Hypofractionated regional nodal irradiation for breast cancer: Examining the data and potential for future studies

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Abstract

Limited data are available examining the role of hypofractionated radiation schedules in the management of women requiring regional nodal irradiation (RNI). The purpose of this review is to examine the available literature for the efficacy (where available) and toxicity of hypofractionated radiation schedules in breast cancer with RNI limited to the axilla and supraclavicular regions. Multiple randomized and prospective studies have documented the feasibility of hypofractionated RNI but the limited numbers prevent definitive conclusions and limited efficacy data are available. With regard to possible toxicity affecting organs at risk with RNI, key structures include the breast, skin, heart, lungs, axilla (lymphedema), and brachial plexus. Based on data from several randomized trials, hypofractionated radiation is not associated with significant changes in breast toxicity/cosmesis or cardiac toxicity; the addition of hypofractionated RNI would not be expected to change the rates of breast or cardiac toxicity. While RNI has been shown to increase rates of pulmonary toxicity, hypofractionated RNI has not been associated with more frequent pulmonary complications than standard RNI. Moving forward, future studies will have to evaluate for increased lung toxicity. With regard to lymphedema, data from randomized hypofractionated WBI trials failed to demonstrate an increase in lymphedema and smaller studies utilizing hypofractionated RNI have failed to as well. Data from head and neck cancer as well as hypofractionated breast radiation therapy (WBI) alone. Subsets from these randomized trials and smaller prospective/single-institution studies have documented the feasibility of hypofractionated RNI but the limited numbers prevent definitive conclusions and limited efficacy data are available. With regard to possible toxicity affecting organs at risk with RNI, key structures include the breast, skin, heart, lungs, axilla (lymphedema), and brachial plexus. Based on data from several randomized trials, hypofractionated radiation is not associated with significant changes in breast toxicity/cosmesis or cardiac toxicity; the addition of hypofractionated RNI would not be expected to change the rates of breast or cardiac toxicity. While RNI has been shown to increase rates of pulmonary toxicity, hypofractionated RNI has not been associated with more frequent pulmonary complications than standard RNI. Moving forward, future studies will have to evaluate for increased lung toxicity. With regard to lymphedema, data from randomized hypofractionated WBI trials failed to demonstrate an increase in lymphedema and smaller studies utilizing hypofractionated RNI have failed to as well. Data from head and neck cancer as well as hypofractionated breast radiation with RNI have failed to demonstrate an increase in brachial plexopathy with the exception of older trials that used much larger dose per fraction (>4 Gy/fraction) schedules. At this time, published data support the feasibility of hypofractionated RNI and the need for a prospective randomized trial addressing clinical outcomes and toxicity of hypofractionated RNI compared with standard fractionation RNI.

Keywords: Breast cancer; Radiation therapy; Hypofractionated; Toxicity; Regional nodal irradiation

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Breast cancer represents the most common non-cutaneous malignancy in women, with over 300,000 new cases diagnosed each year in the United States [1]. While there has been a reduction in the incidence of locally advanced malignancies secondary to increased mammographic screening and awareness, the utilization of regional nodal irradiation (RNI) has increased recently in some countries in response to data suggesting a benefit for those with limited nodal involvement (1–3 nodes positive) [2,3], a cohort where data supporting the use of RNI were previously limited to patients receiving post-mastectomy radiation [4], as well as recent data supporting the use of RNI in place of axillary lymph node dissection for patients with a positive sentinel lymph node [5]. Radiation treatment that incorporates RNI is typically prescribed over 5–6½ weeks utilizing standard fractionation of 1.8–2 Gy per day. Shorter courses of radiation are more cost-effective and open up the capacity of treatment facilities and reduce patient treatment duration [6].

Over the past decade, in an attempt to decrease healthcare spending and improve patient satisfaction, there has been increased utilization of hypofractionated radiation therapy for patients undergoing breast conserving treatment who require treatment to the breast only. This is based in part on new radiobiological data which have shown the radiosensitivity of breast cancer is not as...
dependent on dose per fraction as was previously thought [7]. Strategies, including accelerated partial breast irradiation and hypofractionated whole breast irradiation (WBI), have been utilized with mature data demonstrating comparable outcomes to standard fractionated therapy. Some of the strongest data come from Canada and the United Kingdom where Phase III trials have demonstrated no difference in local control with hypofractionated WBI with long term follow up [7,8].

