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LETTERS TO THE EDITOR

Radiation-induced lung injury after concurrent neoadjuvant chemoradiotherapy for locally advanced breast cancer

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Outcomes for women with locally advanced breast cancer (LABC) remain poor, with a five-year survival of approximately 50%, despite aggressive treatment with a combination of chemotherapy, surgery and radiotherapy, all delivered sequentially [1,2]. Achieving a pathological complete response (pCR) to neoadjuvant systemic therapy (defined as no residual disease in the breast or axilla at surgery) is a major favorable prognostic factor [3–5]; however, rates of pCR are low: a large meta-analysis demonstrated that 17% of women, on average, achieve a pCR after neoadjuvant treatment [3]. In LABC, concurrent chemoradiotherapy has been associated with higher rates of pCR [4,6]. In an attempt to improve the pCR rate for LABC, a phase II trial was launched to evaluate the efficacy of a regimen consisting of neoadjuvant docetaxel concurrent with locoregional radiotherapy. At the recommendation of the data safety monitoring committee, the trial closed early due to a higher-than-anticipated rate of symptomatic radiation pneumonitis (RP). The goal of this study was to evaluate predictors of symptomatic RP and CT-based radiation-induced lung injury (RILI) in a unique cohort of breast cancer patients treated with concurrent neoadjuvant chemoradiation therapy.

Material and methods

Patient selection and treatment details

From August 2009 to June 2011, 32 patients with biopsy-confirmed T3/T4 and/or N2/N3 LABC were accrued for this Research Ethics Board approved protocol. Patients with prior malignancies, systemic treatment within the last five years, or prior radiotherapy to the head, neck, breast or thorax, were excluded. Patients with the diagnosis of inflammatory breast cancer were also excluded.

Neoadjuvant chemotherapy used in this study represented a standard anthracycline-based regimen. It consisted of three cycles of intravenous 5-fluoruracil (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2) administered every three weeks (FEC). This was followed by a period of concurrent chemoradiotherapy. Weekly IV docetaxel (35 mg/m^2) was given over nine weeks, with daily external beam radiation therapy [intensity-modulated radiation therapy or three-dimensional (3D)-conformal radiotherapy, calculated using a collapsed cone algorithm for dose calculation] administered concurrently during the first six weeks. A dose of 45 Gy in 25 fractions was given over five weeks, and a boost

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dose of either 5.4 Gy in 3 fractions or 9 Gy in 5 fractions was given during the sixth week if residual disease was present. Lung volume at risk was calculated as both lungs in total. Radiation treatment was delivered on megavoltage machines using 6 MV energy or greater. Five weeks after the last dose of docetaxel, patients underwent a modified radical mastectomy.

Image registration and lung density measurements

This report examines symptomatic RP and CT-based RILI. Oncologic outcomes (pCR rates and survival) will be reported separately once the survival data matures. Of the 32 patients enrolled, one progressed with distant metastases during the neoadjuvant chemotherapy phase, and thus 31 patients were eligible for this sub-study of symptomatic RP and RILI. All 31 patients were scored for possible symptomatic RP using the National Institute of Health Common Terminology Criteria for Adverse Events v3.0 (CTCAE grade ≥ 2). The trial mandated that each patient received at least three MIBI SPECT-CT scans throughout the course of treatment. Any diagnostic thoracic CT scans during or after treatment were at the discretion of the treating oncologists. For the assessment of CT-based RILI, 27 of 31 patients had a baseline CT scan and at least one post-treatment follow-up CT scan available and were evaluable for that endpoint.

