Radiotherapy and Oncology 106 (2013) 15–20

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Accelerated fractionation with a concurrent boost for early stage breast cancer

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ARTICLE INFO

Article history:
Received 4 August 2012
Received in revised form 25 November 2012
Accepted 6 December 2012
Available online 17 January 2013

Keywords:
Breast cancer
Radiation therapy
Hypofractionation
Radiation fractionation
Concurrent boost

ABSTRACT

Hypofractionated radiation refers to treatment with greater than 2 Gy per fraction, usually in fewer number and an overall shorter treatment period, compared to conventional radiation fractionation. Randomized prospective trials of hypofractionated whole breast irradiation (WBI) have demonstrated comparable outcomes as conventional fractionation in early stage postlumpectomy radiation in selected groups of patients. These data have changed the traditional radiobiology estimation of the alpha/beta ratio that predicted fractionation sensitivity for breast cancer, suggesting that further increase in dose per fraction is possible for early stage breast cancer without significantly increasing late effects. Many questions remain regarding hypofractionated WBI and span from optimal patient selection to radiation technique including dose planning optimization and the incorporation of a tumor bed boost. A concurrent radiation boost has been studied in a number of single institution studies and has shown to be feasible with acceptable acute and short-term late toxicity. A phase III trial by the Radiation Therapy Oncology Group (RTOG 1005) in North America and other trials in Europe are currently studying in-breast cancer control from hypofractionated WBI with a concurrent tumor bed boost. Results from these current trials could improve the acceptance and broaden the applicability of hypofractionation treatment courses for the treatment of patients with early stage breast cancer.

Breast-conserving surgery and radiation is a standard alternative to mastectomy for most patients with stage I and II invasive breast cancer [1]. Postlumpectomy whole breast irradiation (WBI) is now associated with very high local control rates of 90–95%, rates that are higher than those seen in the early randomized trials due to improvements in early detection, patient selection, surgical and radiation techniques, and use of systemic therapy [2,3]. This reduction in local recurrence because of postlumpectomy radiation is also associated with improved overall survival [4].

Yet in spite of these benefits of postlumpectomy radiation, the number of women treated with breast-conserving surgery (BCS) but without radiation in the United States is approximately 15–20%, and the percentage of women in whom radiation is omitted is even higher for patients aged $\geqslant$70–80 years [5–7]. One reason for this may be the extended 6–7 week length of treatment. Delivering postoperative WBI in a shorter period of time could result in greater convenience for patients and greater utilization of postoperative radiation. Cost to the individual and third-party payers, governmental or private insurers, could also be significantly reduced by delivering an effective course of postlumpectomy radiation in half the time as a traditional 30–35 treatment course.

Hypofractionation, or use of larger dose radiation treatments compared to conventional radiation fraction sizes of 1.8–2 Gy per day, has been shown in randomized prospective trials to not be inferior to conventional fractionation for WBI in selected patients with early stage breast cancer. Hypofractionation also generally implies (but not always) the delivery of fewer radiation fractions over a shorter elapsed time interval, i.e. fewer number of weeks to complete treatment than conventional WBI schedules. This review will focus on studies of hypofractionated WBI, and whole breast hypofractionation with concurrent boost, in early stage breast cancer. Articles on partial breast irradiation will not be covered.

Hypofractionated WBI for early stage breast cancer

Rationale

Early laboratory and clinical studies in radiobiology showed that tissues could be generally divided into early responding (tumors and tissues responsible for acute effects observed during radiation) and late responding (responsible for late effects of radiation). Modeling of dose response showed that early responding tissues were less sensitive to effects of radiation fraction size than late responding tissues. The linear quadratic (LQ) radiobiology model predicted that the effect of radiation is different for cell killing by two different components – alpha (single hit killing) and

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0167-8140/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2012.12.001

beta (two hit killing) [8]. In the LQ model, a tissue that is late responding has a dose response curve modeled best by a low alpha to beta ratio, and one that is early responding a higher alpha to beta ratio. Early radiobiology studies, mostly from squamous cell cancers of the cervix or head and neck, determined that tumor tissue behaved mostly like an acute responding tissue with a high alpha/beta ratio of 10 and normal tissue like a late responding tissue with a low alpha/beta ratio of 3. In that way, smaller fraction sizes of 1.8–2 Gy became customary for radiotherapy in order to exploit this biological differential – maximize local control in tumor tissue while minimizing late effects in late responding normal tissue – over a course of fractionated radiation.

Hypofractionation using a larger radiation fraction size and fewer number of fractions under these assumptions of alpha/beta ratios 10 for tumor effects and 3 for late effects would result in relatively greater late tissue effects for the same tumor control effect. This is generally what was observed clinically in early experiences with large fraction sizes [9]. For the treatment of breast cancer, the early experiences with hypofractionation were also associated with more severe late sequelae [10–12]. The clinical experience with whole breast hypofractionation in breast cancer subsequently improved after better understanding of the LQ model led to a decrease in the *total* radiation dose to approximately 40 Gy [13,14]. This premise was confirmed clinically by the outcome from a series of randomized clinical trials from the United Kingdom from Royal Marsden Hospital (RMH) and the Standardization of Breast Radiotherapy (START) Group [15–18]. These trials concluded that breast cancer has an alpha/beta ratio for tumor control of 4.6, and normal breast tissue an alpha/beta ratio of 3.4 [17]. When the alpha/beta ratios of the tumor and normal tissue are more approximate to one another such as this, the relative benefit of normal tissue sparing with conventional fractionation is diminished and there is more of a rationale for hypofractionation [19]. Radiobiologic models using this newer understanding of the alpha/beta ratio for breast cancer show that increasing fraction size with a sufficiently large reduction of the total radiation dose can keep late toxicity comparable to that seen with conventional fractionation without decreasing the rates of tumor control [20].

