Radiotherapy and Oncology 104 (2012) 1–10

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Relationship between irradiated breast volume and late normal tissue complications: A systematic review

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ARTICLE INFO

Article history:
Received 1 November 2011
Received in revised form 29 March 2012
Accepted 30 April 2012
Available online 8 June 2012

Keywords:
Breast neoplasm
Radiation
Cosmesis
Fibrosis
Normal tissue

ABSTRACT

The concept of radiation dose–volume effect has been exploited in breast cancer as boost treatment for high risk patients and more recently in trials of Partial Breast Irradiation for low risk patients. However, there appears to be paucity of published data on the dose–volume effect of irradiation on breast tissue including the recently published report on Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC). This systematic review looks at the current literature for relationship between irradiated breast volume and normal tissue complications and introduces the concept of dose modulation.

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The aim of radiation therapy is to deliver a tumouricidal dose for optimal loco-regional control with relative sparing of the surrounding normal tissues. The precise knowledge of tumouricidal and tolerance doses to various tissues including dose–volume effect is necessary when using 3D-conformal and intensity modulated radiotherapy techniques. Emami and colleagues [1] were amongst the first to publish a comprehensive review of radiation tolerance for normal tissues, including quantification of late normal tissue complication (NTC) as a function of volume of organ irradiated. This review, although informative was limited by the availability of few comprehensive databases, with most of the data on dose–volume effect interpolated or extrapolated from whole organ data, or based on the experience of the involved clinicians. However it did provide a firm framework for quantifying the volumetric and dosimetric measures which may influence normal tissue complications. Since that publication, an update on the dose–volume effect of radiation on the normal tissues has been published in form of "Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)" report [2]. This report helps in our understanding of the normal tissue radiation tolerance and can be utilised in clinical treatment planning as it provides an estimate of the effect of change in irradiated volume on normal organ tolerance [3,4]. This information can be exploited by dose escalation to the target volume with only a small amount of surrounding normal tissue receiving a higher dose. For example, the rectum is a critical normal structure during dose escalation in prostate cancer radiotherapy. Use of intensity modulated radiotherapy (IMRT) allows safe dose escalation by reducing the volume of rectum receiving high dose with favourable normal tissue complication rates compared to 3D-conformal radiotherapy [5].

For years, the radiation dose–volume effect for the breast has been exploited as boost treatment for breast cancer patients at high risk of recurrence i.e. treating a small volume of breast tissue to a higher dose (boost) to improve local control rates [6–8]. More recently, breast dose–volume effect has been exploited in trials of Partial Breast Irradiation (PBI) for patients at low risk of recurrence: the irradiated volume is confined to the region around the tumour bed with the aim of reducing toxicity whilst maintaining local control rates. Despite there being very good evidence for a radiation dose–volume effect in many organs including lung and rectum, there appears to be a paucity of published data on dose–volume effect of radiation on breast tissue. This systematic review evaluates the evidence for a relationship between the volume of breast tissue irradiated and the late NTCs including overall cosmesis, breast fibrosis, breast induration and telangiectasia. It also explores the hypothesis that a modest dose reduction to part of the breast facilitates dose escalation to the tumour bed, with lower than expected NTC.

Materials and methods

A systematic search was performed via Medline and Embase with the search strategy "breast neoplasm" AND "radiotherapy

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0167-8140
http://dx.doi.org/10.1016/j.radonc.2012.04.025

OR irradiation". This was combined with "AND fibrosis", "AND cosme*", "AND side effect*", "AND toxicity", "AND shrinkage" and "AND normal tissue". The search was expanded to include related articles and a reference list of articles. The effects on NTC for the following parameters are reported in this manuscript:

(a) Boost volume
(b) Partial Breast Irradiation (PBI)
(c) Fractionation regimens

Results

Impact of boost volume on normal tissue complications

EORTC 22881-10882 "boost versus no boost" trial (level I evidence)

The EORTC "boost versus no boost" trial randomised 5318 patients with early breast cancer between extra irradiation to the tumour bed (boost of 16 Gy) versus no boost treatment after whole breast irradiation (WBI) [6]. The boost was delivered using electrons or tangential photon fields in daily fractionation of 2 Gy, or with Iridium-192 implant at a dose rate of 0.5 Gy/h. At 10 years, reduced incidence of local recurrence was seen in the boost arm as compared to the no boost arm (6.2% versus 10.2%; $p < 0.0001$). However, an extra irradiation of 16 Gy to the tumour bed also increased the rates of moderate to severe breast fibrosis by 15% at ten years (28.1% versus 13.2%; $p < 0.0001$). In this trial, 251 patients with microscopically incomplete tumour excision were also randomised to either a low dose boost of 10 Gy (126 patients) or a high dose boost of 26 Gy (125 patients) [9]. The cumulative incidence of moderate/severe fibrosis for low dose and high dose boost at ten years was 24% and 54%, respectively. Hence a dose escalation of 16 Gy to the boost volume in the incomplete tumour excision group increased the rates of moderate/severe fibrosis by 30%, compared with a 15% increase in the complete excision group for the same 16 Gy increase in dose.

On review of the treatment protocol, the boost volume for complete excision group was tumour bed plus 1.5 cm margin as compared to tumour bed plus 3 cm margin in the incomplete tumour excision group. It demonstrates that an increase in irradiated breast volume in the incomplete excision group doubled the risk of moderate/severe fibrosis for the same dose escalation of 16 Gy, supporting a dose–volume relationship for breast tissue. Furthermore, Collette et al. [10] reported on factors predicting the risk of breast fibrosis at ten years. The boost volume was associated with an increased risk of moderate or severe fibrosis in univariate analysis. Vrieling et al. [11] from the same group had previously reported worse cosmetic outcome in patients with boost volume >200 cm^3 as compared to $\leqslant$200 cm^3 (odds ratio 0.47 95%CI 0.29–0.76; $p = 0.002$) in univariate analysis after three years of follow up. However, boost volume was not a significant variable affecting fibrosis and cosmesis in multivariate analysis.