One concern regarding hypofractionated schedules is the potential for increased acute and late long term toxicities based on commonly used radiobiological models and data from other treatment sites [9]. In regard to breast cancer patients, concerns regarding late toxicity after hypofractionated therapy to the heart, lungs, axilla (lymphedema), and brachial plexus along with skin and breast cosmesis exist and limited published data in the post-mastectomy and RNI settings are available. Therefore, this review is to evaluate the potential for hypofractionated RNI in intact and post mastectomy breast radiation based on a review of published literature.

Materials/methods

This review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; however, a systematic review was not performed [10]. No official review protocol was created for this review. Eligibility criteria for this review included published studies in English, that addressed hypofractionated radiation therapy in breast cancer (excluding accelerated partial breast irradiation), or hypofractionation with effect on target organs of concern. Required information included a reviewable abstract, number of patients, length of follow-up, radiation therapy details (total dose, fraction size and treatment field), and clinical outcomes (recurrence or toxicity). A twenty year interval of publication was chosen in order to focus on more recent literature which included modern surgical and radiation therapy modalities. Sources of information for the review included articles known to the authors, found via Medline/PubMed, and those found in references from the major articles identified. The PubMed search was conducted by two of the authors (CS and SB) to identify publications with the following MeSH headings: (1) accelerated, breast, radiation, and hypofractionated, (2) hypofractionation, heart, lungs, brachial plexus, breast, radiation, regional irradiation, and lymph nodes. When multiple updates from a single study were available, the most recent data were utilized unless results presented were unique to each publication. All searches were completed by July 28, 2013.

Based on the initial searches, a total of 148 articles were identified including 12 articles that were known to the authors while 136 articles were acquired from the literature search; after duplicates were removed, each of the eligible studies were screened independently by two authors (SB and CS) with 33 excluded. Of the remaining 115 studies, full-text articles were assessed for eligibility with data from selected studies extracted including the type of study (prospective v. retrospective), institution, number of patients, follow-up, use of radiation therapy, and outcomes. Studies were excluded due to small numbers of patients (<20), lack of clear radiation receipt, or outcomes presented that were not within the scope of the review. Due to the differences across studies, data were unable to be pooled. For whole breast irradiation only publications, we included only prospective studies due to the large number of randomized and prospective studies available. When evaluating post-mastectomy and regional nodal hypofractionated studies, all studies were included due to a paucity of data. A total of 25 studies were included in this portion of the review with five studies identified that included hypofractionated RNI (Table 1). With regard to the review of organs at risk with hypofractionated schedules a total of 40 studies were identified including some previously identified in the search for hypofractionated breast radiation.

Results

**Hypofractionated whole breast irradiation**

Supplementary Materials Table presents a summary of randomized and prospective studies examining the role of hypofractionated whole breast irradiation [7,8,11–29]. At this time, there exist multiple randomized trials that examined the long-term rates of local control after breast conserving surgery and hypofractionated versus standard whole-breast radiation therapy for early stage