Prospective randomized trials of hypofractionated WBI

The prospective randomized clinical trials evaluating efficacy of hypofractionated WBI for in-breast cancer control in comparison to standard WBI are shown in Table 1 [15–18,21]. These phase III randomized trials were similar in their design to test that in-breast cancer recurrence at 5 years in the hypofractionated arms was not inferior to that achieved by standard fractionated WBI.

The Royal Marsden Hospital (RMH), Sutton and Gloucestershire Oncology Centre used a hypofractionated WBI schedule that maintained the same 5 week length of treatment for all three arms [15,16]. The local recurrence rates at 10 years were 12.1% for 50 Gy, 14.8% for 39 Gy, and 9.6% for 42.9 Gy ($p = 0.027$). There was a statistically significant change in breast appearance with the largest daily fraction size of 3.3 Gy to a total of 42.9 Gy compared with the other treatment arms. However, this change in baseline size and shape of the breast was considered mild in most patients, and the number with a severe difference was relatively low (10.1%, 3.4% and 5.6%, respectively).

The START trials consisted of two separate studies evaluating different hypofractionation schedules; START trial A and START trial B [17,18]. There were no differences in 5 year local control between the hypofractionation arms and standard fractionation in each trial (Table 1). Rates of distant relapse, disease-free and overall survival were also similar. There was no significant difference in patient-reported breast, arm, or shoulder-related symptoms between regimens in trial A or B [22]. The rate of moderate or marked change in skin appearance after radiation was significantly lower for 39 Gy versus 50 Gy in trial A (41.6 Gy and 50 Gy did not vary significantly) and for 40 Gy versus 50 Gy in trial B. Symptoms related to the arm and shoulder did not differ significantly between regimens in trial A or B. This is important in addressing potential concerns about increased late effect risks that have historically been associated with larger daily radiation fraction sizes.

In Canada, the Ontario Clinical Oncology Group (OCOG) trial randomized patients to 42.5 Gy in 16 (2.67 Gy) fractions over 22 days versus 50 Gy in (2 Gy) 25 fractions over 35 days without boost [21]. These two radiation schedules were associated with equivalent 10-year local recurrence risks of 6.2% and 6.7%, respectively. The trial also addressed late effect risks and reported that the cosmetic appearance was considered good or excellent in approximately 70% of women in both groups. There were similarly no reported differences in 10-year skin and subcutaneous tissue and cardiac complications.

More recently, the UK FAST trial looked at photographic breast appearance as the primary endpoint (not local control) to evaluate more abbreviated WBI hypofractionation schedules [23]. Patients were randomized to 50 Gy in 25 fractions over 5 weeks, versus a schedule of one fraction a week for 5 weeks using 5.7 Gy per fraction (total 28.5 Gy) or 6.0 Gy per fraction (total 30 Gy). There was a lower incidence of acute RTOG grade 2 and 3 radiation dermatitis in the weekly five fraction regimens compared to conventional fractionation (grade 2/3 35.5/10.9% for 50 Gy versus 11.7/2.7% for 30 Gy versus 8.5%/1.9% for 28.5 Gy). For late effects, there was a significant worsening in 2 year photographic breast appearance and 3 year cosmetic assessment with hypofractionation once-weekly as compared to the conventional fractionation arm. The risk ratio for mild or marked change on photographic breast appearance was 1.7 ($p < 0.001$), and 1.15 ($p = 0.489$), respectively. The cosmetic assessments showed a moderate/marked adverse effect of the breast in 17.3% for 30 Gy ($p < 0.001$), 11.1% for 28.5 Gy

Table 1
Trials of hypofractionated WBI versus conventional fractionation in early stage breast cancer.

Trial	Years conducted	#	Fractionation Gy/# of fractions	Boost (%)	Local recurrence (%)	Time point
RMH/GOC) [15,16]	1986–1998	470	50/25	74	12.1	10 years
		466	42.9/13	75	9.6	
		474	39/13	74	14.8	
START A [17]	1998–2002	749	50/25	60	3.6	5 Years
		750	41.6/13	61	3.5	
		737	39/13	61	5.2	
START B [18]	1999–2001	1105	50/25	41	3.3	5 Years
		1110	40/15	44	2.2	
OCOG [21]	1993–1996	612	50/25	0	6.7	10 Years
		622	42.5/16	0	6.2	

RMH/GOC: Royal Marsden Hospital, Sutton and Gloucestershire Oncology Centre; START: Standardization of Breast Radiotherapy; OCOG: Ontario Clinical Oncology Group.