

# Radiation Therapy to the Lymphatics in Breast Cancer

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**Published Date:** October 30, 2016

## ABSTRACT

Radiation Therapy is an integral part of the treatment of invasive breast cancer. There are both benefits in local control and even overall survival with adjuvant radiation to the primary site and lymphatics in appropriately selected patients. Still, there are added risks of toxicity with coverage of the lymphatics that have led to controversy over when to treat these areas.

Along with surgery and systemic therapy, radiation therapy to the breast or chest wall plays an important role in breast cancer treatment. The majority of adjuvant breast cancer trials showing a benefit with radiation have also included treatment of the axillary, supraclavicular, and internal mammary lymph nodes for higher-risk patients. Based on these studies, nodal radiation is omitted in low risk patients with clinically and pathologically node negative disease (cN0 and pN0). On the other hand, axillary dissection that reveals positive nodal disease, particularly with at least 4 nodes involved, is almost always followed by radiation therapy to at least the undissected axillary and supraclavicular nodes, with or without internal mammary nodal radiation. However, many patients are in between these two extremes and it remains unclear whether or not the regional nodes should be treated at all, and if so, which nodal regions to include, for these patients. Therefore, radiation oncologists are often left to use clinical judgment when evaluating each patient's individual risk factors to decide on which areas to cover in the radiation portal.

**Abbreviations:** ACOSOG: The American College of Surgeons Oncology Group; ALND: Axillary Lymph Node Dissection; AMAROS: After Mapping of the Axilla: Radiotherapy or Surgery; DFS: Disease Free Survival; EBCTCG: The Early Breast Cancer Trialists' Collaborative Group; EORTC- The European Organization for Research and Treatment of Cancer; LVSI- Lymphovascular Space Invasion; OS: Overall Survival; PAB: Posterior Axillary Boost; PMRT: Post Mastectomy Radiation; RT: Radiation Therapy; SCV: Supraclavicular; SLN: Sentinel Lymph Node(s); SLNB: Sentinel Lymph Node Biopsy; SNB: Sentinel Node Biopsy

## INTRODUCTION

There are an estimated 246,660 new cases of invasive breast cancer in 2016, as per the American cancer society. The incidence of mortality is 40,450 per year (<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistic>). One of the primary determinants of outcome is axillary stage [1], and therefore upfront clinical staging with palpation and imaging of the axilla is paramount, and leads to appropriate multimodal therapy of breast cancer, including surgery, chemotherapy, endocrine therapy, and radiation therapy. Typically, surgery is performed first, followed by systemic therapy if needed, and then radiation therapy. In special cases, neoadjuvant chemotherapy is recommended followed by surgery and then radiation. Surgical staging and treatment of the lymphatics is important. In breast cancer, it is important to perform axillary staging as well [2].

Clinical imaging used to stage breast cancer includes mammogram, magnetic resonance imaging of breast, and ultrasound of the breast and/or axilla [3-5]. Many times, this leads to an upfront surgical approach including either axillary dissection or, in more contemporary practice, Sentinel Node Biopsy (**SNB**). Based on the pathological findings, chemotherapy and/or radiation directed to the regional nodes, is often elected.

### Axillary Dissection and Sentinel Node Sampling

Axillary dissection was the standard for many years with an adequate dissection involving dissecting greater than 6 to 10 nodes [6]. Recently, the paradigm has shifted to do less extensive surgery such as SNB alone. A SNB is done by identifying the first node where the primary breast tumor drains and can predict for the presence or absence of additional axillary nodes [7]. The procedure is usually done through use of an azulesulfan blue dye or a radiocolloid or both, which is injected into the periareolar or peritumoral tissue. This identifies the first echelon lymph nodes in the axilla, which is shown by a blue color or by gamma probe which detects radioactivity. The accuracy of sentinel node identification is 97% [8-9]. Therefore, in contemporary practice, staging is often done using a SNB, and if negative, this spares the patient from undergoing more extensive dissection. When the SNB is positive, patients getting breast conserving surgery and whole breast radiation can also avoid Axillary Lymph Node Dissection (**ALND**), due to a very low risk of axillary failure.

