Chronic skin toxicities and quality of life in breast cancer survivors after adjuvant radiotherapy: a systematic review and meta-analysis of different radiotherapy techniques

Henry C.Y. Wong, Jolien Robijns, Stephen Ciocon, Paula Elaine Diniz dos Reis, Sarina Sadeghi, Muna Al-Khaifi, Mami Ogita, Adrian W. Chan, Agata Rembielak, Dan Livesey, Matthew Chong, Zhihui Amy Liu, Mark Trombetta, Wee Yao Koh, Yiat Horng Leong, Gustavo N. Marta, Pierluigi Bonomo, Viola Salvestrini, Vassilios Vassiliou, Pradnya Chopade, Partha Patel, Cindy Wong, Julie Ryan Wolf, Corina van den Hurk, Raymond J. Chan, Michael Jefford, Shing Fung Lee, Edward Chow, Jennifer Y.Y. Kwan on behalf of the Multinational Association of Supportive Care in Cancer (MASCC) Oncodermatology and Survivorship Study Groups

Introduction

- Radiotherapy (RT) techniques influence acute skin reactions; however, their impact on chronic skin reactions and quality of life (QoL) is less understood.
- This review evaluates long-term skin toxicities and quality of life (QoL) in patients receiving adjuvant RT to the breast and/or regional lymph nodes via 3-dimensional conformal RT (3DCRT) compared to modern techniques including Intensity-modulated RT (IMRT), volumetric arc therapy (VMAT)

Methods

- Comprehensive literature search in Embase, MEDLINE, and Cochrane CENTRAL from inception to June 29, 2023, updated April 26, 2024.
- Included human studies in English comparing conventional RT with alternative techniques for adjuvant breast cancer treatment.
- Exclusions: intraoperative and partial breast RT techniques, studies without chronic toxicity or QoL outcomes.
- Data synthesis involved pooled risk ratios (RR) with 95% confidence intervals (CI) using a random-effects model.
- Heterogeneity assessed with Cochran Q and I² statistics.
- Two-tailed p values of <0.05 considered statistically significant.
- The meta-analyses and graphs were generated using Review Manager (RevMan), version 5.4.
- Review registered with PROSPERO (CRD42023443169).

Table 1. Cosmetic outcomes reported by the studies.

Study	Scores	Cosmetic effect		Results		p-value	
				3DCRT (%)	IMRT (%)		
Donovan et al. (2007)	Photographic assessment of change in breast appearance	1-year	None	64.1	74.2	0.008*	
			Mild	28.2	21.0		
			Marked	7.6	4.8		
		2-year	None	56.6	65.1		
			Mild	38.0	30.2		
			Marked	5.4	4.7		
		5-year	None	41.8	60.2		
			Mild	44.3	29.7		
			Marked	13.9	10.2		
Harsolia et al. (2007)	Harvard 4-point Scale	NR	Good to excellent	97.0	99.0	0.60	
Mukesh et al. (2013)	TDI : .	5-year	Good	36.7	42.6	0.038	
	Three-point		Moderate	41.5	45.7		
	score		Poor	21.8	11.7		
Pignol et al. (2016)	EORTC cosmetic rating system	10-year	Good to excellent	82.7	82.0	NR [†]	

IMRT may reduce selected chronic skin toxicities compared to 3DCRT with no consistent long-term differences in cosmetic outcomes or QoL



Author Contact information:

Results

- From 1,305 screened studies, nine articles representing seven studies (2,418 patients) met criteria, including three RCTs.
- Predominant use of conventional fractionation (1.8–2 Gy per fraction); one study used moderate hypofractionation (40 Gy in 15 fractions). All compared IMRT versus 3DCRT
- IMRT associated with significantly lower incidence of grade ≥2 hyperpigmentation (RR: 0.39, 95% CI: 0.17–0.89). (Figure 1)
- No significant differences for grade ≥2 breast fibrosis (RR: 0.78), telangiectasia (RR: 0.60), edema (RR: 0.15), and atrophy/retraction (RR: 1.63). (Figure 1)
- Short-term cosmetic outcomes favored IMRT; no long-term differences observed. (Table 1)
- Three studies utilizing EORTC QLQ-C30 and QLQ-BR23 reported **no** significant differences in QoL between IMRT and 3DCRT.

Figure 1. Forest plots of risk ratios comparing IMRT and 3DCRT: Grade ≥2 (A) hyperpigmentation, (B) breast fibrosis/induration, (C) telangiectasia, (D) breast edema, (E) breast atrophy/retraction. Abbreviations: IMRT, intensity-modulated radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy.

