The Internet Journal of Oncology
Volume 8 Number 2

Internal Mammary Node Evaluation And Elective Nodal Treatment In Medial Breast Cancers: A Case Report And Review Of The Literature.

E Miles, C Cinnamond, C Allgeier, J Nelson

Citation

E Miles, C Cinnamond, C Allgeier, J Nelson. *Internal Mammary Node Evaluation And Elective Nodal Treatment In Medial Breast Cancers: A Case Report And Review Of The Literature.*. The Internet Journal of Oncology. 2012 Volume 8 Number 2.

Abstract

The evaluation and treatment of the internal mammary nodes (IMNs) in patients with axillary node positive breast cancer undergoing breast conservation therapy is somewhat controversial. A recently reported randomized trial of radiation therapy to the local regional nodes (including the IMNs) in patients undergoing breast conservation therapy demonstrated an improvement in disease free survival and overall survival with this additional nodal irradiation. For patients with tumors in the medial quadrants of the breast, consideration of peritumoral sentinel lymph node procedures with or without periareolar injections should be considered as demonstrated lymphatic drainage to the IMNs may indicate a greater need to consider their inclusion in adjuvant radiation therapy fields, regardless of clinical or radiographic involvement. These nodes may be treated either with a separate IMN field or partially-wide tangents. The benefits of this inclusion must be weighed against the risks of side effects of increased radiation exposure of lung, heart and contralateral breast tissue. Additional long-term data from randomized trials currently underway and maturing may help to define the risks versus the benefits of IMN elective nodal irradiation.

NOTES

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense or the United States Government.

Work performed at the Naval Medical Center Portsmouth, Portsmouth, VA.

INTRODUCTION

In 2010 there were approximately 209,000 new cases of invasive breast cancer diagnosed in the United States, with an estimated 40,000 deaths per year. It represents the leading diagnosis of cancer in women and is second only to lung cancer in overall cancer mortality.[1] The rate of internal mammary node (IMN) positivity has been reported in several large series, and varies a great deal with respect to primary tumor location and axillary lymph node status.[2] Positive axillary involvement and to a lesser degree, medial primary tumor location, are strongly associated with positive IMNs with a rate of involvement between 32% and 65%.[3-8] A multinational randomized trial updated in 1983 demonstrated that extended mastectomies (including IMN resection) did not improve overall survival as compared to radical mastectomies.[9] Evaluation and management of the IMNs largely fell out of favor at that time. Several large trials of post-mastectomy radiation therapy of the regional lymph node areas subsequently demonstrated an advantage to this procedure.[10,11] The technical delivery details varied somewhat, but all of these studies included radiation therapy directed at the IMNs. With the advent of breast conservation, local surgical therapy is directed to the primary tumor with evaluation of the axilla aided by sentinel lymph node dissection using lymphazurin blue dye, radioactive tracer with lymphoscintigraphy, or both. It has been noted that superficial (periareolar) injections were unable to accurately identify the IMNs, but that peritumoral intraparenchymal injections were more reliable.[12-18] A recently reported randomized trial comparing breast conservation therapy (lumpectomy and whole breast radiation therapy) with or without local nodal irradiation has demonstrated that the addition of radiation therapy to the local nodal basins, including the IMNs, results in a small, but statistically significant improvement in disease free survival with a trend towards improvement in overall survival.[19]

Herein, we report on a case of breast conservation therapy and sentinel lymph node procedures for infiltrating ductal carcinoma of the breast that required careful assessment of the IMNs. This patient had a positive axillary sentinel lymph node with a medial primary tumor identified with a periareolar injection strategy and did not have a completion axillary dissection. The decision processes involved in planning the appropriate adjuvant radiation therapy and field design are discussed.

CASE PRESENTATION

A 51-year-old post-menopausal woman with a history of fibrocystic breast disease and bilateral breast pain for many years presented to general surgery after she noted a tender right medial breast mass on self-exam. A subsequent diagnostic mammogram demonstrated solid lesions and an ultrasound (U/S) showed a 1.2 cm hypoechoic mass in the lower inner quadrant of the right breast corresponding with the palpable abnormality. U/S-guided biopsy showed Grade I infiltrating ductal carcinoma, with ER/PR receptors positive and Her2 receptor negative. Staging was completed per the National Comprehensive Cancer Network (NCCN) Guidelines.[20] Magnetic resonance imaging (MRI) of the breasts demonstrated only the known right breast lesion. Preoperative laboratory values were normal, as was her preoperative chest x-ray. She was counseled on her treatment options to include breast conservation therapy versus mastectomy. As she had no contraindications to breast conservation, she elected to pursue this option.

