LUNG FIBROSIS IN BREAST CANCER PATIENTS: EFFECT OF TREATMENT MODALITY, SMOKING HISTORY AND BLOOD CYTOKINES

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I. INTRODUCTION

- There are now over 3.5 million long-term breast cancer (BC) survivors in the United States.[1]
- Radiotherapy (RT) is a critical component of breast cancer management, yielding a substantial survival benefit[2] but can result in inadvertent exposure of large volumes of normal tissues to low and moderate doses of radiation.
- 14% of Breast Cancer patients treated with radiation develop clinical pulmonary toxicity, with 4% overall experiencing high-grade clinical toxicity.[3]
- Compared to photon therapy, proton therapy often results in improved lung dosimetry but a clinical benefit in terms of decreased lung toxicity has not yet been quantified.

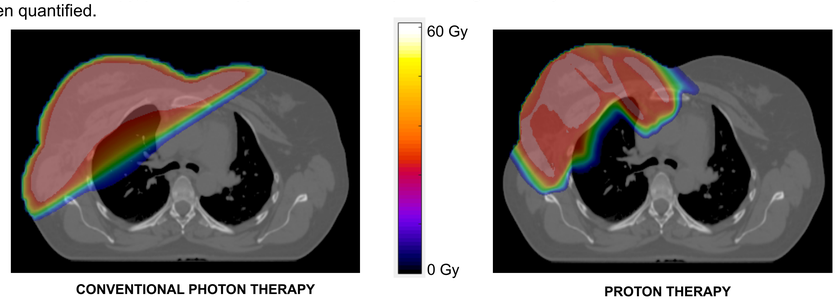

Figure 1: **Treatment Planning for Photon vs Proton Therapy**: These figures represent radiation treatment planning on chest CT scans for right sided breast cancer patients. The colors represent the distribution of radiation exposure. The figure on the left shows radiation treatment planning for conventional X-ray based photon therapy and the figure on the right shows a comparative plan for the same patient but for proton therapy treatment.

OBJECTIVES : 1. Assay radiographic pulmonary changes on serial chest CTs after radiation therapy for breast cancer (Stage II or higher) undergoing conventional photon vs. proton therapy. 2. Correlate with smoking history and blood cytokines (MCP-1, IL-1α, IL-1β, IL-1RA, IL-6, IL-8, VEGF, FGF-2, TNF-α, IFNα2, IFNγ) acquired at the same time points to identify asymptomatic breast cancer patients at high-risk for RILI.

II. METHODOLOGY

Image Acquisition

- Images were acquired involving 64-slice CT systems typically with 1x1x1 mm voxel dimensions using a non-ionic contrast agent and breath-holding for motion correction. Images were acquired at Pre-Treatment and 1, 3, 6, 12 and 24-months post RT
- To date, 37 patients have been enrolled in the study, with 68% (25 of 37) and 51% (19 of 37) attaining 6-month and 1-year follow-up, respectively.

Image Registration, Lung Mask Extraction, Airway and Vessel Mask Extraction

- The follow-up CTs were registered to the planning CT where the dose was defined, using in-house software.
- A lung mask was computed to extract[4] the lung tissue from other surrounding structures.

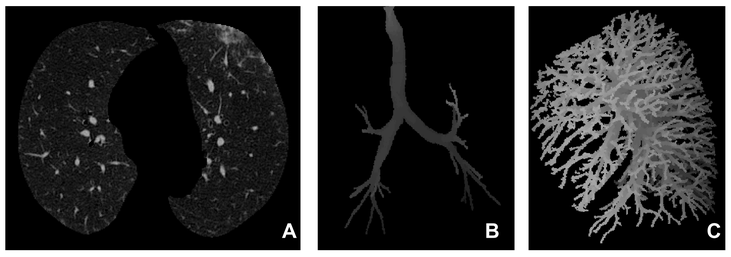

Figure 2. Lung-mask Extraction, Airway and Vessel mask extraction: [A] is the resultant lung-only volume after subtracting other structures from the axial lung CT dataset under examination. [B] and [C] are the depth-enhanced MIP (maximum intensity projection) of the extracted airway and vessel-tree using seeded region growing and a Fast-Marching[5] approach respectively