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Year</th>
<th>Patients</th>
<th>Fractionation</th>
<th>Follow-Up (mo)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsden [12]</td>
<td>Randomized, prospective</td>
<td>1986–1998</td>
<td>1,410 (14% chemo, 20% RNI)</td>
<td>42.9/13 v. 39/13 v. 50/25 (All in 5 weeks)</td>
<td>115</td>
<td>No data regarding RNI subset of patients</td>
</tr>
<tr>
<td>START A [7]</td>
<td>Randomized, prospective</td>
<td>1998–2002</td>
<td>2,236 (36% chemo, 15% PMRT, 14% RNI)</td>
<td>41.6/13 v. 39/13 v. 50/25</td>
<td>61</td>
<td>No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT</td>
</tr>
<tr>
<td>START B [7]</td>
<td>Randomized, prospective</td>
<td>1999–2001</td>
<td>2,215 (22% chemo, 8% PMRT, 7% RNI)</td>
<td>40/15 v. 50/25</td>
<td>72</td>
<td>No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT</td>
</tr>
<tr>
<td>UZ Brussels [15]</td>
<td>Randomized, prospective</td>
<td>2007–2011</td>
<td>70 (33% RNI)</td>
<td>50/25 v. 42/15</td>
<td>28</td>
<td>Reduced skin changes and lung function with hypofractionation at 2 years; no difference in fibrosis, lymphedema, or cardiac function.</td>
</tr>
<tr>
<td>Greece [32]</td>
<td>Prospective</td>
<td>2003–2010</td>
<td>112 (all PMRT, 73 RNI)</td>
<td>35/10</td>
<td>44</td>
<td>97% local control; no cases of pneumonitis. Acute toxicity- 23% Grade 2 + dermatitis in boost, 13% beyond field, No Grade 2 + chest pain, pneumonitis, edema, or erythema. Late toxicity- Grade 2 + edema 4.4%, Grade 2 + fibrosis, 7.1%, Grade 2 + chest wall pain 1.8%. No Grade 2 + pleuro-pulmonary or rib fractures</td>
</tr>
<tr>
<td>Thailand [33]</td>
<td>Retrospective</td>
<td>2004–2006</td>
<td>215 (all PMRT; 67 conventional, 148 Hypofractionated)</td>
<td>50/25 v. 42.4–47.2/2.65</td>
<td>39</td>
<td>No difference in loco-regional control; no difference in chest wall appearance, fibrosis, appearance, pleuropathy, lymphedema, cardiac, pulmonary, or rib fractures</td>
</tr>
</tbody>
</table>
invasive breast cancer. The earliest study came from the Royal Marsden Hospital, Sutton and Gloucestershire Oncology Centre where over 1400 women were randomized to one of three arms following BCS: 50 Gy in 25 fractions, 39 Gy in 13 fractions, or 42.9 Gy in 13 fractions with all schedules delivered over 5 weeks. At 10-years, local recurrence rates were 12.1%, 14.8% and 9.6% for women receiving standard fractionation, 39 Gy in 13 fractions, and 42.9 Gy in 13 fractions, respectively with a significant increase in local recurrence for the 39 Gy cohort compared with the 42.9 Gy cohort [30]. Following this study were the United Kingdom Standardization of Breast Radiotherapy (START) A and B trials which randomized women to alternative hypofractionated schedules over differing treatment durations. START A was a three arm trial randomising women to 50 Gy in 25 fractions, 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions all delivered over 5 weeks. At a median follow-up of 9.3 years no difference in local control was noted between arms with a 10 year follow-up showing reduced complications in the 39 Gy arm compared with the standard fractionation arm [7]. START B compared 50 Gy in 25 fractions with 40 Gy in 15 fractions delivered in 5 and 3 weeks respectively. At a median follow-up of 9.9 years no difference in local recurrence was noted with improved toxicity and appearance outcomes noted in the 40 Gy arm [7]. The Ontario Oncology Group randomized 1,234 women with early stage breast cancer to hypofractionated WBI (42.5 Gy in 16 fractions) or standard WBI (50 Gy in 25 fractions). At 10 years, the rate of local recurrence was 6.2% for the 42.5 Gy arm compared to 6.7% in women receiving standard fractionation [8]. No difference in Grade 2/3 skin or subcutaneous toxicity was noted and there was no difference in cosmesis noted.

**Hypofractionated regional nodal irradiation**

With regard to hypofractionation in the post-mastectomy (PMRT) and/or regional nodal irradiation setting, limited data exist. While the START A (15% PMRT, 14% regional treatment) and B (8% PMRT/7% regional treatment) trials incorporated these patients, comprehensive data on efficacy of hypofractionated RNI for this subset have not been reported [7]. A recent update of these studies evaluated the PMRT subset in a limited fashion; for the START A trial, PMRT patients receiving hypofractionated treatment did not develop significantly more normal tissue effects (based on patient assessment) with regard to chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT. Similar findings were noted in the START B PMRT patients when comparing hypofractionation and standard fractionation. Also, no difference was noted when evaluating chest wall symptoms, shoulder/arm symptoms, and body image in the START A/B trial using the BR23 assessment; however, it should be noted that the hypofractionated arm of the START A trial received radiotherapy over 5 weeks rather than 3 weeks [31]. The initial Marsden study did not include PMRT but did include RNI in 20% of cases; no difference in lymphedema was noted between regimens but a subset analysis was not performed [30].