Brachytherapy boost (level IV evidence)

Borger et al. [12] reported on the dose and volume effect on breast fibrosis after using brachytherapy boost. Four hundred and four patients were treated with external bream radiotherapy, 50 Gy in 2 Gy daily fractions to the whole breast, followed by an iridium implant boost (dose rate 0.57 ± 0.11 Gy/h) of 15 Gy (101 patients), 25 Gy (301 patients) and 20 Gy (2 patients). At a median follow up of 70 months, a fourfold higher risk of fibrosis was observed for each 100 cm^3 increase in irradiated boost volume, and a tenfold higher risk of fibrosis was observed when the total dose exceeded 79 Gy compared to doses below 70 Gy.

McRae and colleagues from Georgetown University Medical Centre reported on the relationship between brachytherapy boost volume and soft tissue complication in 1987 [13]. Retrospective brachytherapy plans for 5 patients with radiation induced soft tissue damage were compared to 51 patients who experienced no severe complication after breast conserving surgery (BCS) and WBI followed by Iridium-192 boost. The mean boost volume for patients who developed soft tissue damage was significantly higher for all dose levels between 10 Gy and 50 Gy when compared to patients with no reported complications ($p < 0.05$), suggesting a volume–NTC relationship at any specific dose.

Olivotto et al. [14] also reported an association between the volume of brachytherapy boost and late cosmetic outcome. Five hundred and ninety-three patients received breast-conserving surgery followed by WBI (46–50 Gy over 4.5–5 weeks). Four hundred and ninety-seven patients received low dose rate Iridium-192 implant boost to bring the tumour bed dose to 60 Gy. At a median follow up of 76 months, the volume of boost, measured by the number of Iridium seeds used, was a significant factor for fair/poor cosmesis. Patients with <70 seeds had a 15% risk of fair/poor cosmesis compared to 38% for patients containing $\geqslant$100 seeds ($p < 0.01$). The use of greater number of seeds would imply a larger volume of irradiated breast tissue, indicating towards a radiation volume effect on cosmesis. Several other single and multi-centre studies have reported on the relationship between volume of brachytherapy boost and NTC risk and are summarised in Table 1.

Intra-operative RT (IORT) boost using low energy X-ray (level IV evidence)

IORT using low energy X-ray of 50 kV can be used to deliver a single fraction of high dose radiation boost to the tumour bed after lumpectomy. Advocates for IORT cite several potential advantages of using this approach: delivery of radiation immediately after surgery prevents tumour cell proliferation; change in cytokines pattern into a less stimulating microenvironment, which is postulated to decrease local recurrence rates; and reduced risk of geographical miss [15,16].

The University of Heidelberg, Germany reported on the late toxicity data (at 3 years) for 79 cases treated with this approach [17]. All patients received 20 Gy intra-operative boost using 50 kv X-ray followed by 46–50 Gy in 2 Gy daily fraction of WBI ± supra/infraclavicular fossa irradiation. Thirty-five percent patients developed grade 2–3 breast fibrosis. They observed the applicator size for IORT significantly correlated with late breast fibrosis (spearman rank correlation coefficient 0.496, $p < 0.001$). A larger applicator size would imply a larger volume of irradiated breast tissue suggesting a radiation volume effect on late normal tissue toxicity.

Cobalt unit based boost (level IV evidence)

Dewar et al. [18] reported on the Institute Gustave-Roussy experience for cosmetic outcome after breast-conserving surgery and radiotherapy. Five hundred and ninety-two patients received WBI (45 Gy in 2.5 Gy per fraction, four times weekly) using two tangential fields, each field treated on alternate days followed by tumour bed boost of 15 Gy in 6 fractions using one-two fields on the cobalt unit. In addition to applied dose per fraction, the area of field to the tumour bed (>30 cm^3) was associated with an increased risk of fibrosis ($p < 0.02$) and telangiectasia ($p < 0.01$) in multivariate analysis.

Other studies (level IV evidence)

The Fox Chase Cancer Center, Philadelphia recently reported on tumour bed boost parameters associated with overall cosmesis and fibrosis for 3186 patients treated at their centre from 1970–2008 [19]. All patients received whole breast irradiation (46–50 Gy) followed by a tumour bed boost of 10–18 Gy using electrons or photons. With a median follow up of 78 months, smaller boost cut-out size was a borderline predictor of excellent cosmesis ($p = 0.05$) and lower risk of breast fibrosis ($p < 0.0001$) on univariate analysis.

Table 1
Effect of brachytherapy boost volume to NTC.

