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The Effects of Smoking on Late toxicity from breast radiation

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A defining success in the treatment of breast cancer has been the declining risk of local-regional recurrence noted over the past three decades. For example, data compiled for the recent Consensus Guideline on Margins indicated that absolute risk of in-breast tumor recurrence (IBTR) decreased by approximately 4–5% per decade of diagnosis from 1980 to 2005.¹ This success is attributable to improvements in diagnostic imaging, surgical resection, pathologic assessment, systemic therapy, and radiation treatment planning.

An underappreciated corollary to this success is that, as baseline IBTR risk decreases, the absolute local control benefit derived from radiation similarly decreases. For example, in the classic NSABP B-06 clinical trial, 20-year IBTR risk was 39% among women treated with lumpectomy alone compared to 14% among women treated with lumpectomy and radiation, a 25% absolute risk reduction.² In contrast, the more contemporary National Cancer Institute of Canada (NCIC) randomized trial reported 10-year IBTR risk of 14% with tamoxifen alone compared to 5% for tamoxifen plus radiation, a 9% absolute risk reduction.³

As the absolute benefit derived from radiation diminishes, small risks of serious adverse effects or deaths from radiation become more relevant to the calculus of determining who should or should not receive radiation. Within this context, the nuanced findings from Taylor et al. provide valuable and clear information with which to guide decision making.⁴ Specifically, Taylor et al. should be commended for moving beyond their initial finding, summarized in Supplementary Figure 1, that women who received radiation experienced a 3.1% absolute excess risk of non-breast cancer mortality. If this estimated excess risk of death were applicable to current patients with early stage breast cancer, then the appropriateness of radiation should be questioned.

However, Taylor et al. demonstrate that risks of late radiation morbidity and mortality for patients treated with modern radiotherapy techniques are considerably lower than might be assumed based on their unadjusted, aggregated data. This lower risk is specifically attributable to three modifiable factors: (1) patient smoking status, (2) normal tissue doses, and (3) radiated target volume.

Regarding smoking, Taylor et al. demonstrate that excess risks of late radiation-induced lung cancer and cardiac mortality are negligible among non-smokers, whereas absolute late

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radiation risks are considerably increased among smokers who continue to smoke. Furthermore, among smokers, smoking cessation is a high value intervention, lowering risk of radiation-induced toxicity close to that of non-smokers. Given these key findings, incorporation of smoking cessation programs for smokers with newly diagnosed breast cancer assumes paramount importance. Such programs require careful patient screening, cessation support, and delivery of this support (both the method and personnel).⁵ Key instruments to enable tobacco cessation include behavioral and motivational counseling, coupled with pharmacotherapy.⁶ In large medical centers such as the Mayo Clinic, Memorial Sloan Kettering Cancer Center, and the University of Texas MD Anderson Cancer Center, dedicated tobacco cessation programs incorporating these combined treatment modalities provide support to patients interested in tobacco cessation, with success rates of up to 46%.^{7,8,9} Other individual, integrated efforts have been made to incorporate tobacco cessation counseling within the oncology clinic. For example, the Department of Radiation Oncology at the University of North Carolina at Chapel Hill integrated a master's level certified tobacco cessation counselor into the department in order to facilitate patient referrals. Preliminary results indicated that 32% of patients quit smoking within one month of referral and another 26% had reduced the number of cigarettes smoked per day at least in half.¹⁰ The majority of physicians do not have access to such resources, but need to be made aware that even a few minutes of behavioral counselling with patients has been shown to significantly increase rates of cessation.⁶

Unfortunately, while most oncologists would seemingly support the idea of encouraging tobacco cessation in their patients, the realities of integrating this into a busy practice remain challenging. A survey of over 18,000 American Society for Clinical Oncology (ASCO) members found that although 90% of respondents ask patients about tobacco use, only 39% offer patients tobacco cessation support.¹¹ This survey also found that although 86% of respondents believed tobacco cessation should be a part of standard oncologic care, only 29% reported having adequate training in tobacco cessation interventions. Similar findings were seen by ASCO's Quality Oncology Practice Initiative, which also found that tobacco cessation services are offered to less than half of all smokers seen in an oncology practice.¹² Sufficient attention to these interventions may be lacking during formalized residency and fellowship training. A survey of radiation oncology residents found that only 18% reported receiving formal training on tobacco cessation counseling during residency training.¹³

Professional organizations such as ASCO¹² and the American Association for Cancer Research (AACR)¹⁴ provide direction to physicians on how to address patients in need of tobacco cessation support. The ASCO website provides easily accessible tools for physicians that follow the 5 A's of tobacco cessation: ask, advise, assess, assist, and arrange.¹⁰ These include step-by-step physician responses to common excuses offered by patients about why they are not ready to quit smoking. Clinical interventions as short as three minutes have been found to increase tobacco cessation rates, although more time intensive interventions are found to be even more effective.¹⁵ And, tobacco cessation counseling by multiple types of healthcare providers, through multiple formats, has been found to improve adherence to tobacco cessation, supporting the role of involving all members of the medical team in these discussions. Since 2004, the National Cancer Institute has sponsored telephone quitlines in multiple languages throughout the United States, available to all patients at 1-800-QUIT-

NOW. This quitline provides free services to patients, including tobacco cessation counseling, referral to cessation resources, and information about FDA-approved medications to assist with cessation. Informational paper pamphlets were found in one large survey of cancer patients to be the preferred means of learning about tobacco cessation,¹⁶ and consideration should be made to having these posted in all oncology clinics.

