

Conservation surgery and radiation therapy in early breast cancer – An update

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Background

Multiple randomised trials and meta-analyses have supported the use of conservative surgery (CS) and radiation therapy (RT) for the treatment of early-stage breast cancer. Following lumpectomy, RT has been shown to decrease the chance of local recurrence and improve overall survival when compared with lumpectomy alone.

Objectives

This update outlines the rationale and outcomes for CS and RT, whether a subgroup exists in which RT may be safely omitted, the process of RT, common side effects and their management, and the latest techniques in the field.

Discussion

Breast conservation remains an effective treatment for breast cancer without a survival disadvantage to a mastectomy. The combination of advanced imaging and fast three-dimensional (3D) radiotherapy planning computer systems have allowed new techniques that deliver RT more accurately, with better tumour control, fewer side effects and improved survival.

Radiation therapy (RT) uses X-rays, discovered by Röntgen in 1895, to destroy cancer cells. Although breast conservation was first used in 1912 by inserting radium needles after surgical excision of the tumour, today, external beam radiation is produced using a linear accelerator. Conservation surgery (CS) removes macroscopic disease and a small margin of normal tissue. As residual microscopic disease is left behind in 40% of cases, often up to 4 cm from the primary site, RT is used to treat the remainder of the breast.¹ The combination of CS and RT results in better cosmesis, is less complicated and associated with more positive body image than mastectomy, while achieving equivalent local tumour control and survival rates.^{2,3} Over the past 20 years, attempts have been made to avoid RT altogether after a lumpectomy, often by adding hormonal treatment (HT) such as tamoxifen, particularly for older patients with small oestrogen-receptor (ER)-positive, node-negative tumours. No consistent subgroup where RT can be avoided has been found, but trials are ongoing (Table 1).

Conservation techniques vary by surgeon, patient's breast size, and location and size of the tumour. Various terms are used, including wide local excision (also called 'lumpectomy'), where the tumour is removed with a small surgical margin, or larger excisions such as quadrantectomy. A recent innovation for patients with larger breasts has been bilateral reduction mammoplasty. Here, excess fat, tissue and skin of both breasts are reduced to

a proportional size for the patient's body shape, and the breast shape is reconstructed by plastic surgery (Figures 1A, C).⁴⁻⁷ This approach reduces the amount of normal tissue that needs irradiation, and is associated with less retraction and better balance and symmetry after radiation. It is also less problematic than the marked imbalance from a unilateral mastectomy for patients with large breasts (Figure 1B).⁸

Studies of breast conservation

The landmark National Surgical Adjuvant Breast and Bowel Project (NSABP)-B06 study accelerated the uptake of CS and RT. Local recurrence rates at 20 years were almost 40% with lumpectomy alone versus 15% with CS and RT,⁹ and survival rates were equivalent to those after a mastectomy. Recent studies that evaluated omitting RT for older, lower risk patients found lower local recurrence rates, but patient subgroups that could avoid RT have not been identified (Table 1).¹⁰⁻²⁴ For example, the NSABP-B21 randomised 1009 women with tumours <1 cm to RT, tamoxifen or RT and tamoxifen. Recurrence rates at eight years were 16.5%, 9.3% and 2.8% respectively, indicating that tamoxifen resistance occurs, but the combination of RT and tamoxifen is very effective. Nevertheless, avoiding RT could be considered for highly selected, older, well-informed patients with small, good-prognosis ER-positive tumours, but this is not currently considered best practice. A recently launched Australian and

international randomised trial (EXamining PErsonalised Radiation Therapy for Low-risk Early Breast Cancer [EXPERT]) will address this question by comparing CS, RT and HT to CS and HT for women aged ≥50 years with small, low-grade breast cancer.²⁵

The radiation therapy process

An initial assessment by a radiation oncologist is useful pre-operatively, but

this mostly occurs following surgery. Following a decision to use RT, the option is explained in terms of the benefits and risks, duration, costs (mainly or totally covered by the Medicare Benefits Scheme [MBS]) and logistics. The decision to treat the breast alone, or some or all of the nodal regions, is also made. Following informed consent, a simulation session is performed with the patient in the treatment position, with measurements recorded by radiation

therapists. Here, the breast and scars are marked with wire markers to outline important information on the subsequent inbuilt computed tomography (CT) scan (Figure 2A). Small, black tattoo dots are placed beneath the patient's skin with a fine needle to accurately reproduce the patient's position on daily treatment.