First author, Institute and radiation technique	Number of patients (median follow up)	TNM/ stage	Comments on NTC assessment	Results
Borger et. al. [12] Netherlands Cancer Institute WBI 50 Gy in 25 fractions over 5 weeks followed by low dose rate Iridium implant boost of 15 Gy (101 pts), 25 Gy (301 pts) and 20 Gy (2 pts)	404 patients median follow up 70 months (range 30–133 months)	Stage 1–2	Four trained physicians scored fibrosis by palpating induration in the tumour bed. Four-scale scoring system: no fibrosis = no difference in consistency between the two breasts, grade 1 = a small difference, grade 2 = a moderate difference, grade 3 = a large difference. The scores of the four investigators were averaged to obtain the final result per patient	Implant volume (100% dose) associated with risk of fibrosis Odds ratio 4.2 (95% CI 2.3–8.0) per 100 cm^3 increase in boost volume
McRae et al. [13] Georgetown University Medical Centre, Washington WBI 50 Gy in 25 fractions over 5 weeks using Cobalt followed by low dose rate Iridium 192 boost of 20 Gy	56 patients with a minimum follow up of 2.5 years	Stage 1–3	Radiation injury to connective tissue or fat necrosis requiring prolonged medical or surgical management	Mean boost volume significantly higher for all dose level between 10 Gy and 50 Gy for patients who developed soft tissue damage as compare to patients with no reported complications ($p < 0.05$)
Dewar et. al. [18] Institut Gustave-Roussy, France WBI 45 Gy in 2.5 Gy per fraction using two tangential fields followed by tumour bed boost of 15 Gy in 6 fractions using one to two fields on the cobalt unit	592 patients mean follow up 78 months (standard deviation 35 months)	T1-2 N0-1	Fibrosis and/or telangiectasia of the whole breast/the tumour bed graded as absent, slight, moderate or severe by the radiation oncologist. Cosmetic outcome graded as excellent, good, fair and poor	Area of field to the tumour bed (>30 cm^3) associated with increased risk of fibrosis ($p < 0.02$) and telangiectasia ($p < 0.01$) on multivariate analysis. No relationship between cosmesis and area of field to the tumour bed
Olivotto et al. [14] Joint Center for Radiation Therapy, Boston WBI 46–50 Gy in 4.5–5 weeks, followed by low dose rate Iridium-192 boost (10–27 Gy)	497/593 with Iridium-192 boost Median follow up 76 months (range 37–186 months)	T1-2 N0-1	Overall cosmesis scored as excellent, good, fair or poor by the physician. Excellent if treated breast looked the same as the opposite breast, good if minimal but identifiable effects of radiation, fair when significant effects of radiation and a poor if severe normal tissue sequelae	Boost volume measured by number of Iridium-192 seeds associated with increased risk of fair/poor cosmesis ($p < 0.0001$ for trend)
Clarke et. al. [57] Paul A. Bissinger Memorial Center for Radiation Therapy, Stanford WBI 45–55 Gy in 1.8–2.5 Gy per fraction followed by low dose rate Iridium-192 boost (18–25 Gy)	64/78 patients with Iridium 192 boost Median follow up 42 months (range 30–120 months)	Stage 1–2	Cosmetic result scored as excellent (treated breast looked the same as the opposite breast), satisfactory (mild to moderate breast asymmetry with <l/3 volume loss secondary to surgery or retraction from fibrosis) or unsatisfactory (marked breast asymmetry or severe fibrosis with >1/3 volume loss). Breast fibrosis scored as mild, moderate or severe.	6% patients developed moderate/severe fibrosis with no correlation between fibrosis and implanted boost volume. Surgical factors like poorly planned excision scar and large volume excision main factors for unsatisfactory cosmesis.
Wazer et. al. [58] Tufts University School of Medicine, Boston WBI 50 to 50.4 Gy at 1.8–2 Gy per fraction followed by low dose rate Iridium-192 boost of 20 Gy	127 patients Median follow up 80 months (standard deviation 34 months)	Stage 1–2	Cosmetic score scored by two separate examiners as excellent = perfect symmetry and no visible distortion, good = slight distortion, visible telangiectasia or absent nipple-areolar complex, fair = moderate distortion, hyper pigmentation, prominent skin retraction, oedema or telangiectasia and poor = marked distortion, oedema, fibrosis, severe hyper-pigmentation. The lowest score was used	No correlation between implant volume and cosmetic score.
Wronczewska et. al. [68] Nicolaus Copernicus University, Poland WBI 50–50.4 Gy in 1–8-2 Gy fraction followed by high dose rate Iridium-192 boost of 5–20 Gy	54 patients Mean follow up 65 months (range 41–89 months)		Cosmesis and breast fibrosis assessed by two doctors independently and compared to the contralateral breast	Boost volume receiving 100% (V100) was significantly associated with risk of breast fibrosis ($p = 0.0236$)

However, neither fibrosis nor worse cosmesis remained significantly associated with higher field size on multivariate analysis.

Partial Breast Irradiation (PBI)

Randomised controlled trials of Partial Breast Irradiation (PBI) versus whole breast irradiation (WBI) (level I evidence)

WBI is the current standard of care after breast-conserving surgery and the latest Early Breast Cancer Trialist Collaborative Group (EBCTG) systematic review confirmed an absolute 5% reduction in 15 year breast cancer mortality using WBI [20]. In the last decade, PBI has been explored as an alternative to WBI in low risk patients. PBI involves irradiation of a limited volume of breast tissue around the tumour bed and is currently under investigation in several randomised phase II and III trials (Table 2). It is based on the rationale that the majority of local recurrences are located close to the area of surgical resection/index quadrant, foci of breast disease outside the index quadrant are often new primary tumours [21,22] and irradiating a limited volume of breast would reduce treatment related morbidity. To date, four randomised controlled trials (RCT) comparing WBI versus PBI have reported on their outcome.

The Christie group were the first to report in 1993 [23]. They randomised 708 patients with breast cancer $\leqslant$4 cm in diameter to PBI or WBI plus regional lymph nodes irradiation. PBI involved tumour bed irradiation (average field size 8 cm $\times$ 6 cm) to 40–42.5 Gy in 8 fractions over 10 days using electrons and WBI

Table 2
Phase II–III randomised controlled trials comparing WBI versus PBI.