There are three trials that have compared ALND with SNB alone when a positive SNB is followed by whole breast radiation. The American College of Surgeons Oncology Group (**ACOSOG**) Z0011 study showed that for clinical T1-2 N0 breast cancers treated with lumpectomy and with one to two sentinel nodes positive, an axillary dissection can safely be omitted. Patients were randomized to completion ALND or no further axillary surgery. Ninety-seven percent of patients received systemic therapy and nearly all patients received radiation. The authors note that there was a low nodal burden. In fact, only 13.7% of patients in the ALND group had four or more nodes. The rates of regional nodal failure in the ALND and SNB arms was uniformly low, and were only 0.5% and 0.9% respectively [10]. Possible reasons noted by the authors for the lack of difference in outcomes between the two groups was the use of systemic therapy and radiation therapy in nearly all patients and the low nodal burden. Radiation portals were not standardized, leading to questions by the authors on whether the radiation fields included the level I and II nodal basins that are normally addressed in an ALND. An interesting paper by Jagsi and colleagues addressed this question by retrospectively reviewing port films of patients on Z0011. They found that 81% received tangent only radiation and 15% received Supraclavicular (**SCV**) radiation. Out of those with tangents alone in which the tangential height could be evaluated, 50% actually received high tangents in both groups. In the group in which more detailed records were provided, 18.9% received greater than or equal to three fields with 22 patients in the ALND group and 21 in the SLN group [11]. This study indicates that most patients received some form of nodal Radiation Therapy (**RT**), but it is not clear who these patients were. Some criticisms of Z0011 include that the majority of patients were older ER-positive patients, median follow up was short (6.3 years), the target accrual was not achieved, and radiation therapy was not specified (Which Patients Need Comprehensive nodal RT in 2015. Jagsi, Reshma. Powerpoint at Lynn Sage Breast Symposium 2015). Overall, this study has changed the surgical axillary management for early stage breast cancer patients with 1-2 sentinel nodes positive. These changes are now widely implemented in surgical management and have improved complication rates such as lymphedema, paresthesias, shoulder pain, shoulder weakness, and axillary web syndrome [10]. However, it is unclear what radiation fields should be used given the lack of standardization of radiation, and if perhaps, patients with a positive SNB should receive some sort of regional node radiation.

The International Breast Cancer Study group 23-01 trial found that in patients with micrometastasis, those with ALND had 0.2% axillary recurrence rates and those with SNB alone had 0.8% recurrence rate at a median follow up 60 months [12]. Similarly, a Spanish trial showed an axillary recurrence rate of 1% in patients treated with breast-conserving therapy without ALND at a median follow up of 62 months [13].

Lastly, the European Organization for Research and Treatment of Cancer (**EORTC**) After Mapping of the Axilla: Radiotherapy or Surgery? (**AMAROS**) trial randomized patients with a positive SNB to either ALND versus axillary radiation to the axilla, SCV, and lower neck. The axillary failure rates in the two arms at 5 years were 0.43% and 1.19%, respectively. There was

no significant difference in Disease Free Survival (**DFS**) and Overall Survival (**OS**). Ipsilateral lymphedema was higher after lymph node dissection versus radiation therapy at 1 year, 3 years, and 5 years [14]. The conclusion of this trial was that for SNB positive patients, nodal radiation is a less morbid option in lieu of axillary dissection.

These studies have a unifying theme that early stage breast cancer patients can avoid ALND if the SNB is positive and radiation and systemic therapy are given. They do not give a clear idea of the ideal radiation fields, since these differed among studies; however, with the available data, it seems that most of these patients did get regional node radiation. These studies fit well with some of the older studies that have shown that axillary radiation can replace an axillary dissection. The NSABP-B04 trial examined women with clinically negative axillary nodes randomized to radical mastectomy or total mastectomy without axillary dissection but with postoperative radiation or total mastectomy plus axillary dissection only if their nodes became positive. Those women with clinically positive axillary nodes were randomized to radical mastectomy versus total mastectomy without axillary dissection with postoperative radiation therapy. This study found no significant difference among the three groups with negative nodes or between the two groups with clinically positive nodes. End points included DFS, relapse-free survival, distant-DFS, and OS. They concluded that there was no advantage to radical mastectomy. They also found no difference in these outcomes amongst all clinically node negative mastectomy patients with the groups that had no dissection or radiation, lymph node dissection, or regional nodal radiation therapy [15].

## Axillary Radiation and ALND

In many cases, adjuvant radiation therapy is recommended to decrease the risk of recurrence locally and may even decrease the risk of mortality and increase OS. For early stage cancer, the MA20 and EORTC trials showed regional nodal radiation was beneficial for high risk patients. The Danish 82b and 82c, British Columbia, and the Early Breast Cancer Trialists' Collaborative Group (**EBCTCG**) meta-analysis have shown the benefit of post mastectomy radiation in locally advanced breast cancer. Still, there are cases in which radiation therapy can be omitted such as in early stage cancers after mastectomy in which the risk of recurrence to the chest wall and regional nodes is acceptably low. Some studies have shown that radiation can be omitted in the region that has undergone dissection (level 1) [16].

In the past, Post Mastectomy Radiation (**PMRT**) was controversial and was avoided due to lack of survival advantage and significant toxicity [17]. This notion was changed after the Danish 82b/82c and British Columbia trials showed a survival advantage with PMRT for patients with large tumors (>5 cm) and those with large nodal disease burden (>4 nodes) [18-20].