The CT data are used to plan an individualised three-dimensional (3D) RT treatment that is appropriate for that

Table 1. Randomised trials of conservative surgery +/- radiation therapy +/- hormonal treatment

Author, publication date	Patients n	Age ≥50 years (%)	≤20 mm (%)	Node-positive (%)	HT (%)	CT (%)	Median follow-up (years)	Recurrence in ipsilateral breast (%)			
								No RT	RT	RT+HT	HT
Clark, 1996	837	68	71	0	0	0	7.6	35.2	11.3	-	-
Forrest, 1996	589	73	43	23	73	26	5.7	24.5	5.8	-	-
Liljegren, 1999	381	61	100	0	0	0	8.8	24.0	8.5	-	-
Holli, 2001	152	73	100	0	0	0	6.7	18.1	7.5	-	-
Veronesi, 2001	579	56	84	31	12	17	9.1	23.5	5.8	-	-
Fisher, 2002	2163	60	55	40	Nil	40	20.7	39.2	14.3	-	-
Fisher, 2002	1000	80	98	0	67	0	7.2	16.5	4.8	2.8	16.5
Malmstrom, 2003	1187	81	91	0	7	2	5.1	14.0	4.0	-	-
Fyles, 2004	769	100	83	0	50	0	5.6	7.7	0.6	0.6	7.7
Hughes, 2004	636	100	100	0	50	0	12.6	4.4	0.6	0.6	4.4
Winzer, 2004	361	91	99	0	50	0	5.9	15.7	3.7	3.8	2.8
Ford, 2006	400	51	37	25	70	30.5	13.7	40.6	19.7	-	-
Potter, 2007	869	97	93	0	100	0	4.5	5.1	0.4	0.4	5.1
Blamey, 2013	1135	NS	100	0	50	0	13.9	10.2	3.9	3.9	10.2
Kunkler, 2015	1326	100	88	0	50	0	5	4.1	1.3	1.3	4.1

CT, chemotherapy; HT, hormonal therapy (usually tamoxifen); RT, radiation therapy

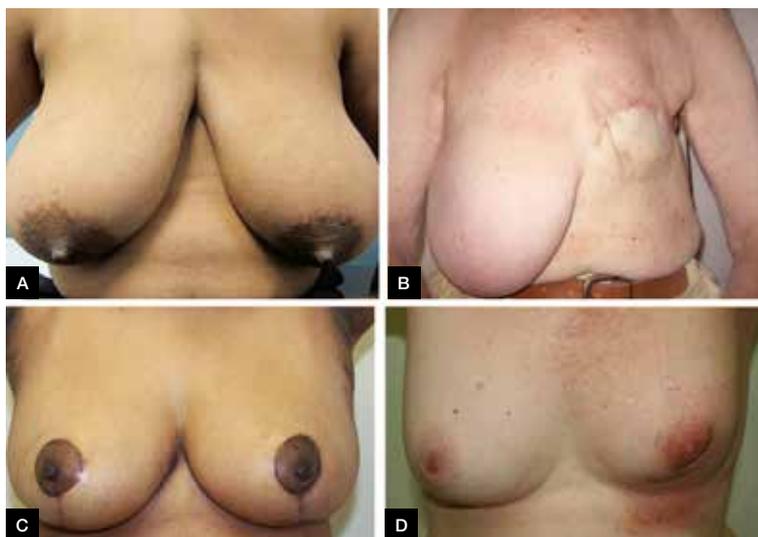


Figure 1. Breast surgical procedures

A. Original intact breasts of a patient with large breasts pre-operation; B. Woman with large breasts following a mastectomy; C. Patient from Figure 1A post-bilateral breast reduction mammoplasty; D. Skin erythema following five weeks of radiation therapy to the left breast and one week boost using electron beam

patient. Using 3D planning software, it is possible to plan a treatment that accurately delivers the prescribed dose and fractionation to the target tissue (outlined by the radiation oncologist using previous imaging, histology reports and clips placed at surgery), while minimising the dose to the surrounding healthy tissue, including the heart, lungs and contralateral breast (Figure 2B).

Following approval of the radiation plan by the radiation oncologist, the data are linked to treatment software of the treatment machine (linear accelerator). It is then ready for the patient to start therapy, usually daily for nine or 10 times per fortnight (Figure 2C). In the head of the gantry are multi-leaf collimators (MLCs), which shield out the radiation to manipulate the dose to deliver the plan. MLCs are tiny rectangular pieces of tungsten, which move per the computer-generated plan to influence the dose distribution, like a camera aperture. Traditionally, a course of RT to the whole breast would be a dose of 50 Gy in 2 Gy fractions (attendances), usually followed by a 10–16 Gy boost dose to the tumour bed, the most common place for a breast cancer recurrence. A boost dose is often delivered via an electron beam (Figure 1D) for superficial tumours, or a photon beam. Current practice variation in Australia has been reported elsewhere.²⁶

The European Organisation for Research and Treatment of Cancer (EORTC) in 2016 examined 5569 women with early-stage breast cancer who were treated with CS and RT with or without a boost. Their results showed that the boost reduced the 20-year local recurrence from 17% to 12% ($P < 0.001$) for all patients. For patients with hormone receptor-negative, high-grade tumours, the boost reduced the breast recurrence rate from 31% to 5% ($P = 0.01$).

