Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2019 April 01; 103(5): 1100–1108. doi:10.1016/j.ijrobp.2018.11.045.

Long-Term Pulmonary Outcomes of a Feasibility Study of Inverse-Planned, Multibeam Intensity-Modulated Radiation Therapy (IMRT) in Node-Positive Breast Cancer Patients Receiving Regional Nodal Irradiation

Alice Y. Ho, MD¹, Ase Ballangrud, PhD², Guang Li, PhD², Gaorav P. Gupta, MD, PhD¹, Beryl McCormick, MD¹, Richard Gewanter, MD¹, Daphna Gelblum, MD¹, Melissa Zinovoy¹, Boris Mueller, MD¹, Borys Mychalczak, MD¹, Pinaki Dutta, MD¹, Karen Borofsky, MD¹, Preeti Parhar, MD¹, Marsha Reyngold, MD¹, Lior Braunstein, MD¹, Mohit Chawla, MD³, Kate Krause, MD¹, Natasha Freeman, MD¹, Chun Ting Siu, B.A¹, Zachary Cost, B.S.¹, Brittany B. Arnold, B.A.¹, Zhigang Zhang, PhD⁴, Simon N. Powell, MD, PhD¹

¹Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

²Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY

³Department of Medicine, Pulmonary Service, Memorial Sloan Kettering Cancer Center, New York, NY.

⁴Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background: Multi-beam IMRT enhances the therapeutic index by increasing the dosimetric coverage of the targeted tumor tissues while minimizing volumes of adjacent organs receiving high doses of RT. The tradeoff is that a greater volume of lung is exposed to low doses of RT, raising concern about the risk of radiation pneumonitis (RP).

Methods: Between 7/2010–1/2013, patients with node-positive breast cancer received inverse-planned, multibeam IMRT to the breast/chest wall and regional nodes including the internal mammary nodes (IMN). The primary endpoint was feasibility, predefined by dosimetric treatment planning criteria. Secondary endpoints included the incidence of grade 3 RP and changes in pulmonary function measured by CTCAE v3.0 scales, pulmonary function tests (PFTs) and

Corresponding Author: Dr. Alice Y. Ho, Department of Radiation Oncology, Massachusetts General Hospital; 100 Blossom Street; Boston, MA 02114; telephone: 617-724-1160; fax: 617-726-3603; alice.ho@mgh.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier NCT 01127373

Presentations: Recently presented in part at American Society for Radiation Oncology Annual Meeting, San Diego, California, September 25, 2017 and American Society for Radiation Oncology Annual Meeting, Boston, Massachusetts, September 25, 2016.

Disclaimers: None.

community acquired pneumonia (CAP) questionnaires, obtained at baseline and at 6 months post-IMRT. Clinical follow-up was q6 months up to 5 years.

Results: Median follow-up was 53.4 months (0–82 months). Of 113 patients enrolled, 104 completed follow-up procedures. Coverage of the breast/chest wall and IMN was comprehensive (median 48.1 Gy and 48.9 Gy, respectively. Median volume of lung receiving high dose (V20Gy) and low dose (V5) was 29% and 100%, respectively. The overall rate of respiratory toxicities was 10.6% (11/104) including 1 grade 3 RP event (.96%). No differences were found in PFT or CAP scores following IMRT. The 5-year rate of locoregional recurrence-free, disease-free and overall survival was 93.2%, 63.6%, and 80.3%, respectively.

Conclusions: Multi-beam IMRT in breast cancer patients receiving RNI was dosimetrically feasible, based on early treatment planning criteria. Despite the large volume of lung receiving low dose RT, the incidence of grade 3 RP was remarkably low, justifying inverse-planned IMRT as a treatment modality for high-risk breast cancer patients in whom conventional RT techniques prove inadequate.

Summary:

Multi-beam IMRT increases the dosimetric coverage of targeted tissues while minimizing volumes of adjacent organs receiving high doses of RT, however exposes a greater volume of lung to low doses of RT, raising concern about radiation pneumonitis (RP). Our pilot study evaluated the dosimetric feasibility of inverse-planned, multibeam IMRT and incidence of RP. Coverage of targeted tissues was comprehensive, with low rates of grade 3 RP (.96%) and high 5-year locoregional recurrence-free survival (93.2%).

