University of Groningen

International comparison of cosmetic outcomes of breast conserving surgery and radiation therapy for women with ductal carcinoma in situ of the breast

BIG 03-07/TROG 07.01 trial investigators; Olivotto, Ivo A; Link, Emma; Phillips, Claire; Whelan, Timothy J; Bryant, Guy; Kunkler, Ian H; Westenberg, A Helen; Purohit, Kash; Ahern, Verity

Published in:
Radiotherapy and Oncology

DOI:
[10.1016/j.radonc.2019.07.024](https://doi.org/10.1016/j.radonc.2019.07.024)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

BIG 03-07/TROG 07.01 trial investigators, Olivotto, I. A., Link, E., Phillips, C., Whelan, T. J., Bryant, G., Kunkler, I. H., Westenberg, A. H., Purohit, K., Ahern, V., Graham, P. H., Akra, M., McArdle, O., Ludbrook, J. J., Harvey, J. A., Maduro, J. H., Kirkove, C., Gruber, G., Martin, J. D., ... Chua, B. H. (2020). International comparison of cosmetic outcomes of breast conserving surgery and radiation therapy for women with ductal carcinoma in situ of the breast. *Radiotherapy and Oncology*, 142, 180-185.
<https://doi.org/10.1016/j.radonc.2019.07.024>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Original Article

International comparison of cosmetic outcomes of breast conserving surgery and radiation therapy for women with ductal carcinoma in situ of the breast

Ivo A. Olivetto^{a,*}, Emma Link^{b,c}, Claire Phillips^c, Timothy J. Whelan^d, Guy Bryant^e, Ian H. Kunkler^f, A. Helen Westenberg^g, Kash Purohit^h, Verity Ahernⁱ, Peter H. Graham^j, Mohamed Akra^k, Orla McArdle^l, Joanna J. Ludbrook^m, Jennifer A. Harvey^e, John H. Maduroⁿ, Carine Kirkove^o, Guenther Gruber^p, Joseph D. Martin^q, Ian D. Campbell^r, Geoff P. Delaney^{j,s}, Boon H. Chua^j, on behalf of the BIG 03-07/TROG 07.01 trial investigators¹

^a University of Calgary, Canada; ^b University of Melbourne; ^c Peter MacCallum Cancer Centre, Melbourne, Australia; ^d McMaster University, Hamilton, Canada; ^e University of Queensland, Brisbane, Australia; ^f University of Edinburgh, UK; ^g Radiotherapiegroep, Arnhem, Netherlands; ^h University of Sheffield, UK; ⁱ University of Sydney, Westmead; ^j University of New South Wales (NSW), Sydney, Australia; ^k University of Manitoba, Winnipeg, Canada; ^l Royal College of Surgeons in Ireland, Dublin, Ireland; ^m University of Newcastle, Australia; ⁿ University Medical Centre Groningen, Netherlands; ^o Universite Catholique de Louvain, Brussels, Belgium; ^p University of Berne, Switzerland; ^q Cancer Trials Ireland and University Hospital, Galway, Ireland; ^r University of Auckland, New Zealand; ^s Ingham Institute for Applied Medical Research, Liverpool, Australia

ARTICLE INFO

Article history:

Received 21 March 2019

Received in revised form 19 July 2019

Accepted 19 July 2019

Available online 17 August 2019

Keywords:

Breast cancer
Radiotherapy
Cosmetic outcomes
Fractionation
Boost
Breast conservation

ABSTRACT

Purpose: To assess the cosmetic impact of breast conserving surgery (BCS), whole breast irradiation (WBI) fractionation and tumour bed boost (TBB) use in a phase III trial for women with ductal carcinoma in situ (DCIS) of the breast.

Materials and methods: Baseline and 3-year cosmesis were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Cosmetic Rating System and digital images in a randomised trial of non-low risk DCIS treated with postoperative WBI +/- TBB. Baseline cosmesis was assessed for four geographic clusters of treating centres. Cosmetic failure was a global score of fair or poor. Cosmetic deterioration was a score change from excellent or good at baseline to fair or poor at three years. Odds ratios for cosmetic deterioration by WBI dose-fractionation and TBB use were calculated for both scoring systems.

Results: 1608 women were enrolled from 11 countries between 2007 and 2014. 85–90% had excellent or good baseline cosmesis independent of geography or assessment method. TBB (16 Gy in 8 fractions) was associated with a >2-fold risk of cosmetic deterioration ($p < 0.001$). Hypofractionated WBI (42.5 Gy in 16 fractions) achieved statistically similar 3-year cosmesis compared to conventional WBI (50 Gy in 25 fractions) ($p \geq 0.18$). The adverse impact of a TBB was not significantly associated with WBI fractionation (interaction $p \geq 0.30$).