A retrospective study at MD Anderson in Houston, TX examined regional recurrence and distant metastasis in 1031 patients from five clinical trials that were treated with modified radical mastectomy and doxorubicin-based systemic therapy without radiation. With a median follow up of 116 months, only 3% or 21 patients recurred within the lower mid axilla. Of those, 16 were

isolated regional failures without chest wall failure. They found that the risk of failure in the low-mid axilla was not significantly higher for those with higher number of involved nodes, higher percentage of involved nodes, larger nodal size, or gross extranodal extension. In the 100 patients with less than 10 nodes examined, only three recurrences were in the low mid axilla. There was an 8% rate of recurrence in SCV/axillary apex region. The main predictors for failures in this region were greater than 4 involved axillary nodes, greater than 20% involved axillary nodes, and the presence of gross extracapsular extension. Surprisingly, the extent of axillary dissection and the size of the largest involved node were not predictive of failure in this region. This study concluded that the level I and II axilla is not a common location for recurrence after mastectomy and chemotherapy. This suggests that radiation therapy to dissected axilla may not be warranted for these patients. Still, in those with 4 or more nodes, more than 20% involved nodes, and gross extracapsular extension have a higher risk of failure in the axillar apex and SCV region which may warrant radiation in these undissected regions. The axillary dissection is done “en bloc” at most institutions which theoretically could sterilize this region hence lowering the recurrence rate [16].

It is important to understand the risk of axillary nodal failure after lymph node dissection in order to make an educated decision on adjuvant nodal radiation. Studies have shown that axillary failure rates are low after levels I to II ALND are performed as long as a minimum of 6 to 10 nodes are removed [16,21]. Still, in cases with 8 or more positive nodes, T2-3 tumors with 4 or more nodes or if less than 10 nodes are removed; the failure rate can range from 7-10% or higher [22]. The presence of extracapsular extension does not increase the risk of axillary failure but may impact OS [16,22-25]. Currently, in the era of SNB, axillary recurrence rates are even lower. A newer meta-analysis of 30 studies found that in patients with sentinel nodemicrometastasis, the axillary recurrence rate was 0.3% and in those with sentinel node macrometastasis, the axillary recurrence rate was only 0.7% [26].

## SCV Nodal Radiation

Recurrences of SCV are considered rare with most recurrences associated with patients that have four or more nodes involved. While older series report these patients have 7 to 10% failure rate in the SCV, newer studies report 3% to 5% failure rates. The proportion of involved nodes also plays a role in determining the risk of SCV nodal risk [22].

There are other studies that have shown Lymphovascular Space Invasion (**LVSI**) and grade are also risk factors for SCV relapse [16,27-28]. One study in Taiwan showed that those with higher tumor grade, with four or more nodes, and positive nodes in level II or III had higher SCV failure rates [29]. Another study found that LVSI, having 2-3 positive nodes, extracapsular extension, and involved nodes at level II or III were independent risk factors for SCV failure. If these patients had two or more risk factors, the 5 year SCV failure rate was 27% versus 3% if there were only one or no risk factors [30]. The tumor grade and number of involved nodes has been used to create risk

groups in one London study [31]. With multiple risk factors of grade 3, LVSI, ER negative tumor, and three positive nodes, the 10 year regional nodal failure rate was found to be 12% [32].

## Internal Mammary Nodal (IMN) Radiation

Even less common than SCV failures are IMN failures. In general, metastasis to IMN is about 5% or less with pathologically negative axillary nodes and about 20-50% with positive nodes [33-34]. Generally, the tumor location, size and number of involved nodes influence the risk of disease to the IMNs. Still, it is actually quite common to see the IMN as the sentinel node [35]. It is important to note that only 10-25% of the time, these are involved pathologically [36-39]. Clinical IMN recurrence is very rare at 1% or less in most studies [40].

Although the recurrence rate of IMNs is very rare, it is controversial on whether these nodes should be treated or not. Multiple post mastectomy trials have shown an OS benefit of post mastectomy radiation in those patients with four or more nodes [18-20]. The large EBCTCG meta-analysis also showed an OS benefit even in those women with 1-3 positive axillary nodes [41]. The MA20 and EORTC trials looked at regional nodal radiation in randomized trials and found a benefit when added [42-43]. All of these trials included regional nodes including the IMN chain. Therefore, some believe that treating the IMNs was instrumental to the improvement in outcomes. Still, treatment of the IMNs does add some lung dose and on the left side there is known increase in cardiac toxicity.

A French trial looked at patients with mastectomies with tumors larger than 1 cm, with any node positive or medial/central tumor with or without positive nodes. The trial treated all patients with radiation to the chest wall, SCV region and randomized them to IMN radiation (first 5 intercostal spaces) or no IMN radiation. The trial was powered to show a 10% OS difference which was not achieved. About two thirds of patients had medial tumors and about two thirds of patients were node negative. There was no statistical difference in between the no IMN radiation versus IMN radiation groups in 10 year DFS (53.2% and 49.9% respectively) or OS (59% and 63% respectively). Cardiac events were not statistically significant [44].

