VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Effects of Smoking on Late Toxicity From Breast Radiation

Simona F. Shaitelman, Rebecca M. Howell, and Benjamin D. Smith, *The University of Texas MD Anderson Cancer Center, Houston, TX*

See accompanying article on page 1641

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.[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 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.[2] 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.[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[4] in the article accompanying this editorial provide valuable and clear information with which to guide decision making. Specifically, Taylor et al[4] 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[4] 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[4] 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).[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%.[7-9] 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.[10] 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.[6]

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.[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 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.[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 in tobacco cessation counseling during residency training.[13]

Professional organizations such as ASCO[12] and the American Association for Cancer Research[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 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.[15] 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 al[4] 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 al[4] 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 al[4] 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 al[4] 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

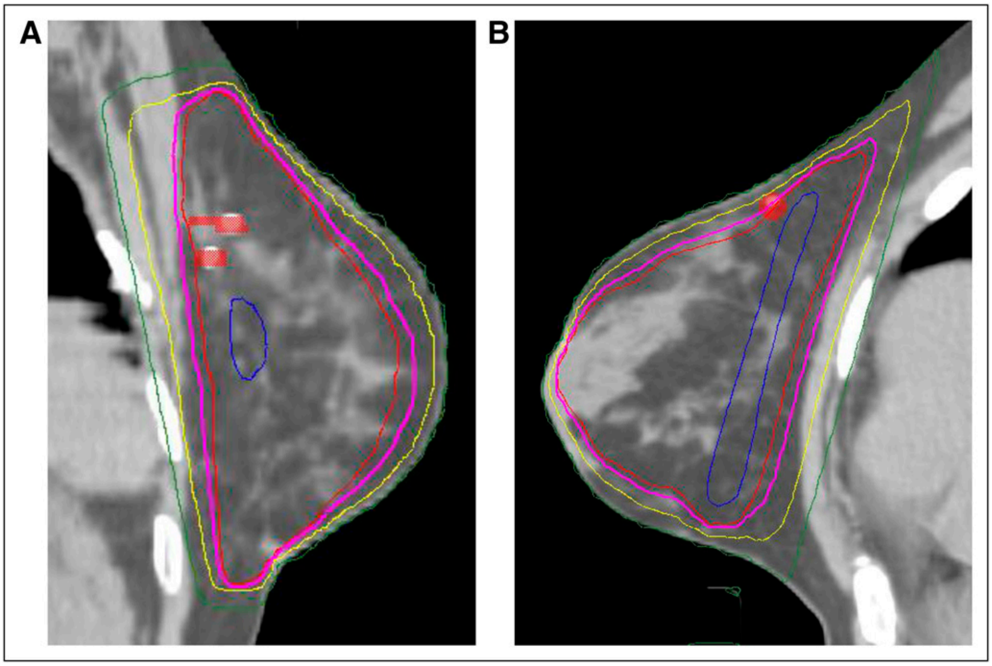

Fig 1. A 44-year-old woman with a 27 pack-year smoking history presented with a pT1c N0 (i+, sn) invasive ductal carcinoma of the upper outer quadrant of the left breast, intermediate grade, estrogen receptor-positive, progesterone receptor-positive, and human epidermal growth factor receptor 2–negative. She underwent margin-negative breast-conserving surgery with sentinel node biopsy. Onco*type* DX score was 9. She was treated with 40 Gy in 15 fractions in the prone position, followed by 10 Gy in a 5-fraction boost in the lateral decubitus position. Prone positioning with judicious tangent beam placement was used to achieve a mean heart dose of 0.6 Gy and a mean total lung dose of 0.2 Gy. (A) Parasagittal slice of radiation treatment plan. (B) Axial slice of radiation treatment plan. Tumor bed clips are shown in red. Isodose lines are as follows: 106%: blue; 100%: red; 98%: purple; 90%: gold; 50%: green.

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)

Patient Group	Mean Heart Dose, Gy (IQR)	Mean Total Lung Dose, 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 (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 (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 plus SCV (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 plus SCV (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 plus SCV plus IMN (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 plus SCV plus IMN (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)

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, supraclavicular fossa (targeting the level III axilla and supraclavicular lymph nodes).