Α	IMRT		3DCRT		1820000 10 10	Risk Ratio		Risk Ratio			
Study or Subgroup	Events					M-H, Random, 95% CI Yea		M-H, Random, 95% CI			
Harsolia et al. (2007)	6	93	13	79	79.0%	0.39 [0.16, 0.98] 200					
Hardee et al. (2012)	1	49	4	36	14.5%	0.18 [0.02, 1.57] 201					
Zhao et al. (2021)	1	129	0	94	6.6%	2.19 [0.09, 53.23] 202	1				
Total (95% CI)		271		209	100.0%	0.39 [0.17, 0.89]		•			
Total events	8		17				520				
Heterogeneity: Tau ² = 0			7	= 0.45); $I^2 = 0\%$		0.0	1 0.1 1 10	100		
Test for overall effect: 2	Z = 2.24 (F	P = 0.03	3)				.3.3.3	Favors IMRT Favors 3DCRT	3355		
В	IMR	г	3DCR	т		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	r	M-H, Random, 95% CI			
Harsolia et al. (2007)	0	93	5	79	18.8%	0.08 [0.00, 1.38] 200	7 ←				
Hardee et al. (2012)	4	49	2	36	37.8%	1.47 [0.28, 7.59] 201	2	-			
Zhao et al. (2021)	5	129	3	94	43.4%	1.21 [0.30, 4.96] 202	1				
Total (95% CI)		271		209	100.0%	0.78 [0.18, 3.30]					
Total events	9		10								
Heterogeneity: Tau ² = 0	0.73; Chi ²	= 3.66,	df = 2 (P	= 0.16); I ² = 45%	e)	0.0	1 0.1 1 10	100		
Test for overall effect: 2	Z = 0.34 (F	P = 0.73	3)				0.0	Favors IMRT Favors 3DCRT	100		
С	IMRT 3DCRT					Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	ır	M-H, Random, 95% CI			
Mukesh et al. (2013)	19	228	32	235	95.2%	0.61 [0.36, 1.05] 201	3	-			
Zhao et al. (2021)	1	129	2	94	4.8%	0.36 [0.03, 3.96] 202	1	-			
Total (95% CI)		357		329	100.0%	0.60 [0.35, 1.01]		•			
Total events	20		34								
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.17	df = 1 (P)	= 0.68	$(3); I^2 = 0\%$		0.0	1 0.1 1 10	100		
Test for overall effect:	Z = 1.93 (F	P = 0.0	5)				0.0	Favors IMRT Favors 3DCRT	100		
D	IMRT		3DCRT			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	r	M-H, Random, 95% CI			
Harsolia et al. (2007)	1	93	20	79	55.3%	0.04 [0.01, 0.31] 200	7 ←				
Hardee et al. (2012)	1	49	1	36	44.7%	0.73 [0.05, 11.36] 201	2	-			
Total (95% CI)		142		115	100.0%	0.15 [0.01, 2.72]					
Total events	2		21								
Heterogeneity: Tau ² = 2	2.90; Chi ²	= 2.94,	df = 1 (P	= 0.09); I ² = 66%		-	4 0 4	400		
Test for overall effect: 2	Z = 1.28 (F	P = 0.20))				0.0	1 0.1 1 10 Favors IMRT Favors 3DCRT	100		
E	IMRT		3DCRT			Risk Ratio		Risk Ratio			
Study or Subgroup			Events Total Weight		Weight	M-H, Random, 95% CI Year		M-H, Random, 95% CI			
Hardee et al. (2012)	4	49	1	36	40.4%	2.94 [0.34, 25.20] 201					
Zhao et al. (2021)	3	129	2	94	59.6%	1.09 [0.19, 6.41] 202					
Total (95% CI)		178		130	100.0%	1.63 [0.42, 6.39]					
Total events	7		3			[0.12, 0.00]					
		= 0.49		= 0.48)· I² = 0%		-				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, $df = 1$ (P = 0.48); $I^2 = 0\%$ Test for overall effect: $Z = 0.70$ (P = 0.48)						0.0		100			
Tool for overall effect.	_ 0.70 (1	0.40	٠,					Favors IMRT Favors 3DCRT			

Limitations

 Interpretation is limited by the small number of studies and variability in reporting standards, underscoring the need for uniform outcome measures in future research.