Introduction:

Postmastectomy radiation therapy (PMRT) is an integral component of the treatment of locally advanced breast cancer. A large meta-analysis including several randomized trials conducted in the 1970s demonstrated both locoregional and overall survival benefits of PMRT in women with node-positive breast cancer¹. Unfortunately, these advantages were offset by the disproportionate number of adverse effects including pneumonitis, attributed to the use of 2D techniques that encompassed large volumes of normal tissues²³.

In 2018, 3D-conformal techniques have replaced these older techniques, resulting in the reduction of RT-associated toxicities. Whereas 3D-CRT statically conforms each radiation field to the beam's view of the target tissue, inverse-planned IMRT "paints" subregions of the targeted tissue to different doses so that high doses to critical normal organs may be avoided⁴. At the time this study was initiated, the impact of resource intensiveness and technical challenges of delivering inverse-planned IMRT in breast cancer patients were unknown, prompting the need for evaluating its feasibility, safety and long-term disease outcomes in breast cancer patients receiving regional nodal irradiation (RNI).

Methods and Materials:

Study Design:

This study ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: [blinded]) was approved by the Institutional Review Board at [blinded]. All patients signed written informed consent and were enrolled between July 2010 to January 2013. The design was a single-arm, prospective trial. The primary objective was to determine the feasibility of inverse planned IMRT. Secondary objectives were to assess the rate and severity of pneumonitis and disease control following IMRT.

Patient Selection:

Eligible patients were 18 years old with an ECOG of 0 or 1 performance status, a pathologic diagnosis of primary breast cancer requiring RNI and preclusion of treatment with conventional RT techniques due to left-sided breast cancer with difficult cardiac anatomy as determined by the MD or presence of an immediate implant reconstruction. Indications for RNI included inflammatory breast cancer, 4 positive lymph nodes or 1–3 positive nodes with other high-risk features such as large primary tumor size, lymphovascular invasion, triple negative subtype or young age. Exclusion criteria included distant metastases, prior RT to the ipsilateral or contralateral breast or thorax, primary breast lymphoma or sarcoma and a history of non-skin malignancy <5 years prior to the diagnosis of breast cancer.

Target and Normal Structure Delineation:

Lungs were defined using the autocontour function in Pinnacle (Philips, Eindhoven, Netherlands). The heart was contoured from the bifurcation of the pulmonary arteries extending inferiorly to the left ventricle. The clinical target volume (CTV) included the breast or CW, prosthesis (when applicable) ipsilateral regional lymph nodes, interconnecting lymphatic drainage routes and overlying skin. The regional nodes included the level I–III axillary lymph nodes, supraclavicular nodes and the IMNs, which were included within the first 4 intercostal spaces. The CTVs were contoured according to RTOG breast cancer contouring atlas or Dijkema et al^{5,6}. The CTV was expanded by 2–5 mm non-uniformly to create the planning target volume (PTV).

Treatment characteristics:

All patients received breast-conserving surgery or mastectomy in addition to sentinel node biopsy, axillary dissection or both. Systemic therapy was administered according to institutional standards of care. A minimum of 4 weeks following the last dose of chemotherapy was required prior to IMRT. Concurrent biologic therapy and antiestrogen hormonal therapy was permitted.

The prescription dose was 50 Gy delivered in 25 fractions over 5 weeks. Approximately 8–12 coplanar IMRT beams and 6 MV photons. Daily bolus of 3–5 mm was applied over the chest wall in all mastectomy patients. Dose volume histograms (DVH) were generated for the PTV and critical organs. Patients with conserved breasts received a sequential 10 Gy boost to the tumor cavity. No patients received a chest wall boost. Daily positioning of the patient was verified with either AlignRT (VisionRT, London, UK) or kilovoltage films prior

to each treatment. An example of beam arrangement and dose distribution of a patient treated on protocol with multi-beam IMRT is illustrated in Appendix 1, Supplemental Figure 1.