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

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Moran MS, Schnitt SJ, Giuliano AE, et al: Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 32:1507-1515, 2014

2. Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233-1241, 2002

3. Liu FF, Shi W, Done SJ, et al: Identification of a low-risk luminal A breast cancer cohort that may not benefit from breast tadiotherapy. J Clin Oncol 33:2035-2040, 2015

4. Taylor C, Correa C, Duane F, et al: Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomised trials. J Clin Oncol 35:1641-1650, 2017

5. Warren GW, Sobus S, Gritz ER: The biological and clinical effects of smoking by patients with cancer and strategies to implement evidence-based tobacco cessation support. Lancet Oncol 15:e568-e580, 2014

6. Fiore MC JC, Baker TB, Bailey WC, et al: Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respir Care 53:1217-1222, 2008

7. Garces YI, Schroeder DR, Nirelli LM, et al: Tobacco use outcomes among patients with head and neck carcinoma treated for nicotine dependence: A matched-pair analysis. Cancer 101:116-124, 2004

8. Ostroff JS, Burkhalter JE, Cinciripini PM, et al: Randomized trial of a presurgical scheduled reduced smoking intervention for patients newly diagnosed with cancer. Health Psychol 33:737-747, 2014

9. Karam-Hage M, Cinciripini PM, Gritz ER: Tobacco use and cessation for cancer survivors: An overview for clinicians. CA Cancer J Clin 64:272-290, 2014

10. McCullough A, Goldstein AO, Patsakham K, et al: Integration of tobacco cessation services into a radiation oncology clinic. Int J Radiat Oncol Biol Phys 84:S542, 2012

11. Warren GW, Marshall JR, Cummings KM, et al: Addressing tobacco use in patients with cancer: A survey of American Society of Clinical Oncology members. J Oncol Pract 9:258-262, 2013

12. Hanna N, Mulshine J, Wollins DS, et al: Tobacco cessation and control a decade later: American Society of Clinical Oncology policy statement update. J Clin Oncol 31:3147-3157, 2013

13. Braunstein SE, Singer L, Silveira WR, et al: Tobacco cessation perspectives and practice among U.S. radiation oncology residents. Int J Radiat Oncol Biol Phys 90:S59-S60, 2014

14. Toll BA, Brandon TH, Gritz ER, et al: Assessing tobacco use by cancer patients and facilitating cessation: An American Association for Cancer Research policy statement. Clin Cancer Res 19:1941-1948, 2013

15. Fiore MC JC, Baker TB, Bailey WC, et al: Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD, US Department of Health and Human Services, 2008

16. Sampson L, Papadakos J, Milne V, et al: Preferences for the provision of smoking cessation education among cancer patients. J Cancer Educ PubMed doi: 10.1007/s13187-016-1035-0 [epub ahead of print on April 13, 2016]

17. Formenti SC, DeWyngaert JK, Jozsef G, et al: Prone vs supine positioning for breast cancer radiotherapy. JAMA 308:861-863, 2012

18. Remouchamps VM, Vicini FA, Sharpe MB, et al: Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. Int J Radiat Oncol Biol Phys 55:392-406, 2003

19. Strnad V, Ott OJ, Hildebrandt G, et al: 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial. Lancet 387:229-238, 2016

20. Coles C AR, Ah-See ML, Algurafi H, et al: Partial breast radiotherapy for women with early stage breast cancer: First results of local recurrence data for IMPORT LOW (CRUK/06/003). European Breast Cancer Conference 10, Amsterdam, the Netherlands, March 9-11, 2016, (abstr)

21. Livi L, Meattini I, Marrazzo L, et al: Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 51:451-463, 2015

22. Veronesi U, Orecchia R, Maisonneuve P, et al: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 14:1269-1277, 2013

23. Vaidya JS, Wenz F, Bulsara M, et al: Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 383:603-613, 2014

24. Poortmans PM, Collette S, Kirkove C, et al: Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 373:317-327, 2015

25. Whelan TJ, Olivotto IA, Parulekar WR, et al: Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373:307-316, 2015

DOI: 10.1200/JCO.2017.72.2660; published at jco.org on March 20, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effects of Smoking on Late Toxicity From Breast Radiation

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Simona F. Shaitelman
Consulting or Advisory Role: MD Anderson Cancer Center (Inst)
Research Funding: Elekta

Rebecca M. Howell
No relationship to disclose

Benjamin D Smith
Research Funding: Varian Medical Systems

Acknowledgment

Supported by Grant No. R01 CA201487 from the National Cancer Institute (S.F.S.), Grant No. R01 CA207216-01 from the National Cancer Institute (B.D.S.), and Grant No. RP160674 from the Cancer Prevention and Research Institute of Texas (B.D.S.).

