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 as noted over the past three decades. For example, data compiled for the recent Consensus Guideline on Margins indicated that the absolute risk of in-breast tumor recurrence (IBTR) decreased by approximately 4% to 5% per decade of diagnosis from 1980 to 2005. 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 National Surgical Adjuvant Breast and Bowel Project B-06 clinical trial, 20-year IBTR risk was 39% among women treated with lumpectomy alone compared with 14% among women treated with lumpectomy and radiation, a 25% absolute risk reduction. In contrast, the more contemporary National Cancer Institute of Canada randomized trial reported a 10-year IBTR risk of 14% with tamoxifen alone compared with 5% for tamoxifen plus radiation, a 9% absolute risk reduction.

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 in the article accompanying this editorial provide valuable and clear information with which to guide decision making. Specifically, Taylor et al should be commended for moving beyond their initial finding, summarized in the Data Supplement, that women who received radiation experienced a 3.1% absolute excess risk of nonbreast 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 the risks of late radiation morbidity and mortality for patients treated with modern radiotherapy techniques are considerably lower than might be assumed on the basis of 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 nonsmokers, whereas absolute late radiation risks are considerably increased among smokers who continue to smoke. Furthermore, among smokers, smoking cessation is a high-value intervention, lowering the risk of radiation-induced toxicity to close to that of nonsmokers. Given these key findings, the 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). Key instruments to enable tobacco cessation include behavioral and motivational counseling, coupled with pharmacotherapy. 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%. Other individual, integrated efforts have been made to incorporate tobacco cessation counseling into 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 to facilitate patient referrals. Preliminary results indicated that 32% of patients had quit smoking within 1 month of referral and another 26% had reduced the number of cigarettes smoked per day by at least half. Most physicians do not have access to such resources, but need to be made aware that even a few minutes of behavioral counseling with patients has been shown to significantly increase rates of cessation.

Unfortunately, although 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 more than 18,000 ASCO members found that although 90% of respondents ask patients about tobacco use, only 39% offer patients tobacco cessation support. This survey also found that although 86% of respondents believed tobacco cessation should be a part of standard oncologic care, only 29% reported having had adequate training in tobacco cessation interventions. Similar findings were seen in ASCO’s Quality Oncology Practice Initiative, which also found that tobacco cessation services are offered to less than one half of all smokers seen in an oncology practice. 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 in tobacco cessation counseling during residency training.

Professional organizations such as ASCO and the American Association for Cancer Research 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 five As 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 3 minutes have been found to increase tobacco cessation rates, although more time-intensive interventions have been found to be even more effective.11 In addition, tobacco cessation counseling by multiple types of health care 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-based quitlines in multiple languages throughout the United States, available to all patients at 1-800-QUIT-NOW. The quitlines provide free services to patients, including tobacco cessation counseling, referral to cessation resources, and information about Food and Drug Administration-approved medications to assist with cessation. Informational paper pamphlets were found in one large survey of patients with cancer to be the preferred means of learning about tobacco cessation,16 and consideration should be given to having these posted in all oncology clinics.

The second modifiable factor illuminated by Taylor et al4 is the 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 computed tomography–based treatment planning has afforded the opportunity to develop innovative radiation techniques such as prone positioning and 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 al4 illustrate the population benefits from implementing such normal tissue sparing approaches into routine clinical practice for all patients and underscore the fact that smokers have the most to gain from the application of these techniques, as illustrated in Figure 1.

Given the relationship between lung and heart doses and late radiation morbidity and mortality, radiation oncologists must understand which normal tissues doses are achievable in various clinical scenarios. The systematic review incorporated by Taylor et al4 provides important data on the mean heart and lung doses in radiation regimens published between 2010 and 2015; however, the review is limited because it does not distinguish between those regimens treating the whole breast alone and those treating 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 to 7.4 Gy) and ipsilateral lung (5.5 to 12.6 Gy) doses, suggesting that dramatic differences in normal tissue doses are likely to exist among 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 listed in Table 1, mean heart doses were considerably lower than those reported by Taylor et al,4 and mean lung doses varied by the extent of regional nodal irradiation.

The third modifiable factor, suggested indirectly by Taylor et al,4 is the chosen radiation target volume. There is now growing data suggesting that for postmenopausal women with early, estrogen receptor-positive breast cancer, the radiation target volume may be reduced safely to include only the breast tissue immediately adjacent to the resected malignancy.19-23 Many techniques, such as external beam, brachytherapy, and 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, the mean heart and lung doses are considerably higher, and thus the decision to include this target volume should weigh the anticipated benefits against the risks of late toxicity, particularly considering normal tissue doses and smoking status.

Ironically, although the study by Taylor et al1 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 patients with breast cancer 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, with the exception of smokers who continue to smoke.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at jco.org.

**AUTHOR CONTRIBUTIONS**

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**REFERENCES**


**Table 1. Mean Heart and Lung Doses Achieved at The University of Texas MD Anderson Cancer Center in Consecutive Patients Treated in 2013 (N = 223)**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Mean Heart Dose, Gy (IQR)</th>
<th>Mean Total Lung Dose, Gy (IQR)</th>
<th>Mean Ipsilateral Lung Dose, Gy (IQR)</th>
<th>Mean Contralateral Lung Dose, Gy (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All left cases (n = 129)</td>
<td>2.1 (0.5-3.1)</td>
<td>4.7 (2.3-7.0)</td>
<td>9.6 (4.7-14.5)</td>
<td>0.4 (0.1-0.4)</td>
</tr>
<tr>
<td>All right cases (n = 94)</td>
<td>1.1 (0.3-1.9)</td>
<td>6.3 (2.8-9.5)</td>
<td>11.0 (5.2-16.4)</td>
<td>0.3 (0.1-0.3)</td>
</tr>
<tr>
<td>Left tangent whole breast (n = 42)</td>
<td>0.5 (0.4-0.6)</td>
<td>2.2 (1.7-2.8)</td>
<td>4.6 (3.6-5.8)</td>
<td>0.1 (0.1-0.1)</td>
</tr>
<tr>
<td>Right tangent whole breast (n = 46)</td>
<td>0.3 (0.3-0.4)</td>
<td>3.1 (2.3-3.8)</td>
<td>5.5 (4.3-6.9)</td>
<td>0.1 (0.1-0.1)</td>
</tr>
<tr>
<td>Left tangent plus SCV (n = 3)</td>
<td>0.9 (0.7-1.0)</td>
<td>4.7 (4.5-5.0)</td>
<td>10.0 (9.4-11.0)</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Right tangent plus SCV (n = 2)</td>
<td>0.6 (0.5-0.6)</td>
<td>6.2 (5.2-7.2)</td>
<td>10.4 (9.0-11.9)</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Left tangent plus SCV plus IMN (n = 66)</td>
<td>3.7 (2.7-4.2)</td>
<td>7.1 (6.2-8.1)</td>
<td>14.1 (12.4-16.4)</td>
<td>0.7 (0.3-0.6)</td>
</tr>
<tr>
<td>Right tangent plus SCV plus IMN (n = 46)</td>
<td>2.0 (1.4-2.4)</td>
<td>9.6 (8.5-10.2)</td>
<td>16.6 (15.2-17.9)</td>
<td>0.5 (0.2-0.3)</td>
</tr>
</tbody>
</table>

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

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