Treatment Planning Objectives:

Optimization was guided by the target tissue coverage and normal tissue avoidance parameters described in Appendix 1, Supplemental Table 1⁷. Plans were normalized such that 95% of the PTV received at least 95% of the prescription dose (D95 = 95%). Indicators of high lung dose was denoted by V20, the volume of ipsilateral lung that received 20Gy. Dosimetric criteria restricted V20 to be less than or equal to 30% in all study patients. Low lung dose was denoted by V5, the volume of lung that received 5Gy.

Assessment of Pneumonitis:

History and physical examination was performed at baseline, 6–12 weeks, 6±1 months and 12±1 months post-IMRT and then q6±1 months up to 5 years. Respiratory toxicities were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 scale, which characterizes the severity of pneumonitis from grade 1 to 5. PFTs were performed at baseline and 6±1 months at [blinded]. If a respiratory event concerning for pneumonitis was reported prior to the 6-month assessment point, treating physicians were encouraged to obtain PFTs. CAP questionnaires, a validated, 8-item patient survey to evaluate respiratory symptoms and well-being in community acquired pneumonia, were administered at baseline and at 6-month follow-up⁸. The questionnaire generated a CAP score from 0 to 100, with low values indicating more severe symptoms⁹.

Statistical analysis:

The primary endpoint was feasibility, defined as achieving the dosimetric criteria outlined in Appendix 1, Supplemental Table 1, in no fewer than 90% of enrolled patients. We deemed this was an acceptably low threshold for feasibility in a study cohort consisting of patients with high-risk features for whom options for adequate coverage of the target regions with conventional techniques were limited.

The probability of considering IMRT feasible was 99%, 58%, 10% and 0.6%, based on the true feasibility rate of 0.95, 0.85, 0.825 and 0.80, respectively. After considering that a proportion of patients would be inevaluable at the 6-month time point due to disease progression or lack of follow-up, we needed to enroll 100–120 patients.

The Mann-Whitney test was used to assess trends in heart and lung dose over the study period. Non-parametric estimates of the survival or recurrence distribution were obtained by Kaplan-Meier methods. Disease control end points were dated from the date of IMRT completion. Tests were declared statistically significant if the calculated p-value was <0.05. All tests used two-sided p-values. The incidence of respiratory toxicities and its 95% confidence interval were calculated using the binomial distribution.

Results:

Patient and Treatment Population

Figure 1 is a CONSORT diagram illustrating the study population. A total of 113 patients were enrolled. One patient withdrew consent prior to simulation. One patient discontinued RT due to disease progression; 111 patients completed the planned course of IMRT and were assessed for feasibility and clinical outcomes. Their baseline characteristics are described in Table 1. Median age of the study cohort was 49 (range 25–76). The majority (74%) had stage III disease. Median number of positive lymph nodes was 6 (range 0–30). More than half (66%) were left-sided and over one-third had HER2+ or triple negative breast cancer (26% and 17%, respectively), reflecting the bias of treating physicians to enroll patients with high risk subtypes of breast cancer or anatomy that circumvented conventional RT. The majority (88%) of patients had mastectomy and 62% had immediate implant-based reconstruction (30% permanent implant, 32% tissue expanders). All patients received chemotherapy; 44% in a neoadjuvant setting. The majority (93%) of the chemotherapy regimens included a taxane +/- anthracycline. 73% received anti-estrogen therapy (46% tamoxifen and 27% aromatase inhibitor) and 29% received trastuzumab. Seven patients did not receive follow-up PFTs, leaving 104 patients evaluable for the analysis of pulmonary toxicities at 6 months.