Computing Follow-up Lung Tissue-Dose Response

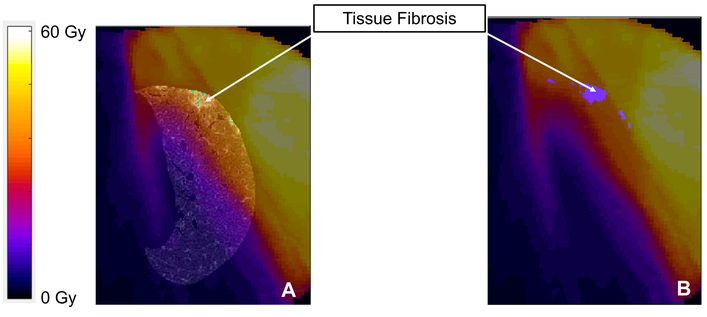

Figure 3. Lung fibrosis dose response: [A] depicts the transformed radiation dose onto the follow-up scan with vessels and airways subtracted to analyse the true lung parenchyma dose response. [B] depicts the transformed radiation dose onto the segmented fibrotic mass. The dose is displayed in color using a 'fire' spectrum where white is the highest dose and dark blue/purple is the lowest dose.

Patient Demographics

Characteristics at Baseline		X-ray therapy (n=21)	Proton therapy (n=16)
Age: Mean (Range), years		51(30-76)	50 (32-68)
Race, n (%)	Black	19%	25%
	White	76.2%	62.5%
	Other	4.8%	12.5%
BMI, Mean (Range)		30.5 (18.9-43.8)	31.1 (22.1-44.2)
Chemotherapy given, n (%)		71.4%	81.3%
Comorbidity existing, n (%)		52.4%	56.3%
Smoking history, n (%)		**47.6%**	**18.8%**
Employed, n (%)		75%	66%
Married, n (%)		50%	52.4%

III. RESULTS

V20 Analysis: Proton Therapy (PT) vs. Photon Therapy (XRT): Mean (SD)/[Range] in %

XRT w/o nodal irradiation (n=6)	XRT with nodal irradiation (n=15)	XRT all (n=21)	PT all (n=16)
9.1% (2.7%) [5.6%-12.7%]	31.1% (4.4%) [24.6%-39.7%]	24.8% (10.9%) [5.6%-39.7%]	21.7% (6.3%) [9.9%-32.9%]

Baseline Cytokine Levels Between Modalities and Smoking Groups: Mean (SD)

Cytokines at Baseline	Photon therapy (n=21)	Proton therapy (n=16)	Smoking history (n=13)	No Smoking history (n=24)
FGF-2	32.1 (10.8)	41.9 (13.5)	34.3 (11.2)	37.6 (13.9)
IFNα-2	33.5 (11.5)	41.2 (12.8)	36.8 (12.7)	37.1 (12.7)
IFN-γ	32.4 (11.1)	41.1 (13.0)	35.3 (10.9)	37.0 (13.7)
IL-1RA	62.4 (22.3)	82.9 (43.1)	63.7 (20.1)	76.0 (39.9)
IL-1-α	143 (138.1)	317.5 (717.8)	77.8 (72.3)	301.8 (598.5)
IL-1-β	47.8 (16.0)	60.5 (21.7)	51.3 (17.3)	54.6 (21.0)
Ratio (IL-1-α+IL-1-β/IL-1RA)	3.1 (2.1)	3.3 (3.3)	2.1 (1.1)	3.8 (3.0)
IL-6	237.2 (286.7)	457.4 (1084.6)	174.3 (299.2)	425.8 (905.5)
IL-8	254.7 (257.5)	381.7 (605.5)	221.1 (296.0)	362.0 (508.4)
MCP-I	3166.5 (998.4)	3210.1 (1057.5)	3376.8 (1053.5)	3077.9 (992.5)
TNF-α	90.8 (20.8)	96.2 (19.5)	95.8 (18.2)	91.7 (21.4)
VEGF	61.8 (71.1)	52.9 (17.6)	54.6 (40.4)	59.7 (60.9)
TGF-β1	1609.1 (2819.0)	1862.5 (2026.4)	1721.4 (2024.9)	1721.9 (2729.9)
TGF-β3	6.9 (0.8)	7.1 (0.7)	6.8 (0.5)	7.1 (0.8)
TGF-β2	96.3 (177.0)	64.8 (40.3)	77.0 (85.4)	85.3 (156.7)