On the morning of surgery, per our institutions standard procedures, she received four divided periareolar injections of a total of 0.95 millicuries (mCi) of ^{99} technetium sulfur colloid. In the operating room, 3 ml of lymphazurin blue dye (Covidien Surgical, Dublin, Ireland) was injected in the subareolar space. A sentinel lymph node was identified in the right axilla with a gamma probe (Neoprobe 2000®, Neoprobe, Dublin, Ohio) and it also contained blue dye. In the operating room, examination of the suspected sentinel node revealed two lymph nodes, with the first containing radioactive tracer and blue dye, and the second node containing radioactive tracer but no blue dye; both were sent to pathology for analysis. The right axilla was screened again with the gamma probe and a 10-second count was below 10% of the activity level of the hottest node so the axilla was closed. Lumpectomy was then completed with resection of the palpable mass lesion with adequate surrounding normal breast tissue with the underlying pectoralis fascia. Pathology demonstrated a 1.2 cm well-differentiated infiltrating ductal carcinoma with widely negative margins, and a 4 mm metastatic deposit in the node that contained radioactive tracer and blue dye. The second sentinel node (containing radioactive tracer but no blue dye) was negative. She was staged as pT1c pN1a (sn), M0, Stage IIA disease.

Her case was discussed at a multidisciplinary tumor board with her surgeons and representatives from Medical Oncology, Radiation Oncology, Radiology, and Pathology in attendance. Per the Memorial Sloan Kettering Cancer Center nomogram, she had a 6% risk of further lymph node involvement in the axilla.[21] Subsequently, she declined a completion axillary dissection and underwent four cycles of systemic chemotherapy with cytoxan and taxotere. She was started on Arimidex hormonal therapy and sent to radiation oncology for completion of her breast conservation therapy with radiation therapy to the right breast and locoregional nodes. A computed tomography (CT) scan was obtained in the treatment position (supine, arms above head, custom foam cradle) for 3D-conformal planning. It was determined that a 4-field beam arrangement consisting of an anterior field to encompass the supra and infraclavicular and axillary nodes, a smaller posterior axillary boost field to cover the mid-line axillary nodes, and tangential breast fields would be necessary to achieve full dose coverage.[22] Because the tumor bed was situated at the medial border of the breast and immediately anterior to the IMNs (see Figure 1), it was possible to include the elective IMNs using a partially-wide angle tangent technique where the medial border of the superior portion of the tangent fields cross the midline so that the IMNs are encompassed.[23] For the purposes of this case study, the results are based on the delivery of 4,600 centigray (cGy), which is delivered to the entire breast and does not include the tumor bed boost. The factors used to evaluate this treatment plan were extracted from a dose-volume histogram. Radiation therapy was well tolerated with no treatment break required. She developed Grade I erythema in the treated breast, but no desquamation was noted. There were no acute or chronic pulmonary complications. She is seen regularly in routine follow-up and at one year post treatment has no evidence of disease recurrence on clinical exam or mammogram.

Figure 1

Table 1 – Ipsilateral lung dosimetric parameters and calculated risk of radiation pneumonitis for the two techniques evaluated.

	V10	V15	V20	MLD	% risk of radiation pneumonitis
Standard Tangents	25.4%	23.3%	21.9%	1,127 cGy	7.9%
Partially-wide tangents	33.3%	29.8%	27.6%	1,347 cGy	10.2%

Figure 2

Figure 1 Â– Skin rendering of planning CT imaging study demonstrating lumpectomy scar (yellow), lumpectomy cavity (red), nipple (orange), internal mammary vessels (green), midline (light blue), sentinel node biopsy site (purple), ipsilateral lung (blue). Note that the tumor bed to axillary node distance is much greater than the tumor bed to IMN distance and the relative location of the periareolar injections which are much closer to the axilla than the either the tumor bed or the IMNs.