Conclusions: Cosmetic failure from BCS was similar across international jurisdictions. A TBB of 16 Gy increased the rate of cosmetic deterioration. Hypofractionated WBI achieved similar 3-year cosmesis as conventional WBI in women treated with BCS for DCIS.

© 2019 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 142 (2020) 180–185

Breast conserving surgery (BCS) followed by radiation therapy (RT) is the primary management for many women with early-stage, invasive breast cancer and ductal carcinoma *in situ* (DCIS) [1–4]. Most women achieve good to excellent cosmesis after BCS

and RT but some experience cosmetic failure, defined as fair or poor cosmetic outcomes [5–17]. However, comparisons of cosmetic outcomes across international jurisdictions using contemporary surgical and RT techniques for DCIS are lacking.

Between 2007 and 2014, in collaboration with the Breast International Group (BIG), the Trans-Tasman Radiation Oncology Group (TROG) coordinated a randomised, phase III trial of tumour bed boost (TBB) following conventionally fractionated or hypofractionated whole breast irradiation (WBI) for women with non-low risk, unilateral, DCIS of the breast treated with BCS (BIG 03-07/TROG

* Corresponding author at: 1032 Walema Avenue, Victoria, British Columbia V8Y 1P1, Canada.

E-mail address: ivo.a.olivetto@gmail.com (I.A. Olivetto).

¹ See Appendix A for a list of trial investigators, participating institutions and collaborating trials groups.

07.01 trial, [Clinicaltrials.gov registration number: NCT00470236](https://clinicaltrials.gov/ct2/show/study/NCT00470236)). The trial was a collaboration of seven clinical trials organisations across four continents. As part of the trial, cosmetic outcomes were evaluated using the validated European Organisation for Research and Treatment of Cancer (EORTC) Cosmetic Rating System [5], and standardised clinical photographs were obtained at baseline (after BCS; prior to RT) and at protocol-specified intervals after RT.

This is a report of an international comparison of cosmetic outcomes at baseline after BCS, and at three years after post-operative WBI with or without a TBB, based on prospective cosmetic assessments and central review of standardised clinical photographs within the BIG 03-07/TROG 07.01 trial.

Materials and methods

Treatments on the BIG 03-07/TROG 07.01 trial

The BIG 03-07/TROG 07.01 trial enrolled women aged ≥ 18 years with unilateral, non-low risk (Appendix B) DCIS treated by BCS with $\geq$ one mm clear radial margins, who were suitable for post-operative RT and available for long-term follow up.

Women were randomised, 1:1, to receive a TBB of 16 Gy in 8 fractions or no TBB following WBI. The permitted WBI schedules were 50 Gy in 25 fractions (conventional fractionation) or 42.5 Gy in 16 fractions (hypofractionation). Each centre, prior to entering their first patient on study, elected to use one of the WBI regimens or participate in a secondary randomisation between the two regimens. Stratification factors were age (<50 , ≥ 50), planned endocrine therapy use (yes, no) and treating centre.

Computer tomography (CT)-based RT planning was mandatory. The TBB dose was delivered to the primary site with a protocol-defined margin using an incident electron beam or megavoltage photons via tangential or other field arrangements that conformed to the dose homogeneity and normal tissue constraints of the protocol. Interstitial brachytherapy was not permitted. The WBI was delivered using tangential 4–18MV photon beams with wedges or sub-fields to optimise homogeneity. A point dose $>110\%$ (to a volume of 2 cc) was a protocol deviation. RT commenced within 12 weeks of the last breast surgical procedure and was delivered once daily. The number of treatment visits required of patients ranged from 16 (hypofractionated WBI, no TBB) to 33 (conventionally fractionated WBI plus TBB). Adjuvant endocrine therapy use was at the discretion of the treating physicians. Chemotherapy was prohibited. Table 1 shows the distributions of baseline patient characteristics, geographic regions and treatments.

Cosmetic scoring by treatment centres

Following BCS and prior to randomisation, treatment centre staff completed baseline cosmetic assessments using the 10-part EORTC Cosmetic Rating System which compared the treated and untreated breasts for size and shape, nipple/areolar location and shape, visibility of surgical scar(s), skin colour and the extent of breast oedema or skin telangiectasia (Appendix C) [18]. A global cosmetic score, categorised as excellent, good, fair or poor was assigned. At baseline, the cosmetic score was a measure of the impact of BCS alone. Cosmetic scores were recorded prospectively to assess the impact of both surgery and RT, at one, three and five years after RT. Baseline and 3-year global cosmetic scores were used in the current study.

