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Editorial

Late toxicity and cosmetic outcomes related to interstitial multicatheter brachytherapy for partial breast irradiation

Accelerated partial breast irradiation (APBI) has been attractive to many patients as a convenient alternative to standard fractionated whole breast radiation therapy. The APBI treatment, furthermore, holds the potential for decreased toxicity by sparing normal tissues from the deleterious effects of radiation with a focused and conformal approach. Although multiple techniques for the delivery of APBI have been developed, interstitial multicatheter brachytherapy (mCathBrachy) was the first popularly used APBI technique. As such, long-term outcomes data are now available.

In this issue of *Brachytherapy*, the 5-year toxicity and cosmetic results of the Radiation Therapy Oncology Group (RTOG) protocol 95-17 are presented. The RTOG 95-17 represents a seminal trial for APBI, as it is the first trial in North America to prospectively evaluate APBI in a multi-institutional, cooperative group setting. With nearly two decades elapsing since the inception of this study, mature data with regard to both efficacy and toxicity can now be gleamed. The efficacy results of RTOG 95-17 have been previously reported and have shown excellent outcomes (1). With a median followup of 7.09 years, the 5-year actuarial rate of ipsilateral breast tumor recurrence was 4% of which about half were outside the treated volume (elsewhere failures). The resulting 5-year disease-free survival and overall survival were 87% and 93%, respectively.

The mature late toxicity and cosmetic outcomes data for RTOG 95-17 are now presented (2). The authors report a 45% rate of Grade 2 and a 13% rate of Grade 3 late skin or soft tissue toxicity. The most common late toxicities reported were skin fibrosis or thickening (45%), telangiectasia (45%), catheter puncture marks (54%), and symptomatic fat necrosis (15%). Cosmetic assessment was available for only about half of patients, and was rated as good to excellent in 68% by the treating physician and in 66% by patient self-assessment. Treating physicians were also asked to assess toxicity as it impacted the cosmetic outcome. They reported skin fibrosis in 46% of the patients with 15% being noted on ''casual'' rather than ''close'' inspection. Skin indentation was noted in 37% of which 24% was on casual inspection, and telangiectasia were noted in 46% of patients with 30% on casual inspection.

How do these outcomes compared with other studies? Table 1 summarizes the published trials of mCathBrachy in the United States and internationally. Although considerable variation exists across studies, it is evident that RTOG 95-17 has a high rate of Grade 3 or greater toxicity, a high rate of any grade toxicity, and a low rate of good-to-excellent cosmetic outcomes. Although this may be concerning at first glance, these results must be taken in the context of the trial design and techniques used. All patients in RTOG 95-17 underwent two-dimensional (2D) treatment planning, and only 40% of the patients underwent even rudimentary optimization (18). Furthermore, the highest toxicity rates reported for RTOG 95-17 were skin related. Most were evident on ''casual'' inspection and presumably lead to compromise in the overall cosmetic outcome. The RTOG 95-17 did not use any skin dose constraints. Since the inception of RTOG 95-17, the practice of brachytherapy has dramatically evolved. Implants are now placed using customized templates with the aid of advanced imaging to more precisely encompass the tumor bed and to obtain even spacing between catheters. Sophisticated 3D planning is used to optimize dose distribution, dose to normal structures such as the skin, and homogeneity across the implant. We are also now guided by analysis of early experience leading to dose constraints for skin, V_{150}, V_{200}, and dose homogeneity index (DHI), which have been associated with late effects and compromised cosmetic outcomes. In a multi-institutional analysis, Wazer *et al.* (19) reported an association of late skin toxicity with V_{150}, V_{200}, and DHI, an association of late subcutaneous toxicity with DHI, and an association of suboptimal cosmetic outcome with V_{150}, V_{200}, and DHI. Furthermore, Polgár *et al.* (13) used strict skin dose constraints (<60% of prescription) and reported low rates of late skin toxicity and telangiectasia. Clearly, the overall quality of the implant with regard to dose constraints and hot spots is critical for late outcomes. The importance of dose optimization in this regard cannot be overstated. Several studies comparing low- (LDR) and high-dose-rate (HDR) implants have shown higher rates of late toxicity using LDR implants. Although several factors may account for these differences, lack of ability to perform dose optimization for an LDR implants is likely of significant importance. Arthur *et al.* (7) reported on the Virginia Commonwealth University experience and showed a 90% rate of good-to-excellent cosmesis with HDR implants and an 80% rate of good-to-excellent cosmesis