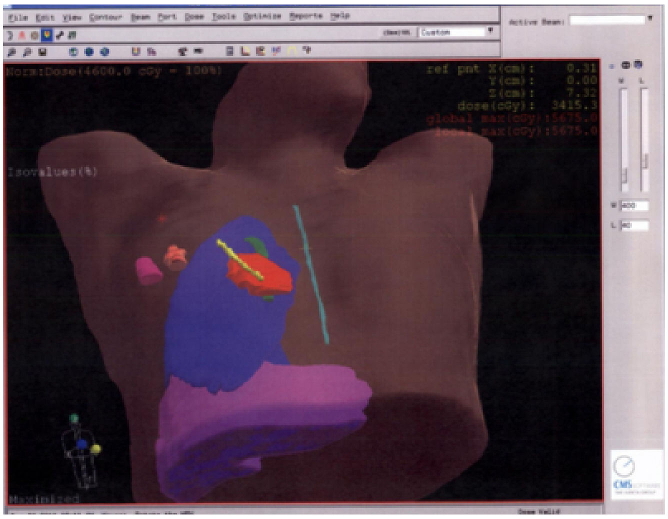


Figure 3

Figure 2 – Axial view of standard breast tangents showing location of lumpectomy cavity and proximity of internal mammary vessels.

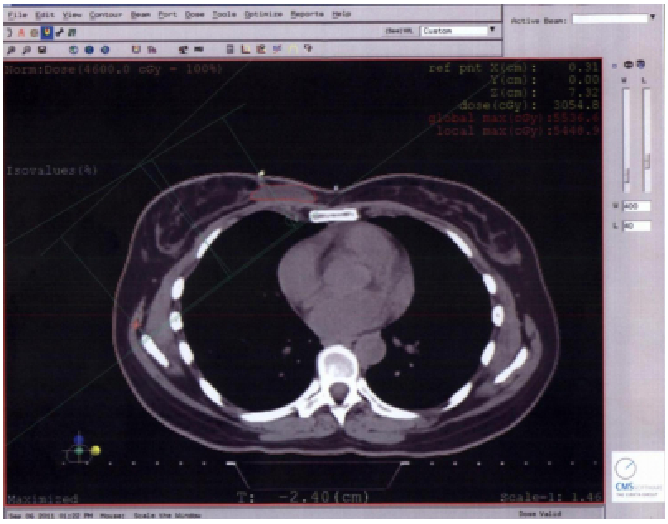


Figure 4

Figure 3 Â– Separate IMN field with modified tangents that match at the skin surface. A mixed photon/electron beam ensures coverage of the IMNÂ's but due to the location of the medial tumor bed; a portion is included in the Â“cold triangleÂ” and would be underdosed with this field arrangement.

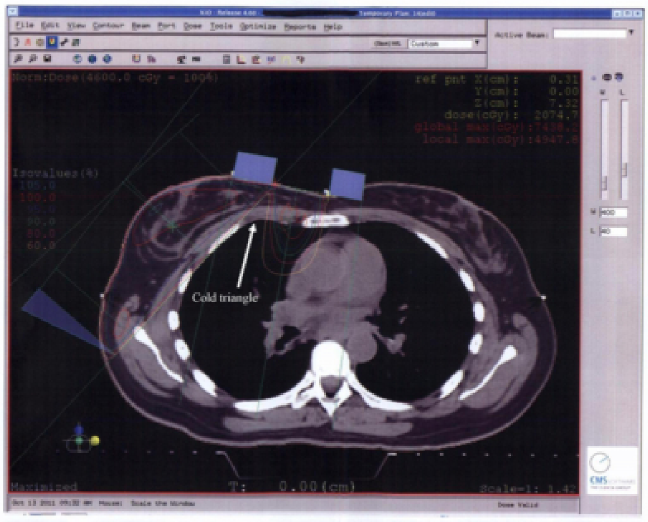
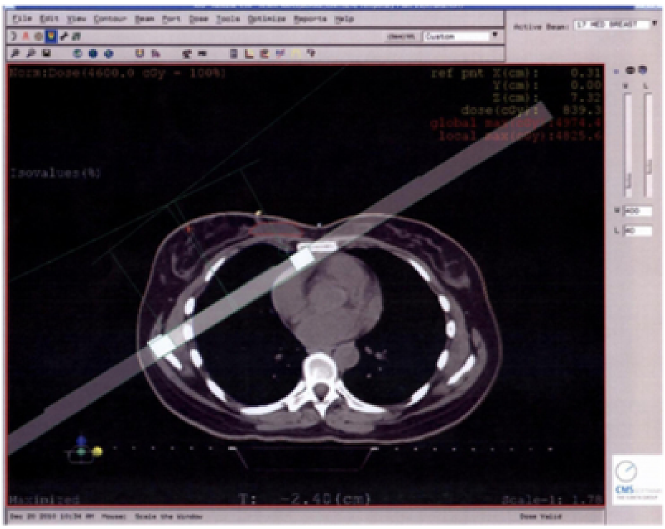


Figure 5

Figure 4 Â– Partially wide tangents showing increased coverage of lumpectomy cavity and internal mammary vessels, but with increased dose to ipsilateral lung tissue and contralateral breast. The superior border of the field-associated shaded area represents the block edge at this axial slice. The inferior border of the shaded area represents the field edge.