Patients are usually reviewed weekly during treatment to assess progress by the radiation therapists, radiation oncologist and/or nurses. Common side effects are listed in Table 2⁴⁻⁷ and Figure 1D. At the completion of the radiation course, a follow-up consultation by the radiation oncologist or other member of the multidisciplinary

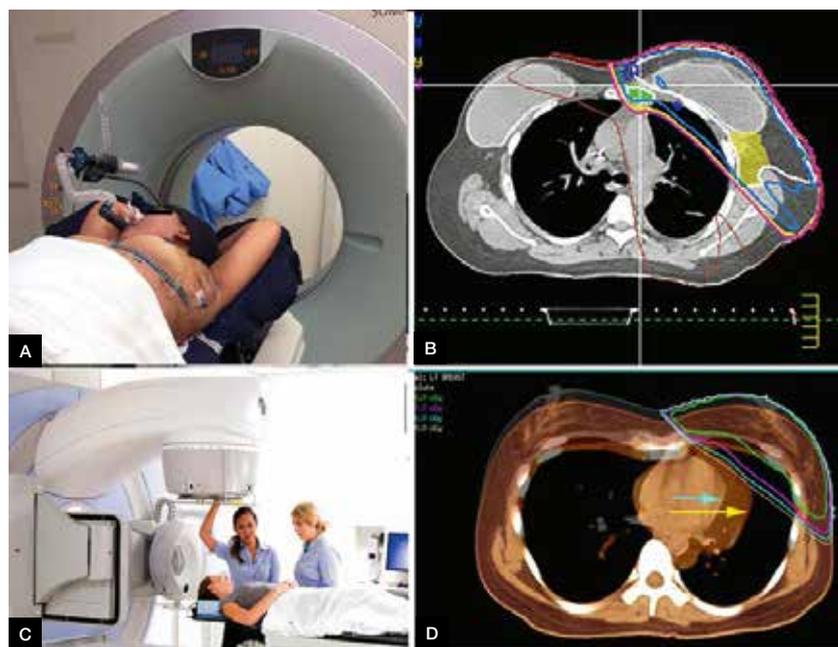


Figure 2. The radiation therapy process

A. Photograph of deep inspiration breath hold (DIBH) setup with mouthpiece; B. Axial slice from planning computed tomography (CT) of implant and radiation dose lines conforming to the target IMC and breast tissue indicated in purple; C. Elekta Synergy – Linear accelerator used in external beam radiotherapy treatment; D. Axial slice from planning CT in Pinnacle planning software for DIBH. The orange scan represents the heart position during free-breathing (yellow arrow) and the black-white underlay shows the heart's position in breath-hold full inspiration (aqua arrow)

team will usually take place six to eight weeks post-treatment to assess physical and psychological health.

New radiation techniques

New techniques in RT make it possible to maximise clinical benefit and minimise toxicity. With 3D planning software, heart and lung doses can be significantly reduced, minimising cardiac and lung toxicity. Deep inspiration breath-hold (DIBH) is a new technique predominantly used in the treatment of left-sided breast cancers. One example of this system uses the Elekta Active Breathing Coordinator (ABC) solution, whereby using a snorkel-shaped mouthpiece and gating system, the patient can be treated only when in full inspiration, which pushes the heart

posteriorly and inferiorly away from the chest wall²⁷ (Figure 2A, B, D). This results in lower heart and coronary artery dose, with less heart toxicity, and assists with daily reproducibility by eliminating the movement of free breathing.²⁸

Accelerated partial breast irradiation (APBI) is a localised form of radiation given over one or two weeks. One technique is brachytherapy, where radioactive sources are inserted in the tumour bed following a lumpectomy. An alternative technique is a single electron beam dose given to the cavity in the operating theatre.²⁹ Another involves a short course of five large treatments of 6 Gy over a two-week period using 3D conformal radiation or modulated techniques.³⁰ There is debate as to which patients would benefit from

this form of radiation therapy as it is known that recurrences can develop outside the primary tumour site.²¹ Clinical guidelines for the use of this technique outside clinical trials were updated in 2016.³¹