Dosimetric Treatment Plans

All 111 enrolled patients met the definition of dosimetric feasibility. In the entire cohort, median D95 to the planning target volume (PTV) was 48.1 Gy (range 47.0 – 50.2 Gy). The median D95 to the PTV of the internal mammary lymph nodes was 48.9 Gy (range 47.2–52 Gy). The median lung V5 was 100% (range 77–100%) and median ipsilateral lung V20 was 29% (range 22.5–30.6%). The median contralateral mean lung dose was 3.88 Gy (range 1.4 – 6.5 Gy).

Trends in Lung and Heart Doses Over Time

The mean MHD in the entire cohort over the study period was 11.7 Gy (range 6.6–20) and 13.2 Gy (8.6–20) for left and 9.7 Gy (6.6–12.8) for right-sided treatment, respectively. Figure 2 demonstrates trends in lung and heart doses over the 30-month study period. There was a significant reduction in high lung dose (ipsilateral lung V20) over the study period (28.8% vs. 27.9%, $p=.003$), which was more pronounced with left-sided compared to right-sided treatment (2.8% vs 2.5 %; $p=.012$ and $.324$, respectively). In contrast, there was no fluctuation in low lung dose (V05Gy), regardless of laterality (0.2%, 0.3% and 0.8%; all $p=NS$). Mean V05 values for overall, left and right-sided treatment were 98.1%, 97.9% and 98.2%.

The mean MHD by 26% over the study period (13.6 Gy to 10.0 Gy, $p<.0001$) and consistently decreased over time. The MHD was 13.6 Gy (range 8.3–19.9) in the first, 11.6 Gy (range 8.0–20) in the second and 10.0 Gy (range 6.6–19.7) in the third tercile of the study, respectively. Overall, the heart Dmax was 46.1 Gy (range 22.0–53.1) and decreased by 6% over the study period (47.9 Gy vs 45.0 Gy, $p=.004$). As expected, the heart Dmax was

greater in left-sided compared to right-sided treatment (47.0 Gy v. 44.7 Gy) and decreased significantly in left-sided patients ($p=.004$).

Disease Control

Median follow-up period of the enrolled cohort was 53.4 months (range 0–82 months). There were 7 LRR, 35 DM and 21 death events, corresponding to a 5Y locoregional-free survival, distant metastases-free survival and overall survival of 93.2%, 66.5%, and 80.3%, respectively. 6/7 LRRs occurred within the irradiated chest wall at a median of 18 weeks (range 0–40) and 1/7 LRRs occurred in the regional nodes. Among them, 4 were ER-negative, 3 were HER2+. 4/7 LRRs were confirmed by pathology and 4/7 LRRs had concomitant DM.

Respiratory Toxicities

The incidence of respiratory toxicities in the entire cohort was (11) 10.6%, 7 grade 1 (6.7%), 3 grade 2 (2.9%), 1 grade 3 (0.96%), 0 grade 4–5 (0%). All four patients with grade 2–3 respiratory toxicities were evaluated by a pulmonologist. Attributions are described in Table 2. The time to development of grade 2 respiratory toxicity in three patients was 6, 8 and 11 weeks post-IMRT. None of the 3 patients with grade 2 respiratory toxicities required steroids. The one patient with grade 3 RP presented at week 10 with dry cough, shortness of breath and low-grade temperatures. She was treated with a course of oral steroids and macrolide antibiotics. The ipsilateral lung V20 of the 4 patients with grade 2 respiratory toxicities was 27.4%, 28%, 29% and 29.3% respectively. The V5 of the 4 patients was 100%, which was not different from the median V5 of 100% observed in the entire study cohort. There were no additional grade 3–4 RP events beyond the follow-up timepoint. All four patients with grade 2–3 RP recovered their baseline function with prolonged follow-up and did not receive any further PFTs beyond the 6-month post-IMRT timepoint.

Pulmonary Function Tests and Community Acquired Pneumonia (CAP) Questionnaires

Table 3 compares key PFT parameters between baseline and 6 months post-IMRT. There were no significant changes in mean FEV₁ (2.6 L vs. 2.6 L, $p=0.42$), mean FEV₁:FVC (80.1% vs. 71.6%, $p=0.56$) and mean DLCO (18.5 v. 18.8 mL/min/mm Hg, $p=0.68$) in the cohort. There were no differences in CAP scores between baseline and follow-up (84.8 v. 83.2, $p=0.21$), suggesting that patient-based evaluation of changes in respiratory symptoms after IMRT were minimal. The change between baseline and post-treatment PFTs in the 4 patients with grade 2 pneumonitis were minimal.