Trial/institute	Control arm (WBI)	Test arms (PBI): treatment modality	Median follow up (months)	Target accrual	Reported
Christie group trial [23]	WBI 40 Gy in 15 fractions with matched field for regional nodes	PBI: 40–42.5 Gy in 8 fractions using electrons	65 months	708	Yes
Yorkshire Breast Cancer Group trial [24]	WBI 40 Gy in 15 fractions with 15 Gy boost	PBI using direct cobalt, caesium or electrons beam or a small mega-voltage tangential pair to a dose of 55 Gy in 20 fractions	96 months	174 (pre-mature closure)	Yes
Hungarian National Institute of Oncology [25]	WBI using Cobalt or photons beam to a dose of 50 Gy in 25 fractions over 5 weeks	HDR Iridium-192 (85 pts) to a dose of 36.4 Gy in 7 fractions over 4 days or Electrons (40 pts) to a dose of 50 Gy in 25 fractions prescribed to the 80% isodose	66	258	Yes
TARGIT [26]	WBI 40–56 Gy with optional boost of 10–16 Gy	PBI: 20 Gy single fraction using Intra-operative 50 kV photons	24 months	2232	Yes
ELIOT [69]	WBI 50 Gy in 25 fractions with 10 Gy boost	PBI: Intra-operative electrons 21 Gy in single fraction	NA	1300 (closed 2007)	No
IMPORT LOW [49,50]	WBI 40 Gy in 15 fractions, no boost	Arm 1: 36 Gy in 15 fractions to the low risk volume of the breast and 40 Gy in 15 fractions to the index quadrantArm2 (PBI): 40 Gy in 15 fractions over 3 weeks to the index quadrant only	NA	2000 (closed 2010)	No
GEC-ESTRO [70]	WBI 50–50.4 Gy in 25–28 fractions with 10 Gy optional boost	PBI: 32 Gy in 8 fractions or 30.3 Gy in 7 fractions HDR or 50 Gy PDR	NA	1170 (activated 2004)	No
NSABP-39 [71]	WBI 50–50.4 Gy in 25–28 fractions with 10–16 Gy optional boost	PBI: 34 Gy in 10 fractions over five days using single/multi-source brachytherapy or 38.5 Gy in 10 fractions over 5 days using 3D-CRT	NA	4300 (activated 2005)	No
RAPID [72]	WBI 42.5 Gy in 16 fractions with optional 10 Gy boost	PBI: 38.5 Gy in 10 fractions BD over 5–8 days using 3D-CRT	NA	2128 (activated 2006)	No
IRMA [73]	WBI 45 Gy in 18 fractions or 50 Gy in 25 fractions or 50.4 Gy in 28 fractions with optional 10 – 16 Gy boost	PBI: 38.5 Gy in 10 fractions BD over 5 days using 3D-CRT	NA	3302 (activated 2007)	No
Danish Breast Cancer Co-operative Group [51]	WBI 40 Gy in 15 fraction	PBI: 40 Gy in 15 fraction using 3D-CRT	NA	628 (activated 2009)	No
SHARE [74]	WBI 50 Gy in 25 fractions + 16 Gy boost or WBI 40–42.5 Gy in 15–16 fractions without boost	PBI: 40 Gy in 10 fractions BD over 5 to 7 days using 3D-CRT	NA	2796 (activated 2010)	No

WBI: whole breast irradiation; PBI: Partial Breast Irradiation; HDR: high dose rate; PDR: pulsed dose rate; LDR: low dose rate; 3D-CRT: 3-dimensional conformal radiotherapy; NA: not applicable.

involved treating the whole breast to 40 Gy in 15 fractions over 21 days using a tangential pair with matched field for regional nodes. After a median follow up of 65 months, recurrence rates were higher in the PBI arm as compare to WBI arm (19.6% versus 11%; $p = 0.0008$). The possible reasons for higher recurrence rates in the PBI arm were difficulty in defining the target volume, leading to geographical miss and including patients with infiltrating lobular carcinoma and ductal carcinoma with an extensive intra-ductal component. Patients with PBI also had significantly higher rates of marked breast fibrosis (14% versus 5%) and telangiectasia (33% versus 12%) when compared to WBI.

The Yorkshire Breast Cancer Group randomised 174 patients between WBI (40 Gy in 15 fractions over 21 days) followed by tumour bed boost (15 Gy in 5 fractions) and PBI using a variety of techniques, including a direct cobalt or caesium beams, electrons or a small mega-voltage tangential pair to a dose of 55 Gy in 20 fractions over 28 days [24]. The trial closed prematurely due to poor accrual with higher loco-regional recurrence rates in the PBI group as compared to the WBI group (24% versus 9%). It has been suggested that higher recurrence in the PBI arm was secondary to difficulty in accurate definition of the target volume (tumour bed). Treatment related morbidity with PBI and WBI has not been reported. Both these trials pioneered the concept of PBI at a time when patient selection and tumour bed localisation was at an early stage of development. Subsequent randomised trials have used more stringent protocols for both of these factors.

The Hungarian National Institute of Oncology PBI trial [25] and TARGIT trial [26] have more recently reported their outcomes. The Hungarian PBI trial randomised 258 patients with T1 N0-1 grade $\leqslant 2$ breast cancer to WBI or PBI after breast-conserving surgery [25]. WBI was delivered using Cobalt or photon beams to a dose of 50 Gy in 2 Gy daily fractions and PBI was delivered using high dose rate (HDR) Iridium-192 brachytherapy (85 pts) to a dose of 36.4 Gy in 5.2 Gy per fraction over 4 days or electrons (40 pts) to a dose of 50 Gy in 2 Gy daily fractions prescribed to the 80% isodose. At a median follow up of 66 months (range 18–101 months), the local recurrence rates were not significantly different in the two trial arms. The cosmetic results using Harvard criteria [27] were favourable in the PBI arm. The rate of excellent to good cosmesis was 77.6% for the PBI group and 62.9% for the WBI group ($p = 0.009$).

The TARGIT-A trial randomised 2232 patients with early breast cancer to WBI (40–56 Gy) ± a boost of 10–16 Gy and intra-operative PBI using low energy X-rays (50 kV) to a dose of 20 Gy to the tumour bed attenuating to 5–7 Gy at 1 cm depth [26]. Patients with adverse histological features including invasive lobular carcinoma or an extensive intra-ductal component also received WBI without boost in the PBI arm. At two years, the local recurrence rate was similar with no significant difference in the rate of toxicity, but the type of toxicity was significantly different in both arms. WBI arm had higher RTOG grade 3–4 toxicity for dermatitis, telangiectasia or breast pain (2.1% versus 0.5%; $p = 0.002$). In contrast,

patients receiving intra-operative PBI experienced a different spectrum of side effects. Breast seroma needing more than three aspirations was more common in the intra-operative PBI group (2.1% versus 0.8%; $p = 0.012$) and more patients reported skin breakdown or delayed healing, required surgical evacuation of haematoma and intravenous antibiotics or surgical intervention for infection. The cosmetic results have not been reported.