Shorter courses of RT, known as hypofractionation, have been studied because of the cost and inconvenience of five to six weeks of treatment. Hypofractionation involves the delivery of higher daily doses of radiation in a smaller number of fractions, with a lower overall dose that is biologically equivalent to a standard dose. A common regimen, proven to have comparable outcomes, is 40.05–42.5 Gy in 15–16 fractions over about three weeks.^{30,32,33} A recent Australia-wide campaign (Choosing Wisely Australia) by The Royal Australian and New Zealand

Table 2. Potential side effects of radiation that are not uncommon^{4–7}

Timing	Symptoms	Incidence	Signs	Treatment
Acute	Skin redness/itch	>50%	Erythema	<ul style="list-style-type: none"> • Vitamin E, sorbolene, aloe vera, MooGoo • Consider hydrocortisone 1% for itchy areas • Avoid wearing tight clothing (eg bras and collars) • Wash the skin gently with warm water and a mild, unscented soap; rinse well and pat dry gently • Avoid using aluminium-based deodorants • Avoid wet shaving within the treatment field • For moist desquamation (usually week four or five) use Solugel or Paw Paw cream. Sometimes silver sulfadiazine is recommended following treatment
		6–10%	Dry desquamation	
			Moist desquamation	
	Swelling of breast	12.6%	Breast oedema	<ul style="list-style-type: none"> • Keep moisturised. If acute redness occurs after post-radiation erythema has resolved, this is usually cellulitis that requires antibiotics
	Sore throat	–	Nil specific	<ul style="list-style-type: none"> • May occur in weeks three to four if radiation is given to the supraclavicular fossa. Paracetamol syrup • Eat soft foods and avoid hot and spicy foods
Sub-acute	Pain in breast	10–50%	Mild shrinkage	<ul style="list-style-type: none"> • Rub moisturising cream (eg sorbolene, vitamin E) into site • Can be scar-related pain or costochondritis • Check vitamin D levels
	Dry cough, fatigue, shortness of breath six weeks to six months after treatment	1–2%	Nil specific	
	Transient swelling following exercise or physical activity	Mild: 6–10%	Lymphoedema	
	Pain, heaviness in the affected limb	Severe: 1–5%		<ul style="list-style-type: none"> • Weight management • Encourage early detection using bioimpedance devices such as L-Dex • Consider referral to appropriately qualified lymphoedema practitioner (www.lymphoedema.org.au)

College of Radiologists (RANZCR) advised 'Don't initiate whole-breast radiation therapy as a part of breast conservation therapy in women aged ≥ 50 years with early-stage invasive breast cancer without considering shorter treatment schedules'.³⁴

Intensity-modulated radiation therapy (IMRT) is a form of external beam radiation therapy whereby the head of the linear accelerator (gantry) can modulate the dose of radiation being delivered while the beam is on. This is made possible by using MLCs in the head of the gantry, which allows segmental blocking capabilities to modulate the shape of the beam.

It is also possible for the gantry to move simultaneously with the MLCs to provide even greater flexibility in treatment delivery and dose rate. This is known as volumetric-modulated arc therapy (VMAT). The plan is displayed using isodose lines, which define areas receiving the same radiation dose. Areas of low, prescribed and high dose can be visualised similarly to isobars on a weather map. Figure 2D shows the isodose lines on the axial views of a VMAT DIBH plan. This technique requires the use of inverse planning systems, whereby objectives or goals required for the plan are prioritised so that a computer algorithm can create the plan that best fulfils them.

These new technologies can reduce the dose to surrounding healthy organs, and produce highly conforming dose distributions and homogeneity around the target area; more normal tissue receives a low dose of radiation. It should also be noted that this may decrease rates of dermatitis, acute moist desquamation (red, exposed dermis and serous oozing), breast oedema and breast fibrosis.³⁵

Conclusion

The CS and RT combination is an effective treatment method for early breast cancer and has been recommended in consensus guidelines for more than 20 years.³⁶ This combination approach has been shown to be equivalent in survival and recurrence rates to mastectomy, minimising the need for extensive surgery. New technologies in RT have made it possible to further

individualise treatment plans, reduce normal tissue toxicity with the aim of further reducing local recurrence rates, and improve survival. Ongoing studies are exploring which patients could avoid RT after CS.