Discussion

Although the major trials demonstrating the survival benefit of postoperative RT in breast cancer vary in treatment era, patient eligibility criteria and receipt of systemic therapy, their common goal is to optimize therapeutic ratio of RT by delivering the desired dose distribution to target tissues while limiting dose to the surrounding normal tissues to acceptable levels^{1,4,10,11}. A large systematic review of studies examining various breast RT regimens published between 2010–2015 demonstrated that lung doses from breast RT can vary widely, depending on RT technique, positioning and anatomic regions targeted,

including the internal mammary chain¹². In the first large, prospective study of inverse planned IMRT in breast cancer patients, we evaluated whether multibeam IMRT could achieve optimal dose conformity without increasing the incidence of respiratory toxicities in locally advanced breast cancer patients receiving RNI. Clinical follow-up, functional and patient-reported measures of pulmonary toxicity were prospectively obtained.

Dosimetric feasibility, the primary endpoint, was achieved in 100% of enrolled patients. In all patients, the indicator of high lung dose, V20, was limited to <30% of the ipsilateral lung while a larger region of the lung received low, volumetric dose (median V5 100%) due to the multiple beams traversing the thorax. Despite this, the secondary endpoint of grade 3 RP was remarkably low (0.96%), while the 5-year rate of locoregional recurrence-free survival was high at 93.2%. Similarly, the rate of symptomatic RP reported in the experimental arm of the NCIC MA.20 trial following RNI was 1.2%, using non-IMRT, 3D-conformal techniques¹¹.

In our study, the coverage of the target tissues was comprehensive, as indicated by the median D95 of the planning target volume and IMNs of 48.1 Gy (96.2% of Rx dose) and 48.9 Gy (97.8% of Rx dose), respectively. Six of seven locoregional failures were in-field (chest wall), indicating that the low rates of RP were not achieved at the expense of reduced coverage of the target tissues.

The timing of RT relative to taxane-based chemotherapy can also influence RT-related respiratory toxicities¹³. Taxanes enhance the cytotoxicity of RT in both in vitro and in vivo studies through different mechanisms^{14–18}. In a retrospective study of breast cancer patients who received concurrent and sequential anthracycline, cyclophosphamide +/- taxane therapy, the crude rate of grade 3 RP was as high as 14.6%¹⁹. The mean time to the development of RP in patients receiving concurrent weekly paclitaxel was significantly shorter compared to those receiving paclitaxel every 3 weeks ($p=0.002$). The median V20 of the ipsilateral lung was 20%. In order to minimize any potential confounding related to the timing of RT, all patients in our study concluded chemotherapy at least 4 weeks prior to the initiation of IMRT.

Inconsistencies in the scoring of RP may be attributed to the lack of sensitivity of tools such as the CTCAE v. 3 scale, which was extrapolated from lung cancer patients who experience RP at a higher clinical frequency than in breast cancer. Recently, PFTs have been incorporated into studies of patients receiving RT for breast cancer to establish a quantitative, objective scoring system for RP. In a study by Lind et al, 64 women underwent PFTs before and 5 months after 3D-conformal RT for BC²⁰. Similar to our study, the ipsilateral lung V20 was limited to <30%. They found no correlation between the dosimetric factors and PFTs changes, except for pre-RT chemotherapy and post-RT DLCO changes. Similarly, we did not find any differences in PFT scores.

More recently, patient-reported outcome (PRO) measures such as the CAP questionnaire, a validated patient-reported outcome tool that asks directed questions about pulmonary symptoms, have been used in clinical trials to assess subclinical respiratory toxicities in breast cancer patients^{8,9}. In our study, there were no differences in baseline and follow-up

scores from the CAP questionnaires. These negative results diminish the role of these tools as sensitive and reliable metrics for the assessment of subclinical pulmonary toxicity in breast cancer patients receiving IMRT. Alternatively, the low event rate may obviate detection by PFTs or any PRO tools.