Case-matched pair studies (level III evidence)

Four case match pair studies have also compared normal tissue complications between partial and whole breast irradiation after BCS. Polgar et al. [28] prospectively selected 45 patients with T1N0-1 breast cancer treated with PBI using HDR Iridium-192 implants to a dose of 30.3–36.4 Gy in 7 fractions over 4 days and matched 80 patients (eligible for PBI) treated with WBI 50 Gy in 2 Gy daily fractions with or without a tumour bed boost of 10–16 Gy. At a median follow up of 7 years, the ipsilateral breast recurrence rates were not significantly different in the two groups. Excellent/good cosmesis using Harvard criteria [27] was seen in 84.4% patients in the PBI arm and 68.3% patients in the WBI arm ($p = 0.04$). However, a trend of increased incidence of RTOG grade 2–3 fibrosis was seen in the PBI group as compare to WBI group without boost (20% versus 5.8%; $p = 0.06$).

The William Beaumont group matched 174 patients treated with PBI (low dose rate Iodine-125 implant, 50 Gy over 96 h, dose rate of 0.52 Gy/h or HDR implant 32 Gy in 8 fractions, each separated by 6 h), with 174 patients treated with WBI with a median total dose of 60 Gy to the tumour bed [29]. With 36 months follow up, cosmetic outcome was more favourable in the PBI group as compared to the WBI group (excellent/good cosmesis 90% versus 83%; $p = 0.17$), although this was not statistically significant.

King et al. [30] matched 51 patients treated with PBI (low dose rate Iridium-192 implant 45 Gy over 4 days or HDR implant 32 Gy in 8 fractions over 4 days) with 94 patients treated with WBI to a mean dose of 59 Gy after breast-conserving surgery. A blinded panel of healthcare professionals scored cosmesis on a four-part scale (excellent, good, fair, poor) after reviewing photographic slides. At 20 months follow up, 75% patients in the PBI group and 84% patients with WBI had excellent/good cosmesis (p = not significant). Grade I and II treatment complications including skin erythema, desquamation, discoloration, hyperpigmentation, dimpling; breast pain, tenderness, shrinkage or fibrosis were significantly more common with WBI than PBI (80% versus 22%, $p = 0.001$). Grade III treatment complications requiring surgical intervention were not significantly different in the two groups (8% versus 5%, p = not significant).

Tata Memorial Hospital, India matched 27 patients treated with PBI using HDR brachytherapy 34 Gy in 10 fractions over 6–8 days with 67 patients treated with WBI (45 Gy in 25# over 5 weeks followed by a tumour bed boost using electrons 15 Gy in 6 fractions or interstitial HDR brachytherapy with a single 10 Gy fraction [31]. At a median follow up of 43 months, cosmetic outcome was superior in the PBI group as compare to the WBI group (excellent/good cosmesis 88.9% versus 56%; $p = 0.003$). No significant difference was seen in the rates of moderate/severe breast fibrosis.

Effect of treatment volume on NTC in PBI series

There are several publications reporting on the efficacy and low toxicity using PBI with only a few evaluating the impact of treatment volume on NTC. The current literature on the volume effect of PBI for 3D-CRT/IMRT, electrons and single/multi-source brachytherapy is summarised below.

3D-CRT/IMRT based PBI (level IV evidence)

Jagsi et al. [32] reported on the cosmetic outcome of 32 patients treated with PBI using IMRT at deep inspiration breath hold. All patients received 38.5 Gy twice daily fractionation over five consecutive days. At a median follow up of 2.5 years, 22% patients were scored as unacceptable cosmesis. Retrospective comparison between patients with acceptable and unacceptable cosmesis showed the mean proportion of breast volume receiving a minimum of 100% of the prescribed dose i.e. 38.5 Gy (V100) was lower in patients with acceptable cosmesis as compare to patients with unacceptable cosmesis (15.5% versus 23.0%; $p = 0.02$). The mean proportion of breast volume receiving a minimum of 50% of the prescribed dose i.e. 19.25 Gy (V50) was also smaller in the acceptable cosmesis group as compare to unacceptable cosmesis ($p = 0.02$).

Hepel et al. [33] also reported on a positive correlation between the volume of breast tissue treated with PBI and overall cosmesis. Sixty patients received PBI to a dose of 38.5 Gy twice daily fractionation over one week using 3D-CRT. At a median follow up of 15 months, 18% patients developed fair-poor cosmesis and 25% developed grade 2–4 subcutaneous fibrosis. In univariate analysis, the size of 3D-CRT target volume in proportion to the overall breast volume (PTV_Eval/WBV) correlated with fair/poor cosmesis ($p = 0.02$) and grade 2–4 subcutaneous fibrosis ($p = 0.10$). These two publications suggested an association between breast volume irradiated in PBI and normal tissue complications.

In contrast, Chen and colleagues from the William Beaumont group reported no association between overall cosmesis and PTV_Eval/WBV [34,35]. Ninety-four patients received PBI to a dose of 38.5 Gy twice daily fractionation over five consecutive days using 3D-CRT. Of the 56 patients with cosmesis assessment of $\geqslant$48 months, 11% patients had fair to poor cosmesis and 3% patients had grade 3 fibrosis with no association between cosmesis/subcutaneous toxicity and PTV_Eval volume.