DISCUSSION

As noted previously, the addition of local nodal irradiation to whole breast radiation therapy in node positive patients, including treatment directed to the IMN's, has been shown in a recently reported randomized trial (NCIC-CTG MA.20) to result in a statistically significant improvement in disease free survival (89.7% versus 84%, p=0.003), and a trend towards improvement in overall survival (92.3% versus 90.7%, p=0.07); albeit with an increased risk of pneumonitis (1.3% versus 0.2%, p=0.01) and lymphedema (7.3% versus 4.1%).[19] Based on the patient's presentation and the current practice guidelines[24], two additional areas of controversy also had to be resolved during the radiation therapy planning process. Should the IMNs be included in the treatment fields and, if so, what was the best method to encompass them while minimizing the risk of radiation induced side effects to the right lung and left breast?

As per the previously mentioned breast cancer treatment guidelines, in the absence of clinical or pathologic IMN involvement, coverage of these nodes in the adjuvant radiation therapy fields is "at the discretion of the treating radiation oncologist."[24] Previous researchers have found that, compared with laterally-located tumors, tumors originating in the medial and central regions of the breast are associated with an increased risk of systemic relapse and mortality, possibly from occult spread to the IMNs.[25,26] Furthermore, positive IMNs have been noted in as many as 30% of patients with 1-3 positive axillary lymph nodes.[27] However, some investigators maintain that there are unnecessary risks to the heart and lungs when including the IMNs in the radiation fields. Randomized trials assessing the benefit of adjuvant radiation therapy specifically to the IMNs in the setting of mastectomy[28,29] and breast conservation surgery[30] have not shown improved survival outcome although more randomized prospective research in this area is currently underway._ [31] A recent review article by Xie et al computed the theoretical benefit in overall survival with elective nodal irradiation of the IMNs in patients with positive axillary nodes (even after accounting for an estimated 2% increase risk treatment-induced mortality) at 6.3%, and notes that previous randomized trials addressing IMN irradiation that failed to show a survival benefit may have been underpowered.[32]

In this patient, with a medially located tumor, no completion axillary dissection to fully assess the level of axillary involvement, and a very short tumor bed to IMN distance (see Figure 1, tumor to IMN vessel distance of approximately 3 cm, tumor to positive axillary lymph node distance of approximately 15 cm), the risk of IMN-positive disease was thought to be high enough to consider inclusion of this nodal drainage area in the adjuvant radiation therapy. A lymphocintigraphy image is not usually obtained at our institution prior to going to the operating room, but may have been useful in this case, particularly if peritumoral injections had been placed.

Three general potential treatment options were evaluated to determine the treatment plan with the most benefit and least amount of risk for this case. Depending on the technique, this could mean an increase in dose to the ipsilateral lung and contralateral breast or a decrease in the dose to the medial aspect of the affected breast tissue. The most important dose constraints considered were the volume of ipsilateral lung exposed to 10 Gy (V10), V15, V20, and mean lung dose (MLD). Recent data demonstrates a 10-20% risk of developing radiation pneumonitis with a V10 of 31-43%, a V15 of 26-34% and a V20 of 26-34% of total lung volume.[33] Above these values, the risk becomes even greater. For this case, the dose volume parameters reported are for the ispilateral lung only. Increased dose to the unaffected left breast was also noted.

The first option was to exclude the IMNs from the treatment fields. A traditional 4-field technique in which the medial edge of the tangential breast field does not cross over the midline (or does so to the minimum extent possible to provide coverage on the medial tumor bed location) would have been implemented. The fields would have been shaped so that the majority of the right breast tissue was included, while conforming to the contour of the chest wall (Figure 2) with a non-divergent posterior border thereby lowering dose to the right lung. This resulted in a V10 of 25.4%, a V15 of 23.3%, a V20 of 21.9%, and an MLD of 1,127 cGy. The left breast received only the expected minimal scatter dose. With this technique, the dose to the right lung is minimized to reduce the risk of developing radiation pneumonitis. It should be noted that due to the geometry of the beams, approximately one-third of the total ipsilateral lung dose is contributed from the anterior supraclavicular and posterior axillary fields.