A new Danish trial published an abstract in a prospective cohort study looking at macroscopic node positive patients younger than age 70. All patients received periclavicular and chest or breast RT. All left sided patients did not receive radiation to the IMN while those with right sided tumors all received radiation to the IMN. Mastectomy was the main surgery in 65% and 80% of patients were ER positive. 59% of patients had 1 to 3 positive nodes while 15% had greater than 10 nodes positive. They found that OS (75.9% versus 72.2%,  $p=0.005$ ), breast cancer mortality ( $p=0.03$ ), and distant recurrence trended towards less recurrence with IMN radiation ( $p=0.07$ ) [45].

Still, we do not know the relative benefit of IMN versus SCV radiation and when it is acceptable to treat the SCV alone and exclude the IMN. This may be the case in left sided patients in which the cardiac toxicity is a concern or in lower risk patients. It is still unclear which subgroup of patients

is most likely to benefit. We know that groups such as those that are triple negative breast cancer, Her2neu positive, or those with positive axillary nodes are at higher risk of recurrence and distant metastasis. It is also not well defined as to what dose constraints are acceptable for the lung V20 and heart mean dose when treating the IMNs.

## Breast Conservation Therapy and Nodal Radiation

As above, when examining patients in the Z0011 trial in which radiation was not standardized, most received tangent radiation (81%) and 15% received SCV radiation [11]. There was no difference in the radiation fields between the two arms. The question of when to treat the regional nodes in this situation was examined in two recent randomized control trials: MA20 and EORTC trial [42-43]. In the MA20 trial by Whelan et al, patients with breast conservation therapy that were node positive or with high risk features and node negative were included. Patients were randomized to whole breast radiation alone versus whole breast and regional nodal radiation. The high risk node negative group included those with greater than a 5 cm tumor, or greater than a 2 cm tumor and less than 10 nodes removed and either grade 3, LVSI, or ER negative. The study required chemotherapy and/or endocrine therapy. Radiation therapy details were included which were whole breast radiation (50 Gy in 25 fractions), with cone down boost to 10-16 Gy with electrons or brachytherapy. The IMNs were treated with either partially wide tangents or anterior field (electron and photon combination) to 50 Gy in 25 fractions. The SCV and axilla were treated either with anterior/posterior (A/P) to 50 Gy or AP/PA to 45 Gy. The full axilla was treated for greater than 3 positive nodes or if less than 10 nodes were dissected. In this study, there were 10% of patients that were node negative and 25% of patients were ER negative. The two arms were equal in terms of number of axillary nodes removed, age, nodal status, tumor size, grade, and adjuvant therapy. Isolated locoregional recurrence was higher in those without radiation (6.8% versus 4.3%,  $p=0.009$ ). Additionally, DFS was better with nodal radiation (82% versus 77%,  $p=0.01$ ). The OS was not different (81.8% without nodal RT versus 82.8% with nodal RT,  $p=0.38$ ). On planned subset analysis, the ER negative subgroup had improved OS with nodal RT (81.3% versus 73.9%,  $p=0.08$ ). Adverse events included lymphedema which was 8.4% in the nodal radiation group versus 4.5% without nodal radiation ( $p=0.001$ ). Radiation pneumonitis (grade 2) was increased from 0.2 to 1.2%. There was no difference in major cardiac events ( $p=0.26$ ) [42].

The EORTC 22922/10925 trial by Poortmans et al was similar to the MA20 trial. This looked at stage I to stage III patients with either node positive disease or node negative disease with central or medial tumors. Arm one received no nodal radiation, while arm two received IMN and SCV radiation. The groups were equally matched in terms of age, type of surgery, tumor stage, pathologic nodal stage and adjuvant treatment. Forty-five percent of patients were node negative in each group. At a median follow up of 10.9 years, the results showed an improvement in distant DFS with regional node radiation (78% versus 75%,  $p=0.02$ ). They did not detect a significant



difference in OS (82.3% versus 80.7%,  $p=0.06$ ). On subgroup analysis, all patients benefited from nodal radiation including node negative patients [43]. Some believe that the reason for this may be inclusion of the IMN chain although this cannot be proven as SCV radiation was also done.

The decision to treat the regional nodes should be patient specific based on clinical and pathologic risk factors such as receptor status, age, nodal status while keeping in mind the risks of adding radiation therapy to these regions.

## Locally advanced disease and Post mastectomy Radiation Therapy

In general patients with stage III disease are treated with a multi-modality approach usually with a combination of surgery, systemic therapy (chemotherapy and endocrine therapy) and radiation therapy. Historically, PMRT was considered toxic due to its high toxicity to the lung and heart. Over time, the toxicities have decreased tremendously with newer technology and radiation techniques which can block the heart and lung. Three seminal trials in PMRT are the British Columbia trial and Danish 82b and 82c trials. These trials showed that there was an OS benefit with PMRT in high risk patients such as large primary tumors or node positive disease.