Cosmetic scoring from clinical digital images

To complement subjective assessments, standardised digital images of the breasts (Appendix D) were obtained and submitted electronically to the TROG database. In other studies, panels of

Table 1
Patient, disease and treatment characteristics.

	Total No. (%)	Boost No. (%)	No Boost No. (%)
Total [No. (%)]	1608 (100%)	803 (100%)	805 (100%)
Age (years) median (range)	58 (31–82)	57 (31–82)	58 (35–81)
Age			
<50 years	268 (17%)	133 (17%)	135 (17%)
≥ 50 years	1340 (83%)	670 (83%)	670 (83%)
Nuclear grade			
Low	105 (7%)	56 (7%)	49 (6%)
Intermediate	600 (38%)	316 (41%)	284 (36%)
High	874 (55%)	409 (52%)	465 (58%)
Missing	29	22	7
Tumour size (maximum dimension)			
≤ 1.0 cm	528 (33%)	288 (36%)	240 (30%)
>1.0 – ≤ 1.5 cm	281 (17%)	132 (16%)	149 (18%)
>1.5 cm	799 (50%)	383 (48%)	416 (52%)
Region			
Australasia*	520 (32%)	259 (32%)	261 (32%)
Canada	300 (19%)	149 (19%)	151 (19%)
UK/Ireland	406 (25%)	205 (25%)	201 (25%)
Rest of Europe	382 (24%)	190 (24%)	192 (24%)
WBI dose/fx group			
Randomized for dose/fx	503 (31%)	251 (31%)	252 (31%)
Selected 50 Gy/25fx	581 (36%)	290 (36%)	291 (36%)
Selected 42.5 Gy/16fx	524 (33%)	262 (33%)	262 (33%)
WBI dose/fx used			
42.5 Gy/16fx	777 (48%)	388 (48%)	389 (48%)
50 Gy/25fx	831 (52%)	415 (52%)	416 (52%)
Planned Endocrine Therapy			
Yes	211 (13%)	105 (13%)	106 (13%)
No	1397 (87%)	698 (87%)	699 (87%)

No. = number; WBI = whole breast irradiation; fx = number of fractions or treatments.

* Australasia = Australia, New Zealand and Singapore.

3–5 experienced clinicians have scored cosmesis from photographs or digital images and average or consensus scores were calculated and used [8,11,12,14]. There would have been considerable logistical challenges in this international trial to assemble, train, demonstrate consistency between, and convene panels in different countries to review 500–1000 digital images each in a timely manner. Similarly, retrospectively digitizing nearly 3000 images for use in the BCCT.core system was not felt to be practical. Thus, for the current study, one radiation oncologist experienced in breast cosmetic evaluation (IAO) scored all the baseline and 3-year post-RT digital images in the trial database as of February 16, 2018. Electronic files of digital images, blinded for patient identifiers, timing (baseline vs. 3 years post RT), treatment centre geographic region, WBI dose-fractionation and TBB use, were created by TROG trial centre staff in Newcastle, Australia, and sent to the reviewer in Calgary, Canada. Visible scars enabled the reviewer to identify treatment laterality in most cases.

The digital images were anterior views of patients in the standing position from the neck to the umbilicus showing both breasts. Each digital image was scored as excellent, good, fair, poor or not suitable for analysis (due to poor image quality, both breasts not wholly visible, significant oncological intervention, or mastectomy at the 3-year evaluation). A spreadsheet with scores was returned to TROG staff for analyses. Analyses excluded subjects with missing or unsuitable images.

To assess reproducibility of the single-reviewer digital image scoring, 100 randomly selected, good quality images were reviewed twice within the first 1000 images assessed. The twice-reviewed images included baseline and 3-year post RT images with treating centre scores ranging from excellent to poor. *A priori*, the BIG 3-07/TROG 07.01 Steering Committee decided that the

single-reviewer approach would be considered sufficiently consistent if the weighted Kappa statistic was ≥ 0.7 for a dichotomised endpoint (excellent/good vs. fair/poor) [19]. For the overall study, images of subjects with a change in score from excellent/good to fair/poor, or the converse, between baseline and 3-years post RT were re-reviewed to approximate the use of average or consensus scores across multiple independent reviewers used in previous cosmetic analyses based on photo panels [8,11,12,14]. If necessary, scores were adjusted for one, neither or both images. Final scores were used for analysis.

Statistical analyses

The centre-reported and digital image-reviewed global cosmetic scores were dichotomised as excellent/good (cosmetic success) vs. fair/poor (cosmetic failure). Secondary analyses evaluated cosmetic outcome as a 4-part variable. Cosmetic deterioration was a change from a score of excellent/good to fair/poor over time. These definitions of cosmetic failure and deterioration have been shown to be sensitive to patient, surgical and RT technical factors [6–17]. To assess the single-reviewer consistency between initial and repeat scores and agreement between site reported and single reviewer scores, weighted kappa statistics were calculated.