A second method, often used before the development of three dimensional planning, was to include the IMNs in a 5-field technique that included an anterior mixed photon/electron beam in addition to the traditional fields. This gives adequate depth to encompass the nodes and yields similar dose-volume results as the traditional 4-field plan. However, the complex geometry of the mixed angles and modalities would have resulted in a “cold” (50% of the prescribed dose) triangle of tissue at the junction of the beams under the skin surface (Figure 3). This would have been problematic in this particular case as the “cold triangle would have been localized to the lumpectomy cavity due to the medial location of the original tumor site. The volume of this “cold triangle” can be minimized by several techniques, including overlapping the separate IMN field on the skin with the tangents, or angling the separate anterior IMN fields towards the angle of the tangents, but these techniques minimize and do not eliminate this effect. Overlapping fields can also cause localized overdose with resultant toxicity. Both of these techniques are further complicated by the small, but non-zero, daily set-up error. Therefore, this technique was not considered a viable option for this patient.

The final technique, and the one eventually used to treat this patient, was to increase the field size of the medial border to create so-called partially-wide tangent fields.[34] This technique permitted deeper tissue coverage which allowed the IMNs to be included (Figure 4). As expected, there was increased dose to the right lung as well as the contralateral breast. The right lung V10 was 33.3%, V15 was 29.8%, and V20 was 27.6% with an MLD of 1,347 cGy. Table 1 compares the dosimetric parameters associated with pulmonary toxicity as well as an estimate of the percent risk of radiation pneumonitis calculated from the MLD using a method described by Xie et al in their recent review article.[32] Because of the partially wide angle tangents, the medial border of the tangential field crossed over the midline of the patient resulting in 2% of the left breast receiving half of the prescription dose (2,300 cGy). Although the volume of lung treated was higher than that of the regular 4-field arrangement, the dose volume values still fell within a reasonable range, allowing for a more aggressive approach and possibly a better outcome with only a slightly increased risk for adverse pulmonary side effects. It was concluded that due to the relatively unknown extent of total nodal involvement, including the axilla and the IMNs, the medial location of the tumor, and the favorable anatomy of this patient that the benefit of including the IMNs in her adjuvant radiation therapy outweighed the risks associated with a slight increase (2.3%) in the potential for pulmonary side effects.

CONCLUSION

In conclusion, evaluation and treatment of the IMNs in patients with axillary node positive breast cancer undergoing breast conservation therapy is somewhat controversial. For patients with tumors in the medial quadrants of the breast, consideration of peritumoral sentinel lymph node procedures, with or without periareolar injections, should be considered as demonstrated lymphatic drainage to the IMNs may indicate a greater need to consider their inclusion in adjuvant radiation therapy fields, regardless of clinical or radiographic involvement. If the index of suspicion of IMN involvement is high, particularly in axillary node positive patients with medial tumors, consideration should be given to inclusion of the IMNs in the adjuvant radiation therapy fields (as was the case in the recent randomized trial that showed a benefit in terms of disease free survival in node positive patients), either with a separate IMN field or partially-wide tangents. The benefits of this inclusion must be weighed against the risks of side effects of increased radiation exposure of lung, heart and contralateral breast tissue. Additional long-term data from randomized trials currently underway and maturing may help to define the risks versus the benefits of IMN elective nodal irradiation.

