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EDITORIAL

Hypofractionated radiotherapy in the treatment of early breast cancer

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Abstract

Radiotherapy (RT) after tumorectomy in early breast cancer patients is an established treatment modality which conventionally takes 6-7 wk to complete. Shorter RT schedules have been tested in large multicentre randomized trials and have shown equivalent results to that of standard RT (50 Gy in 25 fractions) in terms of local tumor control, patient survival and late post-radiation effects. Some of those trials have now completed 10 years of follow-up with encouraging results for treatments of 3-4 wk and a total RT dose to the breast of 40-42.5 Gy with or without boost. A reduction of 50% in treatment time makes those RT schedules attractive for both patients and health care providers and would have a significant impact on daily RT practice around the world, as it would accelerate patient turnover and save health care resources. However, in hypofractionated RT, a higher (than the conventional 1.8-2 Gy) dose per fraction is given and should be managed with caution as it could result in a higher rate of late post-radiation effects in breast, heart, lungs and the brachial plexus. It is therefore advisable that both possible dose inhomogeneity and normal tissue protection should be taken into account and the appropriate technology such as three-dimensional/intensity modulated radiation therapy employed in clinical practice, when hypofractionation is used.

Key words: Breast conservation; Early breast cancer; Hypofractionation; Radiotherapy

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INTRODUCTION

Breast-conserving therapy is a widely accepted treatment in the management of early breast cancer. It includes wide local excision of the tumor followed by radiotherapy (RT) to the breast (and of course the necessary treatment for lymph-drainage areas). The major benefit of breast-conserving therapy is preservation of the affected breast with all the consequent advantages in terms of patient quality of life. Large randomized trials have demonstrated the equivalence of this therapy, compared to mastectomy, in terms of long-term disease-free and overall survival rates[1,2]. Conventional RT after breast-conserving surgery requires 6-7 wk of daily treatment. The most widely used schedule is 50 Gy in 25 fractions (2 Gy per fraction) over 5 wk plus 3-8 fractions to boost the dose on the tumor bed[1,2]. Such a long treatment schedule has major implications on both patient quality of life and RT departments, as a high number of breast cancer patients receive RT. A shorter breast RT schedule would be more convenient for patients (especially those coming from remote areas to RT facilities) and for

health care providers, as it would increase the turnover in RT departments. The use of a 16-fractions, instead of a 25-fractions regime, for instance (see below), would save 900 treatment sessions per 100 patients (2500 - 1600 = 900). This corresponds to an additional 56 (900:16) patients who could be treated with the same number of fractions. This would result in substantial economic benefit as breast cancer patients represent the majority of patients treated in RT departments.

RADIOBIOLOGY AND FRACTIONATION

A broad variety of RT schedules, hypofractionated or not, have been used in clinical practice, but there is no consensus on the optimum fractionation. A survey of Ontario RT centres alone identified 48 different dose fractionation schedules[3].

However, there are some reservations regarding the shorter RT schedules[4] with a high (> 2 Gy) dose per fraction, which are mainly related to the theoretically expected higher rate of late post-radiotherapy complications. With conventional fractionation, the Early Breast Cancer Trialists' Collaborative Group reported that radiation therapy reduced the annual mortality from breast cancer by 13%, but increased the annual mortality rate from other causes (mainly cardiovascular causes) by 21%[5]. Data from long-term follow-up on late lung and cardiac morbidity and survival rates has yet to emerge for the current hypofractionation schedules, as the cardiac adverse effects may not emerge until 15 years after treatment. However, hypofractionation studies and clinical results reported so far do not suggest a higher risk of late reactions.

Radiation oncologists are generally sceptical about using a RT regime with a higher than the standard (1.8-2 Gy) dose per fraction. One of the main principles of radiobiology is that the late effects of normal tissues are strongly dependent on the size of dose per fraction, so that the higher the dose per fraction the greater the susceptibility of healthy tissues to radiation. This is known as "fractionation sensitivity". Fractionation sensitivity of tissues is quantified, in terms of linear-quadratic (LQ) isoeffect formulation, by the α/β ratio[6,7]; the higher the sensitivity to the size of dose per fraction, the lower the α/β ratio is. Late reacting normal tissues (connective tissue, neural tissue, *etc.*) have an α/β ratio of about 1.5-3 Gy. Late post-radiation effects of breast are fibrosis, oedema, tenderness, telangiectasia and a combination of these effects, in addition to impaired cosmesis and have an α/β = 3 Gy[6,7]. We should mention here that for the assessment of late post-radiation effects on the treated breast, most authors take photographs post-surgery and pre-radiotherapy and then at predetermined times, e.g. 2 and 5 years to assess changes to the breast based on change in size, shrinkage, and shape. Scoring on a 3 or 4 graded scale is carried out in most studies. Changes in breast appearance may be scored by more than one observer usually blind to the treatment arm and year of follow-up.