Volume of Lung Fibrosis vs. Treatment Modality, V20 and Smoking History

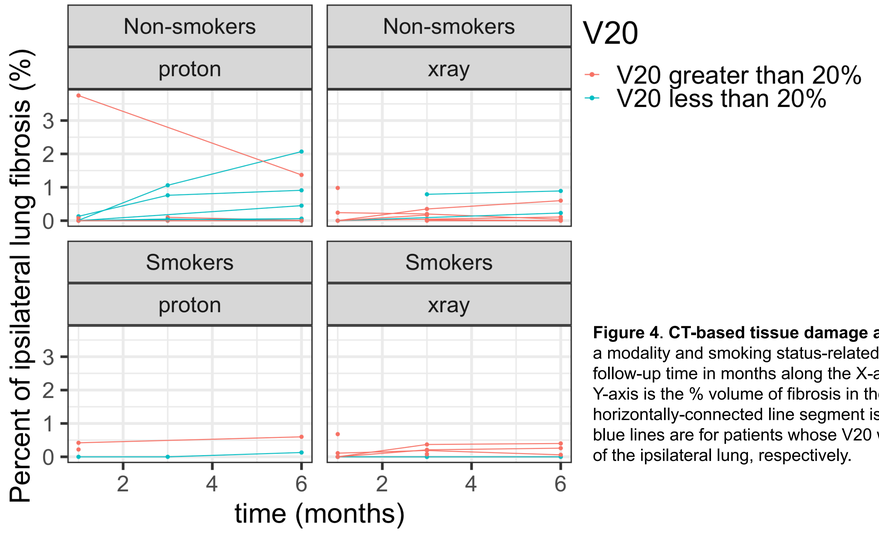

Figure 4. CT-based tissue damage analysis: Each grid represents a modality and smoking status-related fibrosis response for the follow-up time in months along the X-axis: 1, 3, 6 and 12 months. The Y-axis is the % volume of fibrosis in the ipsilateral lung. Each horizontally-connected line segment is a unique patient. The red and blue lines are for patients whose V20 was greater and less than 20% of the ipsilateral lung, respectively.

IV. CONCLUSIONS & FUTURE WORK

- A history of smoking showed association with a lower volume of lung fibrosis across both treatment modalities.
- Although PT patients had lower V20, this did not confer a significantly lower volume of lung radiation fibrosis. This might be attributed to the lower number of smokers in the PT (19%) vs. XRT (48%) groups.
- No cytokine demonstrated a >50% Kendall Correlation Coefficient with volume of fibrosis in this limited, exploratory data set.
- Limitations: Patient-reported smoking status, so exact reliability undetermined; results based on ongoing study, so current sample size is small.
- Future analyses will help us address: higher-than-expected fibrosis with PT due to hypothesized RBE >1.1 at the distal end of Bragg peak that falls in the lung for breast PT; the existence of an improvement in the therapeutic ratio using PT; the role of smoking and baseline cytokines in predicting RILI; and the role for routine imaging in clinical follow-up care of breast cancer patients for identification of early symptoms of RILI.

V. REFERENCES

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ACKNOWLEDGEMENTS

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