Dose and fractionation may impact ability to achieve lung constraints and impact upon toxicities. Mainstream parameters of lung dose such as V5 and V20 did not appear to be sensitive indicators of respiratory toxicity in this study. The low rate of RP and uniform results of V5 (median 100%) and V20 (limited to <30% in all patients) made it impossible to test associations between lung parameters and respiratory events. Other potential lung parameters such as mean lung dose of ipsilateral and both lungs, V10, V15, V20 and V40 were analyzed but not reported, given their negative results. However, these results do not necessarily obviate the potential role of other lung parameters in predicting toxicities breast cancer patients receiving IMRT-based treatment planning. Furthermore, this study was not purpose-designed to assess other acute toxicities such as esophagitis, skin toxicities or impact on reconstructive outcomes, which merit further study after inverse-planned IMRT in breast cancer.

Despite the well tolerated effects of IMRT in this study, we are cognizant that late adverse effects such as cardiac morbidities or in-field secondary malignancies may be observed with prolonged follow-up. The heart doses in this study were appreciably higher compared to what is achieved in current practice with newer modulated techniques such as VMAT, another form of modulated RT which enables IMRT using arc rotational techniques, leading to reduced monitor units and quicker delivery time than the IMRT techniques reported in this study^{21–23}. Notably, a precipitous decline in heart dose was observed over the 30-month study period (26% $p<.0001$), which is commensurate with efforts to refine IMRT delivery beyond the normal tissue parameters provided in the study protocol.

These results must be interpreted in context of the limited available treatment planning options for these patients at the time, who were selected based on the anticipation by the radiation oncologist that conventional RT techniques would lead to poor coverage of the target or unacceptably high doses to the adjacent organs. Left-sided breast cancer and implant reconstruction constituted a significant proportion of the study cohort. The study pre-dated the use of alternative forms of RT for node-positive breast cancer such as deep-inspiratory breath hold, VMAT, and proton therapy, which have led to significant improvements in MHD in the setting of RNI since the initiation of this study.

In summary, this study demonstrated the feasibility and safety of inverse-planned IMRT in locally advanced breast cancer patients who are at high risk of local recurrence and require comprehensive coverage of the chest wall and regional lymph nodes. Despite the large volume of lung receiving low dose RT, the incidence of grade 3 RP was remarkably low, providing rationale for the wider use of modulated radiation techniques for select breast cancer patients who require more comprehensive coverage of the tumor tissues than conventional RT techniques may provide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the members of the Department of Medical Physics, the Pulmonary Function Laboratories, and the radiation therapy and clinical research teams in the Department of Radiation Oncology at Memorial Sloan Kettering Cancer Center for their dedication, patience and expertise in the development and delivery of IMRT for this study. We extend special gratitude to all of the patients who participated in this trial.

Funding: Supported by the NIH/NCI Cancer Center Support Grant P30 CA008748.