A recent prospective randomized trial from Brussels included post-mastectomy and regional nodal irradiation patients and compared a hypofractionated schema (42 Gy in 15 fractions) to standard fractionation; of the 70 patients in the trial, 40% (n = 28) received PMRT and 50% (n = 35) received chemotherapy. Though not stratified by surgery type, the rate of Grade 3+ acute skin toxicity was 8% in the hypofractionated arm with no increase in chronic fibrosis or lymphedema and no change in cardiac function were noted. A reduction in lung toxicity was noted with the hypofractionated technique [15]. A study from Greece treated 112 patients with hypofractionated PMRT with 98 receiving chemotherapy; with a median follow up of 44 months, no cases of clinical pneumonitis were noted, and 23% developed acute desquamation. Clinical outcomes were consistent with previous series with a 97% local control rate and 84% disease specific survival at 5 years [32]. A retrospective review from Thailand compared conventional and hypofractionated (2.65 Gy × 16–18 fx) PMRT; the series of 215 patients found no difference in clinical outcomes and no difference in chest wall appearance, skin fibrosis, brachial plexopathy, arm edema, pulmonary and cardiac events, or rib fractures with 39 month follow-up [33]. At this time, the data are promising with regard to hypofractionated PMRT and RNI; however, more data are needed in the form of prospective trials examining clinical efficacy as well as toxicity profiles.

**Organs at risk and toxicities associated with RNI**

**Breast**

Both acute and late normal tissue toxicity are important concerns when treating the breast with a hypofractionated regimen. Based on data from randomized trials as well as prospective data, with the exception of one fractionation scheme used in the UK FAST trial [11], there is no worsening of acute or late breast toxicities (appearance or cosmesis) with hypofractionated WBI schedules and in some cases hypofractionation has improved chronic breast appearance outcomes compared to standard fractionation [6,7,13,31]. As noted above, the Ontario Oncology Group found equivalent cosmesis and comparable Grade 3 skin toxicity and subcutaneous fibrosis [8]. Similar findings were noted in the START trials with the 39 Gy arm of the START A arm demonstrating reduced breast changes and the 40 Gy arm of the START B trial demonstrating reduced breast changes compared with standard fractionation [7,31]. The UK FAST trial compared standard fractionation WBI (50 Gy in 25 fx) to 28.5 or 30 Gy in five once-weekly fractions of 5.7 or 6.0 Gy, respectively. Patients in the 30 Gy arm had significantly worse rates of mild/marked breast changes, as assessed by blinded observers, and non-blinded physician assessed moderate/marked adverse effects in the breast compared to patients in the 28.5 Gy arm or patients in the standard WBI arm [11].

In cases where large doses per fraction were utilized (ex. 30 Gy in 5 fractions), prospective data have shown mixed results when demonstrating significant increases in acute or chronic breast toxicity compared with standard fractionation [11,16,24]. Due to increased inhomogeneity and studies demonstrating higher rates of toxicity with standard fractionation, there is concern about the potential risk of increased breast toxicity in larger breast women undergoing hypofractionated schedules. Corbin et al. evaluated 92 large breast patients comparing rates of toxicity with standard and hypofractionation; hypofractionation (42.6 Gy/16 fx) was associated with a reduction in focal moist desquamation (26% vs. 11%) which was confirmed by a retrospective study from William Beaumont Hospital [34,35]. Similarly, Goldsmith et al. evaluated a subset of 279 patients with large breasts in the UK FAST hypofractionation trial and found that larger breast size was a significant risk factor for change in breast appearance [36]. Based on these data and treatment techniques utilized to deliver RNI (mono-isocentric, matched 3rd field, IMRT), it would be unexpected to see an increase in acute and/or late breast toxicities with the addition of hypofractionated RNI to hypofractionated WBI/PMRT, at previously tested fractionation schemes, as the RNI field would add minimal dose to the breast; however, future prospective studies are required to verify these data.