The Danish 82b trial randomized high risk pre-menopausal patients who underwent mastectomy for pathologic stage II or III to receive eight cycles of Cyclophosphamide, Methotrexate, and Fluorouracil (**CMF**) plus radiation of the chest wall and regional nodes versus nine cycles of CMF alone. High risk patients were defined as one or more of the following: a) axillary lymph node involvement b) tumor size greater than 5 cm (T3) or c) invasion of cancer to skin or pectoral fascia. At a median follow up of 114 months, locoregional recurrence alone or distant metastasis was 9% in the radiation arm versus 32% in the chemotherapy alone arm ( $p<0.001$ ). DFS was 48% at 10 years in the radiation arm and 34% at 10 years in the chemotherapy alone arm ( $p<0.001$ ). Additionally, OS was also significantly better at 10 years at 54% in the radiation arm and 45% in the chemotherapy alone arm ( $p<0.001$ ). Multivariate analysis showed that adding radiation improved DFS and OS regardless of tumor size, number of positive nodes, or histopathological grade [18]. Some limitations of the study were that there was an exceptional high percent of local failure in the axilla (44%) with chemotherapy alone and the Chemotherapy (**CMF**) is now outdated and not standard. The Danish 82c included post-menopausal women that were randomized patients after mastectomy to adjuvant tamoxifen alone versus tamoxifen plus post mastectomy radiation. This trial also found improved local control, DFS, and OS with addition of radiation [19]. A limitation of both studies was that the number of lymph nodes removed was on average 7 nodes which is considered an inadequate dissection ( $<10$  nodes) [18-19]. On subgroup analysis of patients with 8 or more nodes removed, the OS rate at 15 years was 39% with radiation versus 29% without radiation ( $p=0.015$ ). Radiation was also seen to reduce the 15 year local failure rate from 51% to 10% ( $p<0.0001$ ) in those with 4 or more nodes and reduced the local failure rate from 27% to 4% in those with 1-3 positive nodes. The survival benefit was seen both in the four nodes or more group and in the 1-3 nodes group. This concluded that even patients with 1-3 nodes benefit from PMRT [20].



Similarly, a trial in British Columbia by Ragaz et al randomized pre-menopausal women with invasive breast cancer after modified radical mastectomy to radiation and chemotherapy (**CMF**) versus chemotherapy alone. Radiation therapy was to the chest wall and locoregional lymph nodes including the IMNs. At 15 years of follow up, those that received radiation had a 33% reduction in rate of recurrence and 29% reduction in mortality. At 20 years of follow up, there was an improved OS with the addition of radiation therapy to chemotherapy (47% vs 27% respectively,  $p=0.03$ ). Long term toxicity including cardiac deaths was not different and was minimal for both arms [20].

Recently, EBCTCG meta-analysis on PMRT in 1-3 positive nodes found that radiation reduced the risk of both recurrence and breast cancer mortality in patients with one to three positive lymph nodes. This held true even if systemic therapy was given. These trials included women treatment from 1964-1986 which may be outdated based on today's systemic therapy and radiation techniques. Still, it is important to consider which subgroup of these patients with 1-3 positive nodes will benefit the most from radiation therapy with today's systemic therapy and modern RT techniques. This question is still yet to be answered [41].

We know that there are certain groups of locally advanced patients in which PMRT may be avoided such as those with T3,N0,M0. This group has been described as a specific biological entity that presents with a large primary with no lymph node involvement. Things are more complicated by the fact that some of these patients are now getting neoadjuvant chemotherapy which makes it hard to know their initial lymph node status. One retrospective study by Floyd et al found that the local failure rate in T3 N0 patients after mastectomy without PMRT was only 7%. Overall, treatment decisions in these patients should be based on other pathologic and biologic factors in addition to their staging [46].

A new trial is looking at the role of chest wall irradiation in intermediate risk breast cancer patients following a mastectomy. The Selective Use of Postoperative Radiotherapy AftErMastectOmy-called SUPREMO- trial is randomizing intermediate risk patients to either chest wall irradiation or no chest wall radiation. Patients in this study include pT1, pN1, M0, or pT2, pN0 (with grade 3 histology and or LVSI will undergo a simple mastectomy with a minimum of 1 mm clear margins. For node positive patients, an axillary clearance with a minimum of 10 nodes is required. For node negative patients, a sentinel node biopsy or axillary node sample is valid. Patients with breast reconstruction will be included in this trial. Exclusion criteria includes patients who have undergone neoadjuvant chemotherapy, bilateral breast cancers, or known BRCA1 or BRCA 2 mutation carriers or if positive internal mammary nodes on SLN are seen. Patients that are eligible will be randomized to no chest radiation (standard) and chest wall radiation (experimental arm). The primary end point will be OS and secondary endpoint will be chest wall recurrence, disease-free survival and distant metastasis-free survival, acute and late morbidity, quality of life and cost-effectiveness. This study will help to identify those patients that benefit the most from PMRT in the "grey zone(Selective Use of Postoperative Radiotherapy after MastectOmy, SUPREMO, an MRC phase III randomized trial to assess the role of adjuvant chest

wall irradiation an “intermediate risk” operable breast cancer following mastectomy. (BIG-2-04). UK Medical Research Council, Scottish Cancer Trials Breast group.”