References

- Clarke M, Collins R, Darby S, et al.: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366:2087–106, 2005 [PubMed: 16360786]
- Giordano SH, Kuo YF, Freeman JL, et al.: Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 97:419–24, 2005 [PubMed: 15770005]
- Jagsi R, Griffith KA, Koelling T, et al.: Rates of myocardial infarction and coronary artery disease and risk factors in patients treated with radiation therapy for early-stage breast cancer. *Cancer* 109:650–7, 2007 [PubMed: 17238178]
- Hartford AC, Galvin JM, Beyer DC, et al.: American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) Practice Guideline for Intensity-modulated Radiation Therapy (IMRT). *Am J Clin Oncol* 35:612–7, 2012 [PubMed: 23165357]
- White J: Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions, in Definitions C (ed): Breast Cancer Atlas for Radiation Therapy Planning, RTOG, 2009
- Dijkema IM, Hofman P, Raaijmakers CP, et al.: Loco-regional conformal radiotherapy of the breast: delineation of the regional lymph node clinical target volumes in treatment position. *Radiother Oncol* 71:287–95, 2004 [PubMed: 15172144]
- Goddu SM, Chaudhari S, Mamalui-Hunter M, et al.: Helical tomotherapy planning for left-sided breast cancer patients with positive lymph nodes: comparison to conventional multiport breast technique. *Int J Radiat Oncol Biol Phys* 73:1243–51, 2009 [PubMed: 19251096]
- El Moussaoui R, Opmeer BC, Bossuyt PM, et al.: Development and validation of a short questionnaire in community acquired pneumonia. *Thorax* 59:591–5, 2004 [PubMed: 15223867]
- el Moussaoui R, de Borgie CA, van den Broek P, et al.: Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 332:1355, 2006 [PubMed: 16763247]
- Poortmans PM, Struikmans H, Bartelink H: Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med* 373:1879–80, 2015 [PubMed: 26543931]
- Whelan TJ, Olivetto IA, Parulekar WR, et al.: Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med* 373:307–16, 2015 [PubMed: 26200977]
- Aznar MC, Duane FK, Darby SC, et al.: Exposure of the lungs in breast cancer radiotherapy: A systematic review of lung doses published 2010–2015. *Radiotherapy and Oncology* 126:148–154, 2018 [PubMed: 29246585]
- Lingos TI, Recht A, Vicini F, et al.: Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 21:355–60, 1991 [PubMed: 2061112]
- Milross CG, Mason KA, Hunter NR, et al.: Enhanced radioresponse of paclitaxel-sensitive and -resistant tumours in vivo. *Eur J Cancer* 33:1299–308, 1997 [PubMed: 9301459]
- Milross CG, Mason KA, Hunter NR, et al.: Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. *J Natl Cancer Inst* 88:1308–14, 1996 [PubMed: 8797771]

16. Milas L, Hunter NR, Mason KA, et al.: Role of reoxygenation in induction of enhancement of tumor radioresponse by paclitaxel. *Cancer Res* 55:3564–8, 1995 [PubMed: 7627965]
17. Milas L, Hunter NR, Kurdoglu B, et al.: Kinetics of mitotic arrest and apoptosis in murine mammary and ovarian tumors treated with taxol. *Cancer Chemother Pharmacol* 35:297–303, 1995 [PubMed: 7828272]
18. Liebmman J, Cook JA, Fisher J, et al.: In vitro studies of Taxol as a radiation sensitizer in human tumor cells. *J Natl Cancer Inst* 86:441–6, 1994 [PubMed: 7907149]
19. Taghian AG, Assaad SI, Niemierko A, et al.: Risk of pneumonitis in breast cancer patients treated with radiation therapy and combination chemotherapy with paclitaxel. *J Natl Cancer Inst* 93:1806–11, 2001 [PubMed: 11734597]
20. Lind PA, Marks LB, Jamieson TA, et al.: Predictors for pneumonitis during locoregional radiotherapy in high-risk patients with breast carcinoma treated with high-dose chemotherapy and stem-cell rescue. *Cancer* 94:2821–9, 2002 [PubMed: 12115368]
21. Bedford JL, Warrington AP: Commissioning of volumetric modulated arc therapy (VMAT). *Int J Radiat Oncol Biol Phys* 73:537–45, 2009 [PubMed: 19147018]
22. Rao M, Yang W, Chen F, et al.: Comparison of Elekta VMAT with helical tomotherapy and fixed field IMRT: plan quality, delivery efficiency and accuracy. *Med Phys* 37:1350–9, 2010 [PubMed: 20384272]
23. Verbakel WF, Cuijpers JP, Hoffmans D, et al.: Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. *Int J Radiat Oncol Biol Phys* 74:252–9, 2009 [PubMed: 19362244]

Figure 1.
Consolidated Standards Of Reporting Trials (CONSORT) Diagram

2a.

2b.

2c.

2d.

Figure 2.

