<table>
<thead>
<tr>
<th>Clinical status (at presentation)</th>
<th>Pathologic status (residual invasive disease)</th>
<th>No. of patients</th>
<th>10-year cumulative incidence of LRR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymph node stage</strong></td>
<td><strong>Tumor size</strong></td>
<td><strong>Lymph nodes</strong></td>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>≤5 cm</td>
<td>Positive</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;5 cm</td>
<td>Positive</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*LRR = local-regional recurrence; NCT = neoadjuvant chemotherapy; NSABP = National Surgical Adjuvant Breast and Bowel Project.*
The Axilla: RT Considerations

The optimal assessment of lymph nodes in the setting of NCT remains unclear. Increasingly, sentinel node biopsy is performed after NCT. Pooled data from many single institution experiences show a sentinel node identification rate of about 90% and false-negative rate of 10%. In patients with a negative sentinel node, nodal irradiation is generally not given. Many institutions, including ours, are routinely performing axillary ultrasound with fine needle aspiration of suspicious nodes in patients who will receive NCT. The management of a patient with biopsy-proven nodal involvement before NCT has been axillary lymph node dissection regardless of response to NCT; however, trials testing new approaches will be underway soon (see below).

Future trials will address unresolved issues in the role of RT following NCT and surgery (18). For patients who have no residual disease in the axillary nodes, NSABP-RTOG (NRG) 9353 will enroll patients with clinical T1-3N1 disease and needle biopsy demonstrating axillary nodal disease, who undergo NCT and surgery with axillary lymph node dissection, and are found to have a nodal pCR. Patients who receive RT will undergo either breast irradiation or irradiation to the breast plus regional lymph nodes; patients who received mastectomy will undergo PMRT vs no PMRT.

The Alliance cooperative group (ACOSOG/CALGB/NCCTG) trial A011202 will investigate axillary management in patients with needle biopsy demonstrating axillary nodal disease, with residual nodal disease after NCT. Patients with a positive sentinel lymph node will undergo RT to the full axilla (level I-III) and supraclavicular fossa, vs level I-II completion axillary lymph node dissection with RT to the undissected level III axillary nodes and supraclavicular fossa.

Conclusions

In summary, given a lack of randomized controlled trials, indications for RT following NCT have not been fully established. PMRT is used selectively in patients with stage I-II breast cancer who received NCT and mastectomy, with the most important prognostic factor for LRR being residual nodal disease. The presence of residual breast disease, as well as pretreatment clinical nodal status and primary tumor size, should also be considered. Stage I-II patients with a PCR generally do not benefit from PMRT. RT is routine after NCT and mastectomy for stage III disease, and in any patient who receives NCT and lumpectomy. The main practical benefit to NCT may be an enhanced ability to tailor and limit subsequent local-regional treatment, and this will likely continue with improvements in systemic therapy.

References