To assess international BCS cosmesis, baseline cosmetic scores were tabulated by four geographically-defined clusters of treatment centres: Australasia (Australia, New Zealand and Singapore); Canada; the United Kingdom and Ireland; and the rest of Europe. The purpose of geographic clustering was to balance sample size and potential ethnic or cultural influences. Rates of excellent/good scores and the proportions of subjects with each 4-part score were compared by chi-squared tests and Kruskal–Wallis tests, respectively, between geographic regions using centre-reported EORTC scores and digital image scores. Logistic regression was used to assess scores between geographic regions using both scoring methods. The impact of WBI dose-fractionation and TBB use were similarly evaluated using both scores across all subjects at the two time-points which included patients who may have either deteriorated or improved from baseline to the 3-year assessment. Assessments included adjustment for region when examining baseline scores and both region and baseline score when examining 3-year outcomes by WBI fractionation and TBB use.

Assessment for cosmetic deterioration involved only subjects with evaluable scores or images at both the baseline and 3-year time points. The proportion of subjects with an excellent/good score at baseline who had a fair/poor score at three years post RT, using logistic regression to assess the impact of WBI dose-fractionation and TBB use, adjusted for geography and WBI approach (randomized or centre-selected dose-fractionation). Secondary analyses evaluated the proportion of subjects with fair/poor scores at baseline who had excellent/good scores at three years. $P < 0.05$ was considered statistically significant. Analyses were conducted in SAS version 9.4.

Conduct of the BIG 03-07/TROG 07.01 trial

The trial protocol was approved by the relevant committees of participating clinical trials groups and the institutional research ethics review boards of participating centres. All patients signed written informed consent prior to any study-related procedures.

Results

Between June 1, 2007 and June 30, 2014, 1608 subjects from 136 centres in 11 countries were recruited to the trial (Appendix A). 116 centres contributed cosmetic assessments by February 18, 2018. EORTC global cosmetic scores were recorded for 1543 patients

(96%) at baseline, 1239 patients (77%) at 3 years post RT and 1227 (76%) patients at both evaluation points. Standardised digital images were evaluable for 1428 patients (89%) at baseline, 1034 patients (64%) at 3 years and 999 (62%) patients at both time points. The distributions of patient and treatment characteristics are shown in Table 1.

The use of the two protocol-specified WBI fractionation regimens varied between geographic regions: 62% of subjects in Australasia had WBI fractionation determined by random allocation compared to 4% of subjects in Europe (excluding the UK/Ireland). Including patients whose WBI fractionation was determined by randomisation or centre election, the proportions of patients who had hypofractionated WBI were 33%, 34%, 59% and 78% for subjects from Australasia, Europe (excluding UK/Ireland), UK/Ireland and Canada, respectively. Overall, 831 (52%) subjects were treated with conventionally fractionated WBI and 777 (48%) were treated with hypofractionated WBI. Analyses of the cosmetic impact of WBI dose-fractionation were therefore adjusted for geography. Three of 785 (0.4%) subjects with completed post-treatment dosimetry quality assurance review had minor protocol deviations (3D point dose >110 –115%) and no patients had major dosimetry protocol deviations.

When randomly selected digital images (57 baseline and 43 three-year images) among the first 1000 images assessed, were reviewed twice using the dichotomous cosmetic endpoint, there was strong agreement (weighted kappa = 0.81 [95% confidence interval (CI) 0.67, 0.96]). Thus, the single-reviewer digital image review process was declared to be sufficiently consistent for cosmetic endpoint assessments.

There was fair agreement between the digital image review and centre-reported global cosmetic scores for 1419 subjects with both scores at baseline using a dichotomized endpoint (weighted kappa = 0.39 [95% CI 0.33, 0.46]) and using the 4-part cosmetic outcome endpoint (weighted kappa = 0.31 [95% CI 0.26, 0.35]) as detailed in Appendix E. For the 1003 subjects with both 3-year centre-reported global cosmetic scores and images available, the agreement was moderate for both the dichotomized endpoint (weighted kappa = 0.47 [95% CI 0.39, 0.54]) and the 4-part cosmetic endpoint (weighted kappa = 0.41 [95% CI 0.36, 0.45]).