Single source brachytherapy/multi-source brachytherapy (level IV evidence)

Multi-source brachytherapy has been used for PBI for many years with most publications focusing on local control rates and limited reporting of normal tissue toxicity. Some have reported on factors associated with normal tissue toxicity and have commented on a positive correlation between NTC and the implant volume. Yeo et al. [36] reported on the efficacy and safety of PBI using multi-source brachytherapy for 48 patients with a median follow up of 53 months. A dose of 34 Gy in 10 fractions over five days was delivered to the tumour bed plus a 1–2 cm margin. Fourteen percent patients developed grade 2 subcutaneous toxicity with V100 and V150 significantly higher in these patients ($p = 0.018$ and 0.034, respectively). No patient had poor cosmesis.

Wazer et al. [37] reported on the variables associated with late toxicity and long term cosmetic outcome after multi-source brachytherapy PBI using pooled data from Tufts University, Brown University and Virginia Commonwealth University. The data for 75 patients with a median follow up of 6 years were analysed. The number of dwell positions (i.e. total volume of implanted breast tissue) correlated with late cosmetic outcome ($p = 0.04$). Lawenda and colleagues reported no association between implant volume and overall cosmetic outcome for 48 patients treated with low dose rate brachytherapy at their centre from 1997–2001 [38]. The purpose of the study was to evaluate dose escalation in PBI and the total dose was escalated in three groups of 50 Gy, 55 Gy and 60 Gy and implant volume was divided into four groups. A non significant trend between dose escalation and fibrosis was seen but they also observed a decline in the incidence of breast fibrosis with increase in implant volume, a finding contrary to current published literature.

The Mammosite single source brachytherapy device (Hologic Inc., Medford MA, USA) has been used for PBI since approval by the FDA in 2002. Many groups have reported on its efficacy with

conflicting reports on the correlation between balloon volume and overall cosmesis/fibrosis [39–43]. The American Society of Breast Surgeons Mammosite Breast Brachytherapy registry trial is the biggest series published to date [44]. The series reported on factors associated with optimal cosmetic outcome and includes 1440 patients with a median follow up of 43 months. On multiple regression analysis, the balloon filling volume was not a significant variable affecting cosmesis ($p = 0.085$). Breast related wound infection and balloon to skin distance were found to be the most important variables affecting cosmesis.

Breast fractionation studies

The Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) trial [45] randomised 1410 patients with early breast cancer into three WBI regimens. The control arm consisted of 50 Gy in 25 fractions over 5 weeks. The two test arms were (1) 39 Gy in 13 fractions over 5 weeks and (2) 42.9 Gy in 13 fractions over 5 weeks, respectively. The equivalent dose in 2 Gy fractions (EQD2) using a α/β ratio of 3.1 Gy for palpable breast induration, are 46.7 Gy and 53.8 Gy for test arms 1 and 2, respectively. The risk of moderate to severe induration at 10 years between Arm 1 and 2 was 27% and 51%, respectively suggesting a 24% increased risk of induration with a dose escalation of 7 Gy to the whole breast (3.3% increase per Gy). Compared to this fractionation effect, an escalated dose to tumour bed alone i.e. boost of 15.5 Gy in 7 fractions (EQD_2 of 16 Gy) increased the risk of induration by 17% (1.05% increase per Gy). These data indicate a radiation volume-effect for breast tissue, as the effect of induration per Gy of radiation increases with breast volume irradiated.

Discussion

With the increasing use of CT planning, Partial Breast Irradiation techniques, simultaneous boost techniques and dose escalation studies, a better understanding of the dose–volume relationship for breast tissue is required. The current literature suggests that volumetric parameters affect NTC, although it is poorly quantified with some conflicting clinical results.

This overview faces several challenges. The late normal tissue toxicity post radiotherapy is influenced by several patient and treatment related factors (Table 3). These parameters were variable in the identified studies. A variety of treatment approaches have been used including photons, electrons, intra-operative techniques and brachytherapy. In addition, the reported studies have used different endpoints (fibrosis, cosmesis and telangiectasia) with several different scoring methods and a diverse period of follow up. These challenges make it difficult to draw firm conclusions on the qualitative and quantitative effect of dose–volume relationship for breast tissue. Some studies have also used bra size and chest wall separation as a surrogate for breast size. These methods though useful can have inherent inconsistency; pre-operative bra size may not reflect the true post-operative breast volume and chest wall separation only provide 2-dimensional information of the breast and may not necessarily represent volume of breast above or below the central axis. Breast volume in cm^3 or ml should be a preferred method for reporting breast size.

The study by Borger et al. [12] using low dose rate iridium implants provides the most robust quantitative data on the dose–volume relationship. Seven independent factors were associated with breast fibrosis: old age, long follow up, clinical tumour size, cobalt-60 beam irradiation, total dose, implant volume and chemotherapy. For every 100 cm^3 increase in irradiated boost volume, the risk of fibrosis increase four-fold and a two fold increase in boost volume will result in an 11% decrease in tolerance dose (NTD_{50}). It is however difficult to be certain as to how the low dose rate brachytherapy data can be extrapolated to HDR brachytherapy, electron and photon boost techniques. The RMH/GOC trial [45] which used electron boost provides indirect quantitative information on the dose–volume relationship for NTC. For every Gy increase in boost dose, the risk of moderate to severe breast induration increases by 1% as compared to 3% when the whole breast dose is increased by one Gy.