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References

- Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of T1–2 breast carcinomas implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56(5):979–90.
- Darby S, McGale P, Correa C, 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(9804):1707–16.
- McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383(9935):2127–35.
- Berkey FJ. Managing the adverse effects of radiation therapy. *Am Fam Physician* 2010;82(4):381–88, 94.
- Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. *New Engl J Med* 2001;344(26):1997–2008.
- Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long-term results of a randomised trial. *Radiother Oncol* 2005;75(1):9–17.
- NSW Cl. eviQ Cancer Treatments Online 2016 [Side effects of Breast Radiotherapy]. Everleigh, NSW: Cancer Institute NSW, 2016. Available at www.eviq.org.au [Accessed 27 August 2016].
- Piper ML, Esserman LJ, Sbitany H, Peled AV. Outcomes following oncoplastic reduction mammoplasty: A systematic review. *Ann Plast Surg* 2016;76 Suppl 3:S222–26.

- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *New Engl J Med* 2002;347(16):1233–41.
- Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: Can radiotherapy ever be safely withheld? *Radiother Oncol* 2009;90(1):14–22.
- Blamey RW, Bates T, Chetty U, et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer* 2013;49(10):2294–302.
- Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: An update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 1996;88(22):1659–64.
- Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 2002;20(20):4141–49.
- Ford H, Coombes R, Gazet J-C, et al. Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. *Ann Oncol* 2006;17(3):401–08.
- Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996;348(9029):708–13.
- Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *New Engl J Med* 2004;351(10):963–70.
- Holli K, Saaristo R, Isola J, Joensuu H, Hakama M. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: Results of a randomized study. *Br J Cancer* 2001;84(2):164–69.
- Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31(19):2382–87.
- Liljegren G, Holmberg L, Bergh J, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: A randomized trial. *J Clin Oncol* 1999;17(8):2326–33.
- Malmstrom P, Holmberg L, Anderson H, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: A randomised clinical trial in a population with access to public mammography screening. *Eur J Cancer* 2003;39(12):1690–67.
- Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of a randomized trial. *Ann Oncol* 2001;12(7):997–1003.
- Winzer K-J, Sauer R, Sauerbrei W, et al. Radiation therapy after breast-conserving surgery: First results of a randomised clinical trial in patients with low risk of recurrence. *Eur J Cancer* 2004;40(7):998–1005.
- Potter R, Gnant M, Kwasny W, et al. Lumpectomy plus tamoxifen or anastrozole with or without

- whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007;68(2):334–40.
24. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. 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(3):266–73.
 25. Group AaNZBCT. EXamining PErsonalised Radiation Therapy for Low-risk Early Breast Cancer (EXPERT) 2016 [A randomised trial evaluating radiation therapy versus observation following breast conserving surgery and planned endocrine therapy]. Bethesda, MD: US National Library of Medicine, 2016. Available at <https://clinicaltrials.gov/ct2/show/NCT02889874> [Accessed: 30 December 2016].
 26. Dundas KL, Pogson EM, Batumalai V, et al. Australian survey on current practices for breast radiotherapy. *J Med Imaging Radiat Oncol* 2015;59(6):736–42.
 27. Hayden AJ, Rains M, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. *J Med Imaging Radiat Oncol* 2012;56(4):464–72.
 28. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New Engl J Med* 2013;368(11):987–98.
 29. Holmes DR, Baum M, Joseph D. The TARGIT trial: Targeted intraoperative radiation therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update). *Am J Surg* 2007;194(4):507–10.
 30. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *New Engl J Med* 2010;362(6):513–20.
 31. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol* 2016; pii: S1879-8500(16)30184-9. [Epub ahead of print].
 32. Curry HA, Jaggi R. Utilization of Hypofractionation in an Insured Population. *Int J Radiat Oncol Biol Phys* 87(2):S500–01.
 33. Haviland JS, Owen JR, Dewar JA, 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(11):1086–94.
 34. The Royal Australian and New Zealand College of Radiologists. The Royal Australian and New Zealand College of Radiologists: Tests, treatments and procedures clinicians and consumers should question. A recent Australia-wide campaign (Choosing Wisely Australia) through the Royal Australian and New Zealand College of Radiologists on the use of radiation therapy in breast cancer. Surry Hills, NSW: NPS Medicinewise, 2016. Available at www.choosingwisely.org.au/recommendations/ranzcr [Accessed 30 December 2016].
 35. Hamilton DG, Bale R, Jones C, et al. Impact of tumour bed boost integration on acute and late toxicity in patients with breast cancer: A systematic review. *Breast* 2016;27:126–35.
 36. Gradishar W, Anderson B, Balassanian R. NCCN clinical practice guidelines in oncology: Breast cancer. Version 2, 2015. Fort Washington, PA: NCCN, 2015. Available at www.nccn.org/professionals/physician_gls/f_guidelines.asp [Accessed 17 January 2017].