There were no significant differences between the four geographic regions when cosmesis was evaluated as a dichotomized variable (Table 2). 85% to 90% (mean 88%) of subjects had excellent or good centre-reported global cosmetic scores at baseline ($p = 0.085$). At baseline, there were no significant differences in the rate of excellent/good centre-reported EORTC scores by WBI fractionation received (87–88%; $p = 0.80$) or TBB use (87–88%; $p = 0.91$). Similar results were observed with the digital image scores as shown in Table 2.

Using the four-part centre-reported global cosmetic scores, fewer subjects from Europe (excluding the UK/Ireland) were reported to have excellent cosmesis based on centre-reported global cosmetic scores (38% vs. 45–56% excellent in other regions, $p < 0.001$). However, this difference was not observed using the blinded, digital image review scores (49% excellent in Europe vs. 46–52% excellent in other regions; $p = 0.17$).

Using centre-reported scores, excellent or good cosmesis was recorded for 88% of subjects at baseline and 84% of subjects at 3 years ($p < 0.0001$, unadjusted and $p < 0.0001$ adjusted for region, randomisation approach, TBB use and WBI dose-fractionation). Similar results (84% at baseline and 81% at 3-years, $p < 0.0001$, both unadjusted and adjusted) were observed using the digital image review global cosmetic scores. The observed outcomes at three years included the potential for both deterioration and improvement in cosmesis over time. There were no significant differences in the proportions of subjects with excellent or good global cosmetic scores whether WBI dose-fractionation regimens were

Table 2
Distribution of BASELINE cosmesis by geography, whole breast fractionation and boost use.

	Centre-reported EORTC scores					Digital Image Review Scores				
	Ex/G No. (%)	F/P No. (%)	p	Ex No. (%)	Missing No.	Ex/G No. (%)	F/P No. (%)	p	Ex No. (%)	Missing No.
Total	1351 (88)	192 (12)		766 (50)	65	1225 (86)	203 (14)		703 (49)	180
Geographic region			0.085					0.22		
Australasia*	455 (89)	59 (11)		285 (55)	6	434 (88)	58 (12)		256 (52)	28
Canada	243 (86)	40 (14)		126 (45)	17	219 (83)	45 (17)		127 (48)	36
UK/Ireland	358 (90)	39 (10)		221 (56)	9	296 (85)	51 (15)		161 (46)	59
Rest of Europe	295 (85)	54 (15)		134 (38)	33	276 (85)	49 (15)		159 (49)	57
WBI dose/fx used			0.80					0.050		
50 Gy/25fx	696 (88)	97 (12)		404 (51)	38	640 (88)	91 (12)		369 (50)	100
42.5 Gy/16fx	655 (87)	95 (13)		362 (48)	27	585 (84)	112 (16)		334 (48)	80
Boost use			0.91					0.57		
Boost	667 (88)	94 (12)		383 (50)	42	607 (85)	105 (15)		353 (50)	91
No Boost	684 (87)	98 (13)		383 (49)	23	618 (86)	98 (14)		350 (49)	89

Ex/G = excellent or good cosmetic score; F/P = fair or poor cosmetic score; p = p-value; Ex = Excellent cosmetic score; No. = number; WBI = whole breast irradiation; fx = number of fractions or treatments; Gy = Gray.

* Australasia = Australia, New Zealand and Singapore.

determined by centre selection or randomisation at baseline (87–88% excellent/good; $p = 0.29$, adjusted for region) or at 3-years (82–86% excellent/good; $p = 0.68$ adjusted for region and baseline score). There were also no significant differences in the proportions of patients with excellent or good global cosmetic scores between the two WBI regimens used either at baseline (conventional fractionation 88% vs. hypofractionation 87%; $p = 0.72$, adjusted for region) or at 3-years (conventional fractionation 83% vs. hypofractionation 85%; $p = 0.76$, adjusted for region and baseline score). In contrast, although the proportions of subjects with excellent or good centre-reported global cosmetic scores were similar between the TBB and no-TBB groups at baseline (87–88% excellent or good; $p = 0.92$), patients randomized to receive a TBB had fewer excellent or good cosmetic scores at 3-years (TBB 80% vs. no-TBB 88%; $p < 0.001$, adjusted for WBI fractionation and baseline score).

Among 136 subjects with fair/poor baseline scores and available 3-year digital images, 38 (28%) had excellent or good global cosmetic scores at three years after RT. The cosmetic improvement was due to the resolution of significant haematoma, oedema or erythema observed on the baseline images. Using centre-reported scores, 85 (57%) of 150 patients with fair or poor scores at baseline had excellent or good global cosmetic scores at 3-years after RT.