**Cardiac**

Cardiac toxicity with hypofractionation is a late toxicity and important to consider. While no cardiac data are available from the Ontario randomized study, data from START A and B have failed to demonstrate an increase in ischemic heart disease with the hypofractionated schedules [7]. These findings were confirmed by a
prospective series from Belgium that included a subset of patients receiving hypofractionated RNI and a retrospective series from Thailand that included hypofractionated RNI [15,33]. Planning studies using the linear quadratic model have found that compared with standard fractionation, hypofractionated schedules may actually deliver less dose (EQD2) to the heart than standard fractionation based on tangential fields and an a/b greater than 1.5 [37]. Stokes et al. performed a retrospective analysis of 4,929 women that had received adjuvant radiation to the breast/chest wall +/- regional nodes. After a median follow-up of 11.7 years they found that fraction sizes greater than 2 Gy were not associated with increased cardiac events [38]. A prospective study of 300 patients receiving post-mastectomy radiation on three sequential hypofractionated protocols found a 5% rate of cardiac toxicity as defined as a reduction in LVEF of 10% at 5 years (though echocardiogram was only checked at 2 months on the protocol) [39]. These findings have been confirmed on a larger scale; a retrospective study of over 7000 patients found no increase in cardiac toxicity with fractions greater than 2 Gy with 8 year follow-up [40]. Based on standard RNI planning and the limited data available, it is unlikely that the addition of hypofractionated RNI to hypofractionated WBI would increase the cardiac dose as the RNI field is above the superior cardiac border. The exception would be the inclusion of internal mammary node irradiation for which there are limited data with respect to hypofractionation.

Pulmonary

The primary concern with regard to pulmonary toxicity is the potential for sub-acute pneumonitis and subsequent fibrosis leading to impaired respiratory function and decreased quality of life. Randomized data from START A and B and other prospective series have found the rates of pulmonary fibrosis to be less than 2% for hypofractionated WBI consistent with data from standard fractionation WBI studies including the recently published MA-20 trial which found a Grade 2+ pneumonitis rate of 0.2% for WBI alone [3,7,39]. The addition of RNI does potentially increase the rate of pneumonitis as more lung is exposed to treatment fields and was noted to increase pneumonitis rates in the MA-20 trial compared to WBI without RNI (1.3% vs. 0.2%, p = 0.01) [3]. While limited prospective data exist regarding hypofractionated RNI and pneumonitis, a small study from Belgium demonstrated a reduced risk of pneumonitis with hypofractionated RNI compared with standard fractionation RNI which was confirmed by non-randomized data from Thailand and Greece [15,32,33]. Further, when examining dose constraints utilized in current stereotactic approaches for early stage lung cancer and the subsequent rates of pneumonitis along with normal tissue guidelines, it is feasible to keep rates of pneumonitis low when utilizing strict pulmonary constraints with hypofractionated RNI [41–44]. Moving forward prospective studies should evaluate the rates of pneumonitis following hypofractionated RNI and planning studies completed to optimize the amount of lung in treatment fields; one potential strategy is to limit the amount of lung within tangents and supraclavicular fields.

Lymphedema

RNI increases the potential for breast cancer related lymphedema (BCRL). The addition of RNI to BCS and sentinel lymph node dissection with WBI has been consistently found to increase the rates of BCRL from 5–10% to 10–50% and when patients undergo mastectomy to greater than 60% in some series; recent data from the MA-20 found that RNI increased BCRL to 7.3% from 4.1% with WBI alone [34–48]. Limited data exist on the radiobiology of the lymphatic system and the potential for increased toxicities with hypofractionated schedules. Toxicity review from START A and B failed to identify higher rates of BCRL in patients undergoing hypofractionated WBI compared with standard WBI, although a small subset received RNI [7,31]. Prospective data incorporating hypofractionated RNI have failed to identify higher rates of BCRL compared with standard RNI, with small numbers of patients; a larger retrospective series from Asia also failed to identify higher rates of arm swelling with hypofractionated RNI incorporated with hypofractionated PMRT [15,33]. Moving forward, one of the challenges with assessing for BCRL is utilizing a consistent diagnostic standard; prospective studies evaluating hypofractionated RNI must use prospective BCRL assessments starting with a pre-treatment assessment to better quantify the risk of BCRL with hypofractionated schedules [45].