Radiotherapy treatment planning CT scans were overlaid onto their post-treatment CT scans in order to measure changes in lung density over time (Supplementary Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.871387). The relationship between dose and lung density changes was assessed similarly to previous studies [7]. Briefly, isodose levels (5 Gy, 10 Gy, 20 Gy, 30 Gy, 40 Gy) were converted into contours and transferred from the planning scans onto follow-up scans after coregistration of the scans (MIM Software 5.5, OH, USA). Deformable registration was attempted, since it provides more accurate registration for thoracic follow-up scans than does rigid registration, but it is prone to errors if scans contain substantial anatomic differences (e.g. development of RP or effusions) [8]. In this study, due to the substantial differences between pre-radiotherapy and post-radiotherapy scans in patients with RILI, deformable algorithms produced inadequate registrations, and as such non-deformable algorithms were used instead. Contours were then examined and manually adjusted if necessary. To assess changes in lung density over time, HU density changes in each 'dose band' (5–10 Gy, 10–20 Gy, 20–30 Gy, 30–40 Gy, >40 Gy) were generated and compared among scans. Contralateral lung receiving <5 Gy was considered unirradiated and used as a control to correct for baseline differences between scans.

Statistical analyses

Descriptive statistics were generated for baseline patient, tumor and treatment characteristics. Univariable logistic regression analysis was performed for each available factor to identify predictors of symptomatic RP. T-tests and analysis of variance (ANOVA) were used to identify significant differences in density change stratified by various combinations of: 1) RP grade (≥ 2 versus <2), 2) radiation dose (5–10, 10–20, 20–30, 30–40 and >40 Gy), and 3) time (0–3, 3–6, 6–12 and >12 months). Linear mixed models were generated to examine relationships between radiological lung density changes (dependent variable), radiation dose (fixed effect), time (fixed effect), and other potential predictors (fixed effects). All models additionally accounted for intra-patient correlation and heterogeneity in CT scanner set-up by including patient and CT scan numbers as random grouping variables. Statistical analysis was performed using SAS version 9.2 software (SAS institute, Cary, NC, USA) with two-sided statistical testing at the 0.05 significance level.

Results

Baseline patient demographics, disease characteristics for the 31 evaluable patients are reported in Table I, and radiotherapy planning parameters are reported in (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.871387). In total, 17 (55%) patients developed symptomatic RP (CTCAE v3.0 grade ≥ 2). Eight developed grade 3 pneumonitis, and one died of acute respiratory distress syndrome (ARDS) associated with RP (grade 5 toxicity). Univariable logistic regression of potential predictors of symptomatic RP is shown in (Supplementary Table II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.871387). No treatment, patient, or tumor factors were found to be significantly associated with symptomatic RP. Since all patients received concurrent chemotherapy, the effect of chemotherapy could not be assessed on logistic regression.

In total, 79 follow-up CT scans from 27 patients were co-registered with baseline CT scans and analyzed for RILI, with a median of three follow-up CT scans per patient (range 1–6). Following analysis of post-treatment scans, linear mixed modeling showed both radiation dose and time post-treatment

Table I. Baseline tumor, patient and treatment characteristics of all patients (n = 31).

Characteristic	All patients (n = 31)
Age – median, (min, max)	49 (27, 64)
T stage – n(%)	
T1	1 (3.2)
T2	4 (12.9)
T3	21 (67.7)
T4	5 (16.1)
N stage – n(%)	
N0	9 (29.0)
N1	11 (35.5)
N2	6 (19.4)
N3	4 (12.9)
NX	1 (3.2)
Smoking history – n(%)	11 (35.5)
Left ventricular ejection fraction (LVEF) (%) – median, (min, max)	64 (50, 77)
Her-2Neu status – n(%)	
Negative	17 (54.8)
Positive	8 (25.8)
Equivocal	6 (19.4)
Total docetaxel dose received (mg) – median, (min, max)	522 (360, 666)
Received trastuzumab (herceptin) – n(%)	11 (35.5)
Radiation delivery – n(%)	
3D-CRT	16 (51.6)
IMRT	13 (41.9)
Tomotherapy	2 (6.5)

to be highly predictive of CT RILI ($p < 0.001$ and $p = 0.021$, respectively).

Overall, density changes at low dose levels (< 10 Gy) were minor, but increased markedly at higher doses, with regions receiving ≥ 20 Gy exhibiting density increases of 100 HU or more (Figure 1). RILI changes were seen early, evident between 0 and 3 months, and peaking in the high-dose region (> 40 Gy) at 6–12 months post-treatment (Figure 1). For both 6–12 months and > 12 months post-treatment, significant differences in density change were observed across all dose bands (both $p < 0.001$), with greater differences observed for higher dose bands compared to lower dose bands, respectively. This trend was also observed during the 3–6 month period, although was not found to be significant ($p = 0.058$).