Cosmetic deterioration was evaluated among subjects with excellent or good scores at baseline and evaluable scores at both time points. Of the 1227 subjects with both baseline and 3-year centre-reported global cosmetic scores, 1077 (88%) had an excellent/good score at baseline. Of the 999 subjects with usable digital images at both baseline and 3 years, 863 (86%) had an excellent/good cosmetic score at baseline. Subjects who received a TBB were more than twice as likely to experience cosmetic deterioration from excellent/good to fair/poor at 3-years (odds ratio 2.04; 95%

CI 1.39, 2.98; $p < 0.001$ using centre-reported global cosmetic scores, and 2.82; 95% CI 1.76, 4.50; $p < 0.001$ using the digital image review scores) as shown in Table 3. Using the digital image scores, among subjects with excellent/good scores at baseline, 6% of patients in the no-TBB group and 16% who received a TBB had fair/poor scores at 3 years. The adverse impact of TBB was similar whether the WBI was delivered with conventional or hypofractionation. The p-values for interaction between WBI fractionation and TBB use were 0.57 using centre-reported and 0.30 using the digital image review global cosmetic scores.

The rates of cosmetic deterioration did not differ between the two WBI regimens. Eleven to 13% of subjects with excellent/good scores at baseline had fair/poor scores at 3 years depending on the cosmetic assessment method used and whether the subject received conventional or hypofractionated WBI (Table 4). The odds ratios for cosmetic deterioration comparing conventional WBI to hypofractionated WBI were 1.06 (95% CI 0.72, 1.57; $p = 0.76$) using centre-reported scores, and 1.40 (95% CI 0.85, 2.28; $p = 0.18$) using digital image assessment scores.

Discussion

This is the first international study of cosmesis in patients with non-low risk DCIS treated by BCS and post-operative RT. Cosmetic outcomes after BCS were comparable across 11 countries on four continents. Our study also demonstrated that hypofractionated WBI achieved statistically equivalent cosmetic outcomes compared to conventionally fractionated WBI, validating the findings of two large randomised trials conducted among women with invasive breast cancer [9,10]. The use of a 16 Gy in 8 fractions TBB was associated with a significantly increased risk of cosmetic deterioration as was shown in another study which tested the

Table 3
Odds Ratios for cosmetic deterioration by boost use.

	Centre-reported EORTC scores				Digital Image Review Scores			
	Ex/G at Baseline No.	F/P at 3 years No. (%)	Odds Ratio* (95% CI)	P*	Ex/G Baseline No.	F/P at 3 years No. (%)	Odds Ratio* (95% CI)	P*
Total	1077	132 (12)			863	94 (11)		
Boost use			2.04 (1.39, 2.98)	<0.001			2.82 (1.76, 4.50)	<0.001
Boost	538	86 (16)			428	67 (16)		
No Boost	539	46 (9)			435	27 (6)		

Ex/G = Excellent or Good cosmetic score; F/P = Fair or Poor cosmetic score; No. = number; p = p-value.

CI = confidence interval; WBI = whole breast irradiation; Gy = Gray; fx = fractions = number of treatments.

* Odds Ratio for comparison Boost vs. No Boost, logistic regression adjusted for whole breast irradiation approach (dose randomized or centre-selected as conventional or short fractionation).

Table 4
Odds Ratios for cosmetic deterioration by whole breast dose fractionation used.

	Centre-reported EORTC scores				Digital Image Review Scores			
	Ex/G at Baseline No.	F/P at 3 years No. (%)	Odds Ratio* (95% CI)	P ^a	Ex/G Baseline No.	F/P at 3 years No. (%)	Odds Ratio* (95% CI)	P ^a
Total	1077	132 (12)	1.06 (0.72, 1.57)	0.76	863	94 (11)	1.40 (0.85, 2.28)	0.18
WBI dose/fx used								
50 Gy/25fx	542	71 (13)			440	47 (11)		
42.5 Gy/16fx	535	61 (11)			423	47 (11)		

Ex/G = Excellent or Good cosmetic score; F/P = Fair or Poor cosmetic score; No. = number; p = p-value; CI = confidence interval; WBI = whole breast irradiation; Gy = Gray; fx = fractions = number of treatments.
International comparison of cosmetic outcomes of breast conserving surgery and radiation therapy for women with ductal carcinoma in situ of the breast.
^a Odds Ratio for comparison 50 Gy vs. 42.5 Gy, logistic regression adjusted for geography.

same boost dose in women with invasive breast cancer [14]. Only 13% of patients received adjuvant endocrine therapy and no patient received chemotherapy. Thus, the findings of this study largely reflect the impact of local therapies alone.