The EORTC boost trials [6,9] also provided quantitative information on the volumetric effect where increasing the tumour bed margin from 1.5 cm to 3 cm doubles the rates of moderate/severe fibrosis from 15% to 30%. However, it is possible that the increase in NTC is secondary to a combination of larger boost volume and a steeper dose–response curve as total dose increased up to 76 Gy in the incomplete excision group. The EORTC boost trial also reported boost volume as a predictor of moderate/severe fibrosis and worse cosmesis in univariate analysis but not in multivariate analysis. There are several possible explanations for this: (1) There is no true independent volumetric effect. (2) Other factors such as total surgical excision volume, post-operative complications, concomitant chemotherapy, quality of radiation and boost treatment were more dominant variables affecting NTC when compared to the boost volume. (3) Total boost volume was dependent on the boost technique, with the smallest boost volume for interstitial technique (60 cm^3), more than twice the volume with electron boost (144 cm^3) and nearly five times as large with photon boost (288 cm^3) [46]. The rate of fibrosis was similar despite a considerable smaller treatment volume using interstitial brachytherapy. It

Table 3
Patient and treatment factors associated with late normal tissue complications.

Patient factors	Surgical factors	Other radiotherapy factors	Chemotherapy factors
Increasing age [56,75]	Large excision volume [11,14,76]	Total dose [12,47,48,56]	Timing of chemotherapy: concomitant or sequential [56,77–79]
Smoking [53,75]	Post operative complications including haematoma, seroma or infection [10,11,53]	Radiotherapy quality and technique [10,56]	Type of chemotherapy [80,81]
Large breast size [53,56,57,82–84]	Axillary dissection [48,76]	Tumour bed Boost [6]	
Tumour location [11,48]		Boost dose [9]	
Genetic variation [47,85]		Boost technique: electron, photon or brachytherapy [19,86]	
		Nodal irradiation [48,79]	
		Dose inhomogeneity (double trouble) [87,88]	
		Hypofractionation and dose inhomogeneity (triple trouble) [88]	

is possible that the affect of heterogeneity of dose distribution (which may lead to increased fibrosis) is neutralised by a smaller treatment volume. A direct comparison of boost volume using different boost techniques is not practical.

Randomised controlled trials including the Hungarian PBI trial [25] and TARGIT trial [26] provides a strong qualitative indication on a volume–NTC relationship. They report superior cosmetic outcome and reduced NTC rate in the PBI arm when compared to the WBI. However, these are significant differences in the radiotherapy techniques and fractionation schedules between the two groups, making it difficult to draw conclusions on the radiation volume effect on breast tissue. The other reported randomised trial from Christie had reported a higher rate of breast fibrosis and telangiectasia in the WBI arm [23]. A dose–response relationship for late radiation effects including telangiectasia and breast fibrosis is well established [6,47,48] and these dissimilar results can possibly be explained by calculating the 2 Gy equivalent dose (EQD2) for the PBI and WBI groups using an α/β ratio of 3.1 [45] for fibrosis. The WBI group had received a lower dose of 45 Gy EQD2, compared to 63–70 Gy for the PBI group in the Christie trial.

The four matched case series [28–31] comparing PBI and WBI also showed favourable cosmesis and lower NTC risk with PBI except for higher grade 2–3 fibrosis in the Hungarian series [28]. It is possible that significant dose heterogeneity with the mean dose non uniformity ratio of 0.45 using Iridium-192 implants could explain the increased grade 2–3 fibrosis in the PBI arm in the Hungarian series. These case series are a retrospective analysis with a small number of patients and other factors known to influence NTC including breast volume, post-surgical cosmesis, boost radiation, chemotherapy and smoking are not considered. Also, similar to the randomised trials, they evaluated PBI and WBI using different radiotherapy techniques and fractionation.

IMPORT LOW trial and The Danish Breast Cancer Cooperative Group trial (not reported) are two of the few randomised trials comparing Partial Breast Irradiation (PBI) versus whole breast irradiation (WBI) with volume of breast irradiated as the solitary randomisation variable. IMPORT LOW is a randomised Phase 3 trial comparing WBI with two dose level of PBI delivered using IMRT in women with low risk breast cancer and has completed target accrual of 2000 patients in 2010 [49,50]. The control arm (WBI) delivers 40 Gy in 15 fractions over 3 weeks to the whole breast. Arm 1 delivers synchronous 40 Gy in 15 fractions to the partial breast PTV and 36 Gy in 15 fractions to the remainder of the whole breast. Arm 2 (PBI) delivers 40 Gy in 15 fractions to the partial breast PTV alone (Supplementary material-Fig. 1). The primary endpoint is local tumour control in the ipsilateral breast and the secondary endpoints include location of tumour relapse, contralateral primary tumours, regional and distant metastases, late adverse effects in normal tissues, quality of life (QOL) and economic evaluation.

The Danish Breast Cancer Cooperative Group trial is a Phase 2 study comparing PBI to WBI in low risk breast cancer patients with both treatment arms receiving 40 Gy in 15 fractions over 3 weeks [51]. The primary endpoint for this study is grade 2–3 breast fibrosis after radiotherapy and the secondary endpoints are other late morbidity, local recurrence and genetic risk profiling for development of late radiation morbidity. The results on these two trials regarding late normal tissue effects will not become available for several years, but will be able to give definitive data regarding the effects of irradiated breast volume on normal tissue effects.

The 3D-CRT/IMRT based PBI series [32–34] have conflicting reports on the relationship between the treated volume and NTC. These reports have been compared by Bentzen and colleague [52] which may explain these contradictory results. Post surgical defect and cosmesis are important variable influencing overall cosmesis [53] and the mean excision cavity volume was possibly smaller for William Beaumont group as compared to the other two series. Chen et. al. [34] optimised the IMRT plans with hot spots of <110% as compared to the other two series which accepted the hot spots of <120%. In addition, Jagsi et al. [32] used breath hold which may have reduced the spread of planned APBI beams seen with free breathing. Ultimately, mature data from the ongoing Phase 3 NSABP B-39/RTOG 0413 trial will answer if an association between breast volume irradiated in APBI and normal tissue complications is real.