Patients with symptomatic RP were observed to have higher rates of density change across all dose levels (Figure 2), with significant differences observed in the low-dose (5–10 Gy, $p = 0.040$) and high-dose regions (> 40 Gy, $p = 0.024$). Patients who developed RP also had significantly larger CT density changes than patients without RP at both 6–12 months ($p = 0.002$) and > 12 months ($p = 0.013$) post-treatment, suggesting a sustained effect transitioning to fibrosis.

Discussion

In this study of taxane-based concurrent chemoradiotherapy for LABC, more than half of patients developed symptomatic RP and one patient sustained a grade 5 toxicity. In contrast, when locoregional

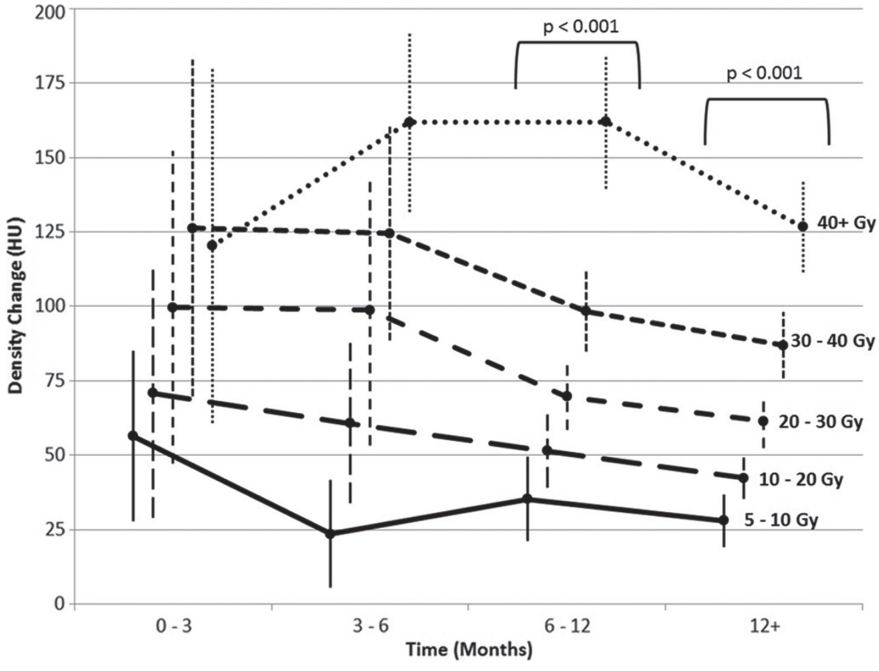

Figure 1. Estimated means (± standard error) for CT lung density changes [in Hounsfield Units (HU)] over time (months), stratified by radiation dose (Gy).