It has to be mentioned that this discussion on hypofractionation does not apply to treatment of lymphatic pathways due to the very high fractionation sensitivity of the brachial plexus (neural tissue). Acute radiation reactions in normal tissues such as the skin or mucosa and squamous-cell carcinomas have an α/β ratio of 10 Gy[6,7]. It has been shown by radiobiological analysis of clinical data, that breast adenocarcinomas have an α/β ratio of around 4 Gy, i.e. close to late reacting normal tissues[8-11]. Consequently, hypofractionation in breast cancer may have a reasonable radiobiological background as more tumor cells will be killed by a high dose per fraction compared with the conventional 2 Gy per fraction, and would potentially compensate for repopulation of tumor cells during RT.

ESTABLISHMENT OF DOSE-RESPONSE

However, this may be difficult to prove because the local control rates in early breast cancer with radiation therapy are already high, and in breast cancer in particular, there are a number of factors that might influence the results of a RT treatment schedule or a relevant clinical study. Therefore, it is difficult to establish a dose-response relationship in postoperative breast RT, that may be relatively higher than other solid tumors due to the following[12]: (1) An unknown proportion of patients have no residual cancer cells after surgery, whereas others have a subclinical (microscopic) number of residual tumor cells that must be eradicated by radiation[12-14]. This is an inherent problem when analyzing the results of any adjuvant therapy; (2) Dose-escalation studies are usually lacking; information should be taken from randomized controlled studies on RT *vs* no RT which have used a narrow range of RT schedules and doses; and (3) There are a number of factors that may affect the homogeneity of clinical data in existing randomized trials: biologic aggressiveness of the treated tumors (ranging from elderly patients with T1N0, Grade 1 hormone receptor-positive tumors to women with multiple positive nodes, hormone receptor-negative, HER2-positive tumors), variable surgical techniques and skills among centres, variable chemotherapy/endocrine regimes and RT techniques. Additionally, local recurrence could be the result of re-growth of tumor at the initial tumor bed, or of tumor in the same breast but outside the initial tumor bed from cells existing at the time of initial treatment, or the development of a new tumor in the same breast.

In our recent study[12], we attempted to estimate a biologically effective dose (BED)-response for adjuvant breast RT in early-stage breast cancer. Clinical results from nine randomized trials (involving more that 6200 patients) of RT *vs* non-RT were reviewed and the tumor control probability (TCP) after RT was calculated for each. We used the LQ formula and Poisson statistics of cell-kill[15-17] to calculate the average initial number of clonogens per tumor before RT and the average tumor cell radiosensitivity[6,15-17]. An α/β ratio of 4 Gy was assumed[8-11] for these calculations.

A linear regression equation linking BED to TCP was derived {equation: -ln[-ln(TCP)] = -ln(No) + a * BED = -4.08 + 0.07 * BED} and a sigmoid BED-response curve was constructed. We concluded that TCP is essentially maximizing for BED values of about 90 Gy[4]. An example of a BED of 85-90 Gy[4] could be a regimen of 40 Gy in 15 fractions plus a boost of 10-12 Gy in 3-4 fractions.

REVIEW OF CLINICAL STUDIES

Clinical reports from various centres have shown almost equivalent results between short and standard RT schedules[9-11,18-27], and it would be interesting to have an overview of the current situation in this field.

In a well-known randomized trial from Canada, Whelan *et al*[18] reported equivalent results (regarding local control, survival, and post-radiation effects) between the standard fractionation schedule of 50 Gy in 25 fractions and a hypofractionated scheme of 42.5 Gy in 16 fractions over 22 d for women with node-negative early breast cancer. This study has been updated recently and, most importantly, results have not changed after a 10-year follow-up[19]. However, the potential limitations of this study are as follows:

The trial was restricted to women who had node-negative, invasive breast cancer with clear margins of excision after lumpectomy; women with large breasts were not included; few women received adjuvant chemotherapy and we should bear in mind that those patients can be at a higher risk for acute and late post-radiation effects; boost irradiation was not used, as by the time the study was initiated, the efficacy of boost irradiation had not been demonstrated[19] and was later shown in studies from Europe[28,29]. However, boost irradiation was used in both Standardization of Breast Radiotherapy (START) trials (see below), and adjuvant chemotherapy was used more widely than in this trial. In addition, a broader spectrum of tumors and patients (node-positive, larger tumors, no limitation of breast size) were included, but no differences have been noted in tumor control and side-effects between standard and short treatments in those trials so far.