Brachial plexus

Brachial plexopathy is a major concern with hypofractionated RNI as toxicity associated with the structure can significantly impair arm/shoulder function and quality of life (pain, motor function, paresthesias) and is related to dose per fraction, total dose, and volume irradiated. Even assuming low a/b ratios of 1.0–2.0 for the brachial plexus, hypofractionated treatment regimens such as 40 Gy in 15 fractions would deliver a lower EQD2 to the brachial plexus than 50 Gy in 25 fractions [49]. With traditional RNI, the rates of brachial plexopathy are less than 5% while paresthesias are seen in up to 20% of patients [50–53]. When evaluating hypofractionated WBI, data from START B evaluated a small subset of patients (n = 82) receiving hypofractionated RNI and found no cases of brachial plexopathy [7,31]. Similarly, review of START A identified only one case of brachial plexopathy in the 41.6 Gy arm [7,31]. Overall, data from START A and B failed to identify worsening of arm or shoulder function compared with standard fractionation treatment [7,31]. A retrospective review examining hypofractionated PMRT with a subset receiving hypofractionated RNI found no increase in rates of brachial plexopathy [33].

When looking at larger datasets, a recent review from Delanian et al. evaluated the risk of plexopathy with hypofractionated RNI schedules; when using fraction sizes >4 Gy/fx, the rates of plexopathy were over 50% in several older series though these studies used outdated radiation planning and delivery techniques [53–56]. However, several studies that delivered below 3 Gy/fx, and limited total dose to less than 45 Gy, found the rates of brachial plexopathy to be consistently less than 5% consistent with standard fractionation RNI [57–59]. These findings were confirmed by a second large review as well as retrospective PMRT data from Sweden that found high rates of plexopathy with older techniques [60,61]. Based on the data above and extrapolating from the head and neck literature where doses of 60–66 Gy are routinely given, hypofractionated RNI, at previously tested fractionation schemes, is promising with respect to shortening treatment duration without significantly increasing rates of plexopathy [62,63]; however, future studies are needed to verify these findings. One difficulty with prospective trials evaluating hypofractionated RNI will be the long term follow-up required to document plexopathy as many cases present beyond 5 years from treatment [64].

Discussion/conclusions

The purpose of this review was to examine the data supporting hypofractionated RNI based on previously published data on hypofractionated schedules in breast cancer, toxicities to organs at risk with hypofractionated RNI and rates of toxicity with standard fractionation RNI. The results of this review demonstrate several key findings: (1) based on several randomized trials and many prospective trials, hypofractionated WBI represents a safe and efficacious treatment modality, (2) data for hypofractionated RNI are limited to small subsets of patients from randomized and prospective trials but is promising though long term efficacy data are limited, (3) data from hypofractionated breast trials as well as extrapolation from hypofractionated schedules in other organ sites

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supports the further study of hypofractionated RNI, (4) RNI with standard fractionation is associated with increased toxicity compared to WBI alone but current data do not support an increased rate of toxicity with hypofractionated RNI compared with standard fractionation RNI. Taken together, these data support the initiation of further clinical trials evaluating hypofractionated RNI schedules. Demonstrating the safety and efficacy of hypofractionated RNI will allow more women to complete adjuvant radiation in a shortened treatment duration, potentially decreasing the underutilization of adjuvant radiation therapy. Further, from a healthcare economics standpoint, shortened schedules reduces the costs to the healthcare system and allows for increased availability of and improved access to expensive radiation therapy delivery platforms.

Finally, with advances in systemic therapy over the past two decades and increased utilization of RNI, one concern that must be evaluated in future studies is the impact of systemic therapy in concert with RNI (standard and hypofractionated). For example, when evaluating cardiac toxicity with hypofractionated regimens, one must take into account the addition of anthracycline based chemotherapy as well as herceptin. Similarly, pulmonary toxicity and lymphedema rates must be evaluated in the context of taxane receipt.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.12.006.

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