The second modifiable factor illuminated by Taylor et al. is normal tissue dose, specifically doses to the lung and heart, which were linearly associated with lung cancer diagnosis and cardiac mortality, respectively. The introduction of CT-based treatment planning has afforded the opportunity to develop innovative radiation techniques, such as prone positioning or deep inspiration breath hold, which allow radiation oncologists to personalize radiation treatment plans to minimize lung and heart doses.^{17,18} Findings from Taylor et al. illustrate the population benefits from implementing such normal tissue sparing approaches into routine clinical practice for all patients and underscore that smokers have the most to gain from application of these techniques, as illustrated in Figure 1.

Given the relationship between lung and heart doses and late radiation morbidity/mortality, radiation oncologists must understand what normal tissues doses are achievable in various clinical scenarios. The systematic review incorporated by Taylor et al. provides important data on the mean heart and lung doses in radiation regimens published between 2010–2015, but is limited as it does not distinguish between regimens treating the whole breast alone versus the whole breast and regional nodal basins (with or without coverage of the internal mammary nodes). The meta-analysis is also noteworthy for the broad interquartile range of reported mean heart (1.9–7.4 Gy) and ipsilateral lung (5.5–12.6 Gy) doses, suggesting that dramatic differences in normal tissue doses are likely to exist between centers. Given the need to define appropriate benchmarks for normal tissue doses, our group evaluated mean heart and lung doses in 223 patients treated sequentially in our center. As can be seen from Table 1, mean heart doses were considerably lower than reported by Taylor et al., and mean lung doses varied by the extent of regional nodal irradiation.

The third modifiable factor, indirectly suggested by Taylor et al., is the chosen radiation target volume. There is now growing data suggesting that for post-menopausal women with early, estrogen receptor positive breast cancer, the radiation target volume may be safely reduced to include only the breast tissue immediately adjacent to the resected malignancy.^{19–23} Many techniques, such as external beam, brachytherapy, or intraoperative radiation, can treat these target volumes with significantly lower lung and heart doses than with whole breast irradiation, thereby mitigating late radiation risks, particularly in smokers. Conversely, for select women with lymph node positive disease, recent data support consideration of including the regional nodal basins as part of the radiation target volume.^{24,25} However, when radiating the regional nodal basins, mean heart and lung doses are considerably higher, and thus the decision to include this target volume should weigh anticipated benefits against risks of late toxicity, particularly considering normal tissue doses and smoking status.

Ironically, while the study from Taylor et al. is likely one of the largest local therapy meta-analyses ever conducted, with 40,871 patients included, the key findings underscore the need to personalize care for breast cancer patients through vigorous promotion of smoking

cessation, judicious radiation treatment planning, and careful minimization of radiation target volume in an evidence-based manner. Through these efforts, late radiation toxicity can be almost entirely avoided in all patients except for smokers who continue to smoke.

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A.

B.

Figure 1.

This is a 44 year old woman with a 27 pack-year smoking history who presented with a pT1c N0 (i+, sn) invasive ductal carcinoma of the upper outer quadrant of the left breast, intermediate grade, ER+, PR+, HER2-. She underwent margin-negative breast conserving

surgery with sentinel node biopsy. Oncotype DX score was 9. She was treated with 40 Gy in 15 fractions in the prone position followed by a 10 Gy in 5 fraction boost in the lateral decubitus position. Prone positioning with judicious tangent beam placement was utilized to achieve a mean heart dose of 0.6 Gy and a mean total lung dose of 0.2 Gy. A – parasagittal slice of the radiation treatment plan, B – axial slice of radiation treatment plan. Tumor bed clips are show in red. Isodose lines are as follows: 106% - blue; 100% - red; 98% - purple; 90% - yellow; 50% - green.

Table 1

Mean heart and lung doses achieved at the University of Texas MD Anderson Cancer Center in 223 consecutive patients treated in 2013

	Mean Heart Dose Gy (IQR)	Mean Total Lung Gy (IQR)	Mean Ipsilateral Lung Dose Gy (IQR)	Mean Contralateral Lung Dose Gy (IQR)
All Left Cases (n=129)	2.1 (0.5–3.1)	4.7 (2.3–7.0)	9.6 (4.7–14.5)	0.4 (0.1–0.4)
All Right Cases (n=94)	1.1 (0.3–1.9)	6.3 (2.8–9.5)	11.0 (5.2–16.4)	0.3 (0.1–0.3)
Left Tangent Whole Breast Cases (n=42)	0.5 (0.4–0.6)	2.2 (1.7–2.8)	4.6 (3.6–5.8)	0.1 (0.1–0.1)
Right Tangent Whole Breast Cases (n=46)	0.3 (0.3–0.4)	3.1 (2.3–3.8)	5.5 (4.3–6.9)	0.1 (0.1–0.1)
Left Tangent + SCV Cases (n=3)	0.9 (0.7–1.0)	4.7 (4.5–5.0)	10.0 (9.4–11.0)	0.2 (0.2–0.2)
Right Tangent + SCV Cases (n=2)	0.6 (0.5–0.6)	6.2 (5.2–7.2)	10.4 (9.0–11.9)	0.2 (0.2–0.2)
Left Tangent + SCV + IMN Cases (n=66)	3.7 (2.7–4.2)	7.1 (6.2–8.1)	14.1 (12.4–16.4)	0.7 (0.3–0.6)
Right Tangent + SCV + IMN Cases (n=46)	2.0 (1.4–2.4)	9.6 (8.5–10.2)	16.6 (15.2–17.9)	0.5 (0.2–0.3)

SCV: Supraclavicular fossa (targeting the level III axilla and supraclavicular lymph nodes); IMN: internal mammary chain (targeting the lymph nodes in the first three intercostal spaces). Approximately 80% of patients with left sided tumors in our practice are treated with deep inspiration breath hold to reduce heart and lung dose.