An EORTC randomised trial showed that a TBB of 16 Gy in 8 fractions improved local control for patients with invasive breast cancer [20], but was associated with worse cosmesis in a proportion of patients [8,14]. The same TBB added to a reduced whole breast dose of 45 Gy was not associated with worse cosmesis [21] and a TBB of 10 Gy in four fractions resulted in a local recurrence odds reduction with overlapping confidence intervals compared to the EORTC study but with no difference in patient-reported cosmesis [22]. The 10 Gy in four fraction boost regimen may be a pragmatic way to achieve the therapeutic benefits of a TBB while minimising the associated adverse effects and treatment inconvenience. The efficacy of TBB to improve local control in patients with DCIS is the primary endpoint of BIG 03-07/TROG 07.01, and will be analysed five years after the end of accrual.

In this study of patients with DCIS, approximately 10–15% had fair or poor cosmesis at baseline after BCS, independent of geography. This was similar to the rates of cosmetic failure after BCS among patients with invasive breast cancer dating to the 1980s [6–11,15,17]. Cosmetic failure has been associated with various patient and treatment factors. In particular, breast cosmesis is strongly impacted by the volume of breast tissue and/or skin resected and wound closure techniques which impact the size and shape of the treated breast, and the location and orientation of the nipple-areolar complex. Since DCIS does not involve the skin, it is concerning to observe that some of these adverse effects of BCS were not ameliorated compared to BCS practices from several decades earlier. The use of onco-plastic surgery was not prospectively recorded in our trial database but during digital image review, only a small number of patients were observed to have had such procedures on one or both breasts.

The use of hypofractionated WBI in our study was much more common in Canada and the UK/Ireland compared to Australasia or the rest of Europe. This finding is consistent with the long-standing practice of using hypofractionation for early-stage invasive breast cancer and the successful conclusion of large clinical trials of breast RT fractionation conducted in the former jurisdictions [9,10,17]. The clinical trials of hypofractionated WBI for invasive breast cancer showed that the shorter fractionation was equally well tolerated compared to the more extended, conventional fractionation, and local control was similar or better with the shorter fractionation [9,10]. There is also suggestive evidence that short fractionation is well tolerated when the regional lymph nodes are part of the treatment volume [23,24]. A large UK trial evaluating whether WBI could be safely delivered in one week for invasive breast cancer has completed accrual and long-term data on the effects of this regimen on breast recurrence, fibrosis and cosmesis is awaited [25]. Time to local recurrence is the primary endpoint of the BIG 03-07/TROG 07.01 trial, and this pending

result may help inform whether hypofractionated WBI could be considered a standard approach in patients with DCIS.

Our study has confirmed that prospective collection of standardised clinical images could be used to evaluate the cosmetic effects of surgery and RT on the breast. The cosmetic scoring of clinical images by a single reviewer, blinded to treatment, geography and timing was more internally consistent than when the digital image review scores were compared to treatment centre-reported scores. The scoring of global cosmesis is subjective and it was interesting to note that centres in Europe were somewhat less likely to provide an excellent score compared to other jurisdictions. In contrast, European centres did not have fewer excellent outcomes at baseline when the digital images were reviewed. In the EORTC boost trial, use of a digitizer to quantify breast changes was reliable but unable to detect elements such as skin changes that might influence the global cosmetic interpretation from images [8]. The single-reviewer system was adopted due to availability of a reviewer with experience in the evaluation of breast cosmesis [11,13,17], and the logistical complexity in a large, international trial, to assemble, train, demonstrate consistency between, and convene image panels in different countries to review images in a timely manner. Whether similar results would be obtained by other single reviewers is unknown. Nonetheless, both the centre-reported and the digital image review processes were able to detect the adverse effects of a TBB on breast cosmesis. It is interesting to note there were statistically fewer excellent centre-reported global cosmetic scores reported from centres in Europe compared to other geographic regions. This was likely due to variation in the application of an excellent score as no differences in the rates of excellent global cosmetic scores were reported using the more internally consistent, single-reviewer system.

A strength of our study is the large sample size contributed from 116 centres in 11 countries with consistent, prospective use of the validated EORTC Cosmetic Rating System. The System entails an assessment of nine parameters that contribute to the overall cosmetic outcome plus an explicit statement about the overall cosmetic appearance of the treated breast in comparison to the non-treated breast [18]. The observed cosmetic results in the BIG 03-07/TROG 07.01 trial likely reflect real-world outcomes in clinical practice.

Our study had a number of limitations. Not all patients had prospectively evaluated cosmetic scores or high-quality digital images available at both baseline and 3-years after RT. This was in part related to follow-up duration at the time of the analysis, quality of the images, and the logistical challenges of timely submission of data and images from a large number of centres in an international trial. However, our study is the largest prospective evaluation of cosmetic outcomes for women with DCIS and, pending the efficacy analysis, will provide robust data on the relative effects of TBB and WBI dose-fractionation on normal tissues and cosmetic outcomes. Patient perceptions of the outcomes of breast

conserving therapies are important. Analyses of patient reported outcomes collected prospectively as part of the BIG 03-07/TROG 07.01 trial will be reported separately. Since adverse cosmetic effects may progress over time, long-term follow up including cosmetic evaluations of study participants will be necessary to confirm the current observations.