## Nodal Radiation and ALND after Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is now becoming more popular in high risk patients with aggressive tumor biology, large primary tumors or involved lymph nodes. Neoadjuvant chemotherapy has multiple benefits including potentially converting mastectomy patients to breast conservation candidates, predicting tumor biology and prognosis and ability to tailor therapy depending on response to chemotherapy. Since the adoption of neoadjuvant chemotherapy, axillary lymph node management with surgery is now being studied in this setting. Unfortunately, the Z0011 trial did not include neoadjuvant chemotherapy and thus we are not able to apply these results. The ACOSOG Z-1071 study addressed the question of whether a sentinel node after neoadjuvant chemotherapy can be trusted in clinical stage T0-T4, N1-2 patients. All patients had pre-chemotherapy axillary nodal disease that was confirmed by fine needle aspiration or core-needle biopsy. After chemotherapy, patients underwent SLN surgery and ALND with primary end point of false negative rate of SLN surgery. They found that the false negative rate was too high at 12.6%. The study did find that if 3 or more SLNs were examined, the FNR dropped to 9.1%. Using both blue dye and radiolabeled colloid also decreased the FNR to 10.8% [48]. Still, it is still not considered standard of care to undergo SLN surgery alone after neoadjuvant chemotherapy in the setting of clinically node positive disease prior to chemotherapy.

The Sentinel-lymph-node biopsy in patients with breast cancer before and after chemotherapy (**SENTINA**) trial also addressed the question of the Sentinel Lymph Node (**SLN**) in the setting of neoadjuvant chemotherapy. This was a four arm study with the primary end point of false negative rate of the sentinel biopsy after neoadjuvant chemotherapy for patients who converted from clinically node positive to clinical node negative. Arm A was clinical node negative patients who underwent Sentinel Lymph Node Biopsy (**SLNB**) before neoadjuvant chemotherapy. If the SLNB was positive (pN1), a second SLNB procedure was done after neoadjuvant chemotherapy (arm B). Those with clinical node positive disease (cN+) received neoadjuvant chemotherapy. Those converted to clinical node negative after chemotherapy (ycN0) were part of arm C and were treated with SLNB and axillary dissection. Patients who remained positive clinically ycN1 went on to have an axillary dissection without SLNB (arm D). The primary endpoint was false negative rate or accuracy of the SLNB after neoadjuvant chemotherapy for patients who converted from cN1 to ycN0 disease during neoadjuvant chemotherapy (arm C). Detection rate in arm A and B were 99.1%. In patients who were clinically node negative, 35% were found to be pN1 or had occult nodes and were thus evaluated in arm B. In arms A and B, no difference in the detection rate was seen with combined radiocolloid and blue dye versus single agent. But when SLNB was done after neoadjuvant chemotherapy, additional use of blue dye in arms B and C showed an increase in detection rate [48].

In patients who converted from cN+ to ycN0 after neoadjuvant chemotherapy (arm C) was 80.1% and false negative rate was 14.2%. The false negative rate was 24.3% for women who had one node removed and 18.5% if two SLNs were removed in arm C. In patients that had a second SLNB procedure after neoadjuvant chemotherapy in arm B had a detection rate of 60.8% and false negative rate was 51.6%. This study concluded that the SNB is a reliable test before neoadjuvant chemotherapy but after systemic therapy the sentinel node has a higher false negative rate [48].

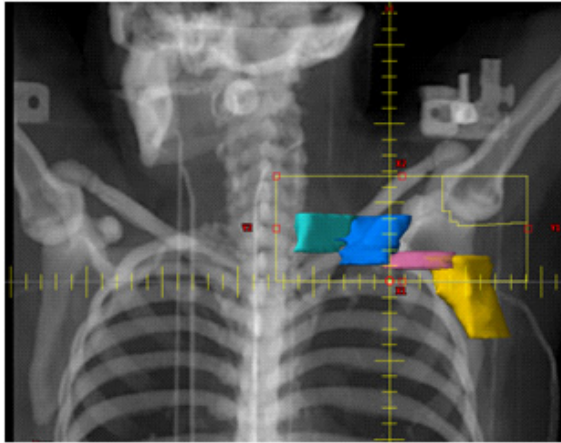
Two new trials, the NSABP B51 and the Alliance trial will help to address the axilla after neoadjuvant chemotherapy in node positive patients. The Alliance trial is randomizing sentinel node positive patients after neoadjuvant chemotherapy to ALND plus breast/chestwall radiation and nodal radiation (without XRT to dissected axilla) versus no further axillary surgery but breast/chest wall and nodal XRT. In B51 patients that are node negative on SNB or ALND after chemotherapy will be randomized to regional nodal radiation versus no regional nodal radiation (NSABP B-51, RTOG 1304 Protocol: A Randomized Phase III Clinical Trial evaluating post-mastectomy chestwall and regional nodal XRT and Post-Lumpectomy regional nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy; Comparison of Axillary Lymph Node Dissection with Axillary Radiation for Patients with Node-Positive Breast Cancer Treated With Chemotherapy: Alliance clinical trial). The results of these trials may be practice changing.