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Table 1
APBI experience using interstitial multicatheter brachytherapy

Institution/study	Study type	Implant type	No. of patients	Median followup (y)	IBTR	Grade ≥3 late toxicity	Other late toxicity	Cosmesis (excellent/good), %
Ochsner Clinic (3, 4)	Single institution Prospective	HDR LDR	160	7	2.5% at 5 y	8%	NR	75
Tufts/Brown Universities (5, 6)	Single institution Prospective	HDR	33	7	6.1% at 5 y	9% (33% when symptomatic fat necrosis included)	17.9% fat necrosis (all) at 5 y 35.7% fibrosis (Grade 2–3) at 5 y 28.6% Skin (Grade 1–2) at 5 y	93
VCU (7)	Single institution Prospective	HDR (31) LDR (13)	44	3.5	0% at 3.5 y	9.1%	11% Fibrosis (significant) 7% Telangiectasia (dense)	80
MGH (8)	Single institution Prospective	LDR	50	11.2	15% at 12 y	9% skin 13% subcutaneous	35% Fat necrosis (all) 54% Fibrosis 34% Telangiectasia (>1 cm)	67
University of Wisconsin (9)	Single institution Prospective	HDR	240	2.5	1.4% Crude rate	NR	8.9% Fat necrosis (symptomatic)	97
University of Kansas (10)	Single institution Prospective	LDR	25	3.9	0% at 4 y	0%	NR	100
University of Washington (11)	Single institution Retrospective	HDR	238	4.7	3% at 5 y	2.1%	17.6% Fat necrosis (all)	95
Soonchunhyang University, Korea (12)	Single institution Prospective	HDR	48	4.4	5% at 5 y	NR	10.4% Fat necrosis (symptomatic) 22.9% Fibrosis (Grade 1–2) 54.2% Skin (Grade 1–2)	90
NIO Budapest, Hungary (13)	Single institution Prospective	HDR	45	11	9.3% at 12 y	4.4%	35.6% Fat necrosis (Grade 1–2) 40% Fibrosis (Grade 1–2) 17.7% Skin (Grade 1–2)	78
Germany/Austria (14)	Multi-institution Prospective	PDR (175) HDR (99)	274	5.3	2% at 5 y	2.6%	5.1% Fat necrosis (histologic) 17.2% Telangiectasia 30% Fibrosis (Grade 1–2)	90
RTOG 95-17 (1, 2)	Multi-institution Prospective	HDR (66) LDR (33)	98	7.1	4% at 5 y	13%	15% Fat necrosis (symptomatic) 45% Telangiectasia 45% Fibrosis 54% Catheter marks	68
WBH (15,16)	Matched pair APBI vs. WBI	HDR/LDR WBI	199 199	10.7	5.0% at 12 y 3.8% at 12 y	0.5% NR	11% Fat necrosis (all) 35% Telangiectasia (mostly Grade 1)	81 NR
NIO Budapest, Hungary (17)	Randomized APBI vs. WBI	HDR/electron WBI (130)	128 130	10.2	5.9% at 10 y 5.1% at 10 y	Not yet reported	Not yet reported	81 63

APBI = accelerated partial breast irradiation; IBTR = ipsilateral breast tumor recurrence; LDR = low-dose rate; HDR = high-dose rate; VCU = Virginia Commonwealth University; MGH = Massachusetts General Hospital; NIO = National Institute of Oncology; PDR = pulsed-dose rate; RTOG = Radiation Therapy Oncology Group; WBH = William Beaumont Hospital; WBI = whole breast irradiation; NR = not reported.