Other studies evaluating the relationship between volume of breast irradiated and NTC are mainly single centre case series. A variety of treatment modalities have been used including brachytherapy, IORT using low energy X-ray, 3D-CRT/IMRT. Overall, most studies support a positive association between the boost/treatment volume and NTC risks. However, this association is confounded by other factors including extent of surgical excision, total delivered dose, dose fractionation, post-operative complications and brachytherapy dose inhomogeneity. Surgical excision volume and baseline surgical cosmesis are significant factors affecting cosmesis [11,54–56]. A larger surgical excision would also imply a larger brachytherapy boost volume and a larger applicator size for IORT. It is difficult to draw strong support on the independent volume effect on NTC based on the results of these case series.

A small number of studies in the literature have suggested no independent dose–volume relationship for breast tissue. The Fox Chase Cancer Center series [19] with more than 3000 patients showed no independent association between boost cut-out size and cosmesis/breast fibrosis. Only the bra cup size and electron energy were found as independent variables associated with fibrosis. This is however a retrospective series of patients treated over 38 years, with a variable boost dose of 10–18 Gy. There was no information on the actual treated boost volume and no distinction was made between physician and patient cosmetic score. Surgical and radiotherapy techniques have also improved over the last four decades, which may also affect overall cosmesis and breast fibrosis. The brachytherapy boost series with no volume–NTC correlation [57,58] had small number of patients with fewer NTC events. It is possible that surgical and other radio-therapeutic parameters variables were dominant in affecting NTC than a small difference in boost volume. Studies using mammosite have also consistently showed a lack of correlation between NTC and mammosite balloon volume. This could be secondary to a small absolute difference in irradiated breast volume with change in balloon fill and a relatively smaller target volume for mammosite brachytherapy as compare to 3D-CRT [59,60].

Future directions

More robust data are required to quantify the impact of volumetric parameter on breast NTC probability. The current PBI versus WBI trials database with mature follow up and prospectively collected dosimetric data will provide more qualitative and quantitative data which may help in creating NTC analytical function in the future. Meanwhile, efforts should be made to avoid unnecessary treatment of normal breast tissue by optimal localisation of tumour bed using implanted surgical markers and/or ultrasound [61,62] and using conformal radiotherapy techniques with simultaneously integrated boost [63]. The use of image guided radiotherapy (IGRT) with correction strategy can reduce irradiated breast tissue during PBI and boost treatment [64], and will need further investigation within clinical trials.

A better understanding of tissue dose–volume relationship can be clinically exploited in high risk patients. For example, dose escalation in prostate radiotherapy exploits the radiation dose–volume principle: a small volume of rectum can receive a higher dose with no increase in toxicity, by reducing the dose to rest of the rectal volume using IMRT [5]. The St. George and Wollongong trial from

Sydney suggests that this modulation effect is also present in breast tissue [65]. The trial randomised 688 patients with T1-2N0-1 breast cancer between standard arm of WBI with 50 Gy in 2 Gy daily fractions (no boost) and test arm of WBI of 45 Gy in 1.8 Gy daily fractions plus a 16 Gy tumour bed boost. The overall cosmesis was scored by a five person panel using digital photographs as excellent, good, fair and poor. 79% patients in the test arm with boost and 68% patients in the standard arm had excellent/good cosmesis ($p = 0.016$). The rate of moderate to severe breast fibrosis at five years was similar in both treatment arms. These results are contrary to the current literature of worse cosmetic outcome and higher rates of breast fibrosis with additional boost radiation. One possible explanation for these results is that a modest dose reduction to the whole breast allowed dose escalation to the tumour bed without the expected increase in normal tissue toxicity.

This dose modulating effect on the breast is further investigated in the IMPORT High trial [50,66] which is currently open to recruitment. The trial randomises high risk patients between three groups; standard arm: 40 Gy in 15 fractions to the whole breast over 3 weeks with a 16 Gy in 2 Gy daily fraction sequential tumour bed boost, Test arm 1: 36 Gy in 15 fraction to the low risk volume of the breast, 40 Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 48 Gy in 15 fractions and Test arm 3: 36 Gy in 15 fractions to the low risk volume of the breast, 40 Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 53 Gy in 15 fractions (Supplementary-Fig. 2). The trial tests the hypothesis that decreasing the radiation dose to the whole breast tissue by a very small amount (40 Gy to 36 Gy) and treating an iso-effective dose to the index quadrant and tumour bed (Arm 1), may result in less normal tissue side effects compared to the control group. It will also test if decreasing the radiation dose to the whole breast tissue by a very small amount allows dose escalation to the tumour bed (area of highest risk of local recurrence) without an increase in normal tissue side effects (Arm 2).

Conclusions

Adjuvant breast radiotherapy reduces local recurrence and improves overall survival but at a cost of increased normal tissue side effects. This can have a significant physical and psychological impact on patients [67]. Many factors influence NTC after breast RT including breast volume, post-surgical cosmesis, boost radiation, chemotherapy and smoking. In addition, the current literature seems to suggest that volumetric parameter is also important. More direct evidence will emerge from the IMPORT LOW, Danish Breast Cancer Co-operative Group trial and the dosimetric data collected prospectively from the various Accelerated PBI trials. There is emerging evidence to support the hypothesis that a modest dose reduction to part of the breast facilitate dose escalation to the tumour bed, and this concept will be tested further within a second larger randomised controlled trial.

Funding sources

Dr. Mukesh Mukesh and Dr. Emma Harris are funded by the Efficacy and Mechanism Evaluation programme, Medical Research Council, UK (Grant No.: 09/150/16).

Dr. Charlotte Coles is supported by the Cambridge National Institute of Health Research Biomedical Research Centre.

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This report is independent research commissioned by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Conflict of interest statement

None.

Acknowledgments

We would like to thank Professor John Yarnold for his helpful advice and comments.

Work at ICR/RMH was partially funded by research grant C46/A2131 from Cancer Research, UK. We also acknowledge NIHR funding to the NHS Biomedical Research Centre.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2012.04.025.

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