References

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300
2. Chen RC, Lin NU, Golshan M, et al: Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review. J Clin Oncol 26:4981-9, 2008
3. Handley RS: Carcinoma of the breast. Ann R Coll Surg Engl 57:59-66, 1975
4. Donegan WL: The influence of untreated internal mammary metastases upon the course of mammary cancer. Cancer 39:533-8, 1977
5. Caceres E: Incidence of Metastasis in the Internal Mammary Chain in Operable Carcinoma of the Breast and 5 Year Results. Acta Unio Int Contra Cancrum 19:1566-9, 1963
6. Lacour J, Bucalossi P, Cacers E, et al: Radical mastectomy versus radical mastectomy plus internal mammary dissection. Five-year results of an international cooperative study. Cancer 37:206-14, 1976
7. Livingston SF, Arlen M: The extended extrapleural radical mastectomy: its role in the treatment of carcinoma of the breast. Ann Surg 179:260-5, 1974
8. Huang O, Wang L, Shen K, et al: Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat 107:379-87, 2008
9. Lacour J, Le M, Caceres E, et al: Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. Cancer 51:1941-3, 1983
10. Ragaz J, Jackson SM, Le N, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337:956-62, 1997
11. Nielsen HM, Overgaard M, Grau C, et al: Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 24:2268-75, 2006
12. Farrus B, Vidal-Sicart S, Velasco M, et al: Incidence of internal mammary node metastases after a sentinel lymph node technique in breast cancer and its implication in the radiotherapy plan. Int J Radiat Oncol Biol Phys 60:715-21, 2004
13. Roumen RM, Geuskens LM, Valkenburg JG: In search of the true sentinel node by different injection techniques in breast cancer patients. Eur J Surg Oncol 25:347-51, 1999
14. Paganelli G, Galimberti V, Trifiro G, et al: Internal mammary node lymphoscintigraphy and biopsy in breast cancer. Q J Nucl Med 46:138-44, 2002
15. Shimazu K, Tamaki Y, Taguchi T, et al: Lymphoscintigraphic visualization of internal mammary nodes with subtumoral injection of radiocolloid in patients with breast cancer. Ann Surg 237:390-8, 2003
16. Benda RK, Cendan JC, Copeland EM, et al: Should decisions on internal mammary lymph node irradiation be based on current lymphoscintigraphy techniques for sentinel lymph node identification? Cancer 100:518-23, 2004
17. Park C, Seid P, Morita E, et al: Internal mammary sentinel lymph node mapping for invasive breast cancer: implications for staging and treatment. Breast J 11:29-33, 2005
18. Paredes P, Vidal-Sicart S, Zanon G, et al: Clinical relevance of sentinel lymph nodes in the internal mammary chain in breast cancer patients. Eur J Nucl Med Mol Imaging 32:1283-7, 2005
19. Whelan T, Olivito, I., Ackerman, J., et al: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol 29, 2011
20. Bevers TB, Anderson BO, Bonaccio E, et al: NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. J Natl Compr Canc Netw 7:1060-96, 2009
21. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al: A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 10:1140-51, 2003
22. Gunderson LL: Clinical Radiation Oncology (ed 2nd.). Philadelphia, Churchill Livingston, 2007
23. Kahn F: Treatment planning in radiation oncology (ed 2nd). Philadelphia, Lippincott, Williams & Wilkins, 2007
24. Carlson RW, Allred DC, Anderson BO, et al: Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 7:122-92, 2009
25. Lohrisch C, Jackson J, Jones A, et al: Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. J Clin Oncol 18:2828-35, 2000
26. Zucali R, Mariani L, Marubini E, et al: Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. J Clin Oncol 16:1363-6, 1998
27. Sugg SL, Ferguson DJ, Posner MC, et al: Should internal mammary nodes be sampled in the sentinel lymph node era? Ann Surg Oncol 7:188-92, 2000
28. Romestaing P, Ecochar, R., Hennequin C., et al: Role of internal mammary chain irradiation on survival after mastectomy for breast cancer: results of a phase III SFRO Trial. Radiother Oncol 56:1, 2000
29. Romestaing P. BA, Hennequin C., et al: Ten-year results of a randomized trial of internal mammary chain irradiation after mastectomy. Int J Radiat Oncol Biol Phys 75:1, 2009
30. Kaija H, Maunu P: Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. Radiother Oncol 36:172-6, 1995
31. Matzinger O, Heimsoth I, Poortmans P, et al: Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). Acta Oncol 49:24-34, 2010
32. Xie L, Higginson DS, Marks LB: Elective regional nodal irradiation in patients with early-stage breast cancer. Semin Radiat Oncol 21:66-78, 2011
33. Schallenkamp JM, Miller RC, Brinkmann DH, et al: Incidence of radiation pneumonitis after thoracic irradiation: Dose-volume correlates. Int J Radiat Oncol Biol Phys 67:410-6, 2007
34. Marks LB, Hebert ME, Bentel G, et al: To treat or not to treat the internal mammary nodes: a possible compromise. Int J Radiat Oncol Biol Phys 29:903-9, 1994

Author Information

Edward F. Miles, M.D.
Department of Radiology, Division of Radiation Oncology, Naval Medical Center Portsmouth

Cade C. Cinnamond, D.O.
Department of Surgery, Naval Medical Center Portsmouth

Christine C. Allgeier
Department of Radiology, Division of Radiation Oncology, Naval Medical Center Portsmouth

John W. Nelson, M.D.
Department of Radiology, Division of Radiation Oncology, Naval Medical Center Portsmouth