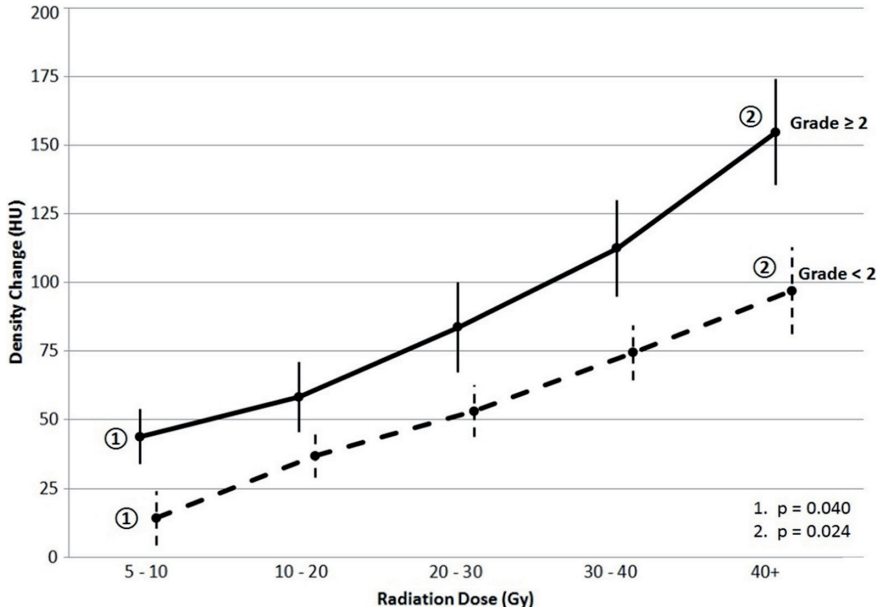

Figure 2. Estimated means (± standard error) for CT lung density changes [in Hounsfield Units (HU)] relative to radiation dose (Gy), stratified by pneumonitis grade ≥ 2 versus < 2.

radiotherapy is delivered as a single modality for breast cancer without concurrent chemotherapy, RP rates are often < 5% [9,10]. The post-treatment scans demonstrated RILI in areas receiving relatively low doses of radiotherapy, with a significant relationship established between radiation dose, time post-treatment, and RILI. Patients with symptomatic RP had significantly greater HU increases, compared to patients without RP, consistent with animal models which show that HU density changes can serve as surrogates of RILI at the microscopic level [11].

The extent of CT-based RILI observed in this cohort of patients appears to be higher than in other studies measuring RILI after radiotherapy alone, or after non-taxane based chemoradiotherapy [7,12,13], although care must be taken in drawing conclusions from comparisons across studies. This finding is consistent with a potent radiosensitzation effect from docetaxel [14–17], and this effect is also apparent in patients treated for non-small cell lung cancer (NSCLC): the use of concurrent taxane chemotherapy (compared to non-taxane chemotherapy) with radiotherapy is a significant predictor for developing pneumonitis, conferring an odds ratio of > 3 for developing RP [18].

Since taxanes have become incorporated into routine oncologic use for node-positive breast cancer, the challenge of maximizing their benefits while minimizing toxicity, namely pneumonitis, has become complex. Limited studies have been conducted using concurrent chemoradiotherapy to treat LABC, but a few small trials have shown promise and are the basis upon which we conducted our phase II trial [4,6,19]. A retrospective review of 44 high-risk breast cancer patients demonstrated the feasibility of concurrent radiation delivered with either paclitaxel or docetaxel every three weeks [19]. Treatment was well tolerated with nine (20%) patients experiencing Grade 3 skin toxicity; however, no cases of pneumonitis were reported. Another study of 44 LABC patients who received 30 mg/m^2 paclitaxel twice weekly with concurrent radiation prior to surgery [4,6] reported acceptable toxicity and no cases of RP. A recent retrospective review encompassing 105 of these patients also demonstrated a 34% pCR and superior DFS and OS compared to those who did not achieve a pCR [4]. These differences in rates of RP may be related to choice of taxane (docetaxel vs. paclitaxel), their dosing, or the frequency of administration, and further research is needed to determine the optimal safe parameters.

The findings of this study must be considered in the context of its strengths and limitations. The clinical data used herein was collected as part of a rigorous, phase II trial, but the analysis of CT-based RILI was an unplanned, retrospective analysis. The CT registration process is associated with some inherent imprecision [8], which we attempted to correct by manually inspecting and correcting isodose line contours, and deformable registration was not possible. Some CT scans were done at the discretion of the treating oncologists, which may introduce unmeasured confounding factors. The small sample size resulted in limited power to detect predictors of RP as have been reported in previous studies [20,21], and the selected nature of the study population may affect the generalizability of our findings.

In conclusion, RP rates and pulmonary CT density changes after concurrent docetaxel-based chemoradiotherapy are higher than would be

expected after breast radiotherapy alone. Mature oncologic outcomes of OS and DFS from this study are required to fully define the therapeutic ratio, but in the interim, concurrent taxane-based chemoradiotherapy for LABC should be used cautiously and in the context of a clinical trial.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figure 1 and Tables I-II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.871387.