Declaration of Competing Interest

All authors declare no commercial conflicts of interests other than per capita or grant funding to their institutions for patient accrual. The funding bodies had no role in the analysis or reporting of results and did not review or edit the text of the manuscript.

Acknowledgements

Supported in part by grants or research support from the National Health and Medical Research Council of Australia, Susan G. Komen for the Cure®, Breast Cancer Now, the OncoSuisse Swiss Federation Against Cancer, the Dutch Cancer Society and the Canadian Cancer Society through the Canadian Cancer Trials Group.

Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.07.024>.

References

- [1] Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowle B, Giuliano A, et al. Standard for breast conservation therapy in the management of invasive breast carcinoma. *CA Cancer J Clin* 2002;52:277–300.
- [2] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16.
- [3] Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015;16:266–73.
- [4] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, Wang Y, Clarke M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr* 2010;41:162–77.
- [5] Van Limbergen E, van der Schueren E, Van Tongelen K. Cosmetic evaluation of breast conserving treatment for mammary cancer. 1. Proposal of a quantitative scoring system. *Radiother Oncol* 1987;8:1–9.
- [6] Van Limbergen E, Rijnders A, van der Schueren E, Lerut T, Christiaens R. Cosmetic evaluation of breast conserving treatment for mammary cancer. 2. A quantitative analysis of the influence of radiation dose, fractionation schedules and surgical treatment techniques on cosmetic results. *Radiother Oncol* 1989;16:159–67.
- [7] Rose MA, Olivetto I, Cady B, Koufman C, Osteen R, Silver B, et al. Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. *Arch Surg* 1989;124:153–7.
- [8] Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. *Radiother Oncol* 2000;55:219–32.
- [9] Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513–20.
- [10] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–94.
- [11] Olivetto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 2013;31:4038–45.
- [12] Haviland JS, Hopwood P, Mills J, Sydenham M, Bliss JM, Yarnold JR, et al. Do patient-reported outcome measures agree with clinical and photographic assessments of normal tissue effects after breast radiotherapy? The experience of the Standardisation of Breast Radiotherapy (START) trials in early breast cancer. *Clin Oncol* 2016;28:345–53.
- [13] Olivetto IA, Rose MA, Osteen RT, Love S, Cady B, Silver B, et al. Late cosmetic outcome after conservative surgery and radiotherapy: analysis of causes of cosmetic failure. *Int J Radiat Oncol Biol Phys* 1989;17:747–53.
- [14] Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC 'boost versus no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups, European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys* 1999;45:677–85.
- [15] Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. *Cancer* 2001;91:2282–7.
- [16] Krishnan L, Stanton AL, Collins CA, Liston VE, Jewell WR. Form or function? Part 2. Objective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. *Cancer* 2001;91:2282–7.
- [17] Olivetto IA, Weir LM, Kim-Sing C, Bajdik CD, Trevisan CH, Doll CM, et al. Late cosmetic results of short fractionation for breast conservation. *Radiother Oncol* 1996;41:7–13.
- [18] Aaronson NK, Bartelink H, van Dongen JA, van Dam FS. Evaluation of breast conserving therapy: clinical, methodological and psychosocial perspectives. *Eur J Surg Oncol* 1988;14:133–40.
- [19] Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. third ed. New York: John Wiley & Sons; 2003.
- [20] Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015;16:47–56.
- [21] Hau E, Browne LH, Khanna S, Cail S, Chin Y, Clark C, et al. Radiotherapy breast boost with reduced whole-breast dose is associated with improved cosmesis: the results of a comprehensive assessment from the St George and Wollongong randomized boost trial. *Int J Radiat Biol Phys* 2012;82:682–9.
- [22] Romestaing P, Lehinque Y, Carrie C, Coquard R, Monbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15:963–8.
- [23] Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivetto IA. Hypofractionated nodal radiation therapy for breast cancer was not associated with increased patient-reported arm or brachial plexopathy symptoms. *Int J Radiat Oncol Biol Phys* 2017;99:1166–72.
- [24] Haviland JS, Mannino M, Griffin C, Porta N, Sydenham M, Bliss JM, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: results from the UK START (Standardisation of Breast Radiotherapy) trials. *Radiother Oncol* 2018;126:155–62.
- [25] Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol* 2016;120:114–8.