Trends in heart and lung mean doses by tumor laterality and treatment era. (a) Ipsilateral Lung V20 (b) Ipsilateral Lung V05 (c) Mean Heart Dose (d) Heart Max Dose P-values calculated using Mann-Whitney tests of 1st and 3rd tercile means for left, any, and right tumor lateralities.

Table 1.**Patient, Disease & Treatment Characteristics (n = 111)**

Characteristic	n (%)
Median age at diagnosis, years (range)	49 (range 25–76)
Clinical T-stage (n=44)	
cT1	3 (7)
cT2	16 (36)
cT3	10 (23)
cT4	15 (34)
Clinical N-stage (n=44)	
cN0	2 (4.5)
cN1	18 (41)
cN2	11 (25)
cN3	13 (29.5)
Pathologic T-stage (n=67)	
pT1	21 (31)
pT2	42 (63)
pT3	3 (4.5)
pT4	1 (1.5)
Pathologic N-stage (n=67)	
N1	12 (18)
N2	25 (37)
N3	30 (45)
Laterality	
Left	66 (59)
Right	45 (41)
Receptor Status	
Triple negative (ER– PR– HER2–)	19 (17)
Hormone receptor positive (ER and/or PR+, HER2–)	63 (57)
HER2+	29 (26)
Tumor Type	
Invasive Ductal	92 (83)
Other	19 (17)
Surgery	
Mastectomy	98 (88)
Breast-Conserving Surgery	13 (12)
Margins	
Negative	107 (96)
Positive	4 (4)
Lymphovascular Invasion	92 (83)
Extranodal Extension	54 (49)
Immediate Reconstruction	

Characteristic	n (%)
None	40 (36)
Expander or Implant	69 (62)
Autologous	2 (2)
Chemotherapy	
Adjuvant	67 (60)
Neoadjuvant	44 (40)
Chemo Regimen	
Taxane ±anthracycline	103 (93)
Other	8 (7)
Hormone Therapy	81 (73)

Abbreviations: ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2.

Table 2.

Grade 2 and 3 Respiratory Toxicity Details (n = 4)

Patient	RP Grade	PFT change	Attribution	Ipsi Lung V20
1	2	2% ↓ FEV ₁ 0% ↓ FEV ₁ :FVC 16% ↓ DLCO	Prolonged exposure to secondhand smoke; “inflammatory response”	29.7
2	2	10% ↑ FEV ₁ 1% ↓ FEV ₁ :FVC 2% ↑ DLCO	Baseline history of asthma	28.0
3	2	1% ↑ FEV ₁ 1% ↓ FEV ₁ :FVC 1% ↑ DLCO	URI suspected when symptoms developed	30.0
4	3	2% ↓ FEV ₁ 11% ↑ FEV ₁ :FVC 7% ↑ DLCO	Moderate restrictive/obstructive ventilatory defect at baseline	27.4

Abbreviations: FEV₁, Forced Expiratory Volume in 1 second, FEV₁/FVC: Forced Expiratory Volume in 1 second: Forced Vital Capacity; URI, upper respiratory infection

Table 3

A comparison of PFTs and mean CAP score at baseline and six months post-IMRT.

Assessment	Baseline Mean (range)	6 months post RT Mean (range)	p-value
FEV1 (L)	2.6 (1.2 – 3.9)	2.6 (1.0 – 3.9)	0.42
FEV1/FVC (%)	80.1 (57 – 93)	79.6 (64 – 98)	0.56
DLCO (mL/min/mmHg)	18.5 (10 – 30)	18.8 (5 – 65)	0.68
CAP score (N=99)	84.8 (33.8 – 100)	83.2 (34.4 – 100)	0.21

p-values generated by Wilcoxon signed-rank test

Abbreviations: PFT: pulmonary function test; CAP: Community Acquired Pneumonia; FEV1: Forced Expiratory Volume in 1 second; FEV1/FVC: Forced Expiratory Volume in 1 second: Forced Vital Capacity; DLCO: Diffuse Capacity of Lung for Carbon Monoxide