## REGIONAL NODAL RADIATION TREATMENT PLANNING

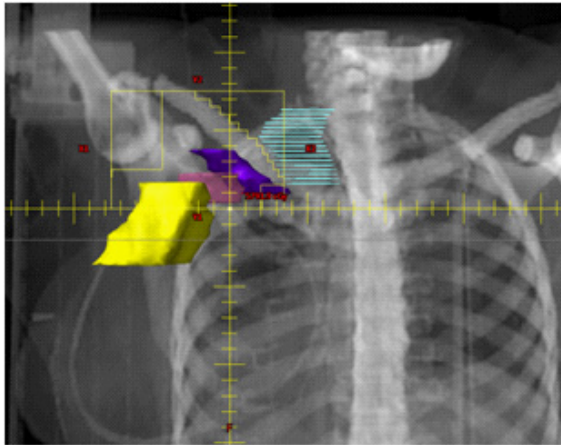
Figure 1 shows a typical SCV field. Typical borders are medially at 1 cm from the anatomical midline to avoid the esophagus. The lateral border is at the coracoid process. Shielding of the shoulder joint and the apex of the lung should be done to avoid fibrosis and lung toxicity. The inferior border will match the tangential field [49].

Figure 2 shows a typical Posterior Axillary Boost (**PAB**). A PAB is typically added as an extra field to cover the axillary nodes that lie deeper than the SCV nodes to ensure adequate coverage of the axilla. The PAB field is defined by 1.5 to 2 cm of the lung medially and laterally at the posterior axillary fold. The inferior border would match the tangent field and the superior border is above the clavicle [49].

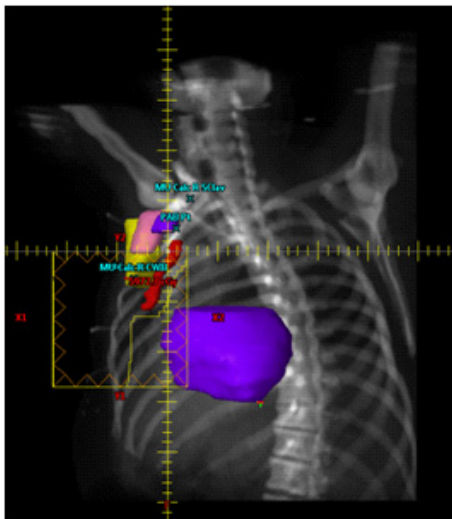
Figure 3 shows inclusion of the internal mammary nodes with a partially wide tangent. Typically, the involved IMNs lie in the first three intercostal spaces between the posterior sternum and parietal pleura [49-51]. An electron or mixed beam can be used to decrease heart exposure [52-54].



**Figure 1:** Supraclavicular field.



**Figure 2:** Posterior Axillary Boost field.



**Figure 3:** Internal Mammary Nodal wide tangent.

## Short and Long Term Side Effects of Radiation Therapy to the Lymphatics

Adjuvant radiation has both short and long term affects including lymphedema, cardiac, pulmonary, neurology and increase risk of secondary malignancy.

The risk of symptomatic edema is approximately 5-10% in patients that have had either SNB, level I to II ALND or radiation alone. In the AMAROS trial, lymphedema defined as arm circumference increase >10% of the ipsilateral arm was seen in 13% in the axillary dissection group and 5% in the radiation alone group at 5 years. The rate of lymphedema in the AMAROS trial was 23% at 5 years in the ALND group and 11% in the axillar radiation group [14,55-56]. In general, as the number of nodes dissected in an ALND increases, the incidence of lymphedema increases [57]. This risk goes up more when axillary radiation is added to a full ALND. Lymphedema usually develops within the first 3 years after treatment [55-56]. Some studies have shown that patients with limited node dissection or SNB and axillary radiation therapy and/or SCV radiation do not have an increased risk of lymphedema [58-64]. Still, in other studies there was an increased risk of edema with radiation [65-67]. The MA20 trial showed that the risk of lymphedema increased from 4.5% to 8.4% with regional nodal radiation [42]. It has been shown in several studies that adding PAB increases the risk of lymphedema (NSABP B-51, RTOG 1304 Protocol: A Randomized Phase III Clinical Trial evaluating post-mastectomy chestwall and regional nodal XRT and Post-Lumpectomy regional nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy) [64,68-70]. Patients with lymphedema can have and diminished quality of life, immobility, and predisposition to cellulitis. Prophylactic manual massage of the arm has not shown to decrease the risk of edema [71]. After lymphedema is seen, some find benefit to manual lymphatic massage along with compression bandages [72].

Nerve injury can also be seen such as intercostal brachial syndrome which includes symptoms of paresthesias, aching and burning pain in the arm, axilla and shoulder region. Nerve blocks to this region can help in some cases [73-72]. Brachial plexopathy secondary to radiation is usually chronic and has an incidence of 0-5% with doses of 50 Gy at 1.8-2 Gy per fraction. It usually surfaces 3 months after radiation and can last for many years [75]. The MA20 trial found no difference in brachial plexopathy with regional nodal radiation versus no regional nodal radiation [42].

Pulmonary toxicity is especially a concern in patient with SCV and IMN radiation as well as when a significant portion of the lung is involved in the tangents. Radiation to the breast and lymphatics can lead to infiltrates on radiograph as well as interstitial fibrosis [76]. Typically, this resolves within 12 months of radiation but may be present for up to 5 years [77]. Rarely, patients may develop clinical radiation pneumonitis which presents with fever, nonproductive cough and infiltrates on radiograph in the location of the radiation portal [76]. Radiation pneumonitis presents around 4 to 9 months after completing RT and has an incidence of less than 5% in

patients treated with a third nodal field with an average lung distance of 3 cm or less [78]. This complication is treated with a long course of steroid taper which usually effectively eliminates symptoms. The MA20 trial found that radiation pneumonitis (grade 2) increased slightly from 0.2% to 1.2% ( $p=0.01$ ) with the addition of regional nodal radiation [42]. The EORTC trial found a 4.4% rate of pulmonary fibrosis with nodal radiation versus 1.7% without nodal radiation ( $p<0.001$ ) [43].

Cardiac toxicity is also concern with addition of radiation to the chest wall/breast and when IMN radiation is done on the left side. Short term toxicity such as pericarditis is very rare with radiation to the breast or chest wall [79]. Long term toxicity has been seen with radiation on the left side but the exact degree of toxicity is debated. Long term toxicity can be seen many years after radiation therapy. Some studies have shown that pre-existing risk factors such as hypertension, diabetes, and smoking may increase the overall risk of cardiac complications [80-82]. One study found that the mean heart dose was an estimate for risk of cardiac toxicity [51]. The MA20 trial found major cardiac events were not statistically different at a rate of 0.4% without regional nodal radiation versus 0.9% with the addition of regional nodal radiation. Of note, regional nodal radiation in the MA20 trial included IMN radiation with partially wide tangents or anterior field of electron and photon combination to 50 Gy in 25 fractions [42]. The EORTC trial found that cardiac fibrosis was slightly higher with nodal radiation at 1.2% versus 0.6% without regional nodal radiation ( $p=0.06$ ). The rate of cardiac disease was not significantly different between the two groups with an overall incidence of 6% [43].

Secondary cancers can occur whenever radiation is delivered. The MA20 trial found no difference in risk of secondary cancers with the addition of regional nodal radiation [42]. Similarly, the EORTC trial found no difference as well [43].

## CONCLUSION

Although there is a vast amount of research published on the topic of breast nodal radiation, there is limited consensus on regional nodal radiation in select situations such as zero to three positive nodes. In these cases, we recommend considering nodal radiation in situations in which other high risk features exist such as T3 or T4 primary tumor, or lympho-vascular invasion, size of nodal metastasis, medial primary tumor, high grade, young age, high recurrence score, extracapsular extension, or triple negative receptor status. Typically, we recommend SCV nodal radiation if the axillary nodes are being targeted with radiation, especially if 4 or more nodes are positive. In general, four field radiation is recommended if there is extensive nodal involvement such as if there are greater than 25% of nodes positive. In early stage cancer with 1-2 positive SLN, the risk of axillary failure is relatively low after breast RT alone. Prophylactic radiation of the IMN is also controversial.

At this time, it is reasonable to omit ALND in low risk patients after a positive SNB per the Z0011 and IBCSG 23-01. The MA20 and EORTC 22922 trials showed there may be a benefit



to adding regional nodal radiation in high risk patients. As we learn about the biology of each individual tumor and its behavior, we will be able to tailor loco-regional management. In cases with a low volume of disease to the axilla, ALND and regional nodal radiation may be eliminated due to advances in modern systemic therapy and radiation techniques. Still, in high risk patients that are at risk for additional nodal disease, comprehensive nodal radiation may have a benefit. Many upcoming trials will answer some of these questions of when it is appropriate to treat regional nodes and when it is reasonable to omit radiation (Which Patients Need Comprehensive nodal RT in 2015. Jagsi, Reshma. Powerpoint at Lynn Sage Breast Symposium 2015).

## ACKNOWLEDGEMENT

Niraj Pahlajani, Radiation Oncology, Baylor Scott and White,

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