Another short RT schedule, 40 Gy in 15 fractions, has been used traditionally at Christie Hospital in Manchester, UK; the reported results of 2159 treated patients are comparable to those reported from other centres[21,22]. This schedule is now becoming the "standard" in the UK, especially after the publication of the START trials.

The START A trial randomized 2236 patients from 17 centres across the UK and reported that 41.6 Gy/13 fractions or 39 Gy/13 fractions are similar to 50 Gy/25 fractions in terms of local-regional tumor control and late normal tissue effects. The START A trial[9] showed that after a median follow-up of 5.1 years, the rate of local-regional tumor relapse at 5 years was 3.6% [95% confidence interval (CI): 2.2%-5.1%] after 50 Gy, 3.5% (95% CI: 2.1%-4.3%) after 41.6 Gy, and 5.2% (95% CI: 3.5%-6.9%) after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0.2% (95% CI: -1.3%-2.6%) after 41.6 Gy and 0.9% (95% CI: -0.8%-3.7%) after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy. The results have shown that breast cancer and late reacting normal tissues respond similarly to change in RT fraction size. 41.6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of local-regional tumor control and late normal tissue effects.

The START B trial[10] randomized 2215 patients from 23 centres across the UK and reported that a RT schedule of 40 Gy/15 fractions offers equivalent results to the standard schedule of 50 Gy/25 fractions. After a median follow-up of 6.0 years, the rate of local-regional tumor relapse at 5 years was 2.2% (95% CI: 1.3%-3.1%) in the 40 Gy group and 3.3% (95% CI: 2.2%-4.5%) in the 50 Gy group. Photographic and patient self-assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy. Although the START trials had a relatively limited follow-up time and differences in their design (inclusion criteria) compared with the Canadian trial, their results were similar.

Our early experience from the routine use of the above "Canadian" schedule of hypofractionated breast RT (42.5 Gy in 16 fractions) has been reported recently[30]. We reported on 339 patients treated for 4 years. An electron boost of 9-10 Gy/3-4 fractions was given to 104/339 patients (31%). Median follow-up time was 24 mo (range: 12-48 mo). Radiation Therapy Oncology Group (RTOG) grades 0, 1, 2, 3, and 4 for acute skin toxicity were 9.7%, 68.7%, 17.5%, 4.0%, and 0.3%, respectively. Radiation pneumonitis (promptly resolved by steroids) was suspected/diagnosed in 11/339 patients (3.2%). A total of 8/11 patients had been treated with RT at regional lymph-drainage areas. The only significant correlation was that of radiation pneumonitis and RT of regional lymphatics. Two patients developed metastatic disease and died 14 and 27 mo after RT; another four patients developed metastases; bone metastases developed in two patients, and liver, lung, brain plus regional recurrence (axilla, supraclavicular) in two patients.

Other non-randomized studies have reported similar results. Fujii *et al*[23] reported acceptable results in terms of local control and toxicity (although the median follow-up of this study was 26 mo) with a short fractionation schedule of 42.5-47.8 Gy/16-20 fractions. In another study from the University of Florence, Italy, Livi *et al*[26] reported similar results in 539 patients.

A schedule of 40 Gy in 16 (not 15) fractions in post-lumpectomy invasive breast cancer patients (with clear tumor margins) has shown similar results with a 5-year actuarial breast-relapse rate of 3.5%, while more that 95% of the patients were satisfied with cosmetic results after a median follow-up of 5.5 years[27].

THE LIMITS OF HYPOFRACTIONATION IN BREAST RT

Another study from the UK, investigating the "limits of

hypofractionation in breast RT" is the FAST trial involving 900 patients across the UK (FASTer Radiotherapy for breast cancer patients). This trial is testing 30 Gy in 5 fractions (6 Gy/fraction) over 35 d (5 wk) *vs* 28.5 Gy (5.7 Gy/fraction) over 35 d *vs* 50 Gy in 25 fractions over 35 d (control arm). The trial has ceased recruiting patients and follow-up is ongoing. In the FAST trial, the women being studied are those with completely excised invasive, less than 3 cm, node-negative carcinoma of the breast who underwent breast-preserving surgery and who are older than 49 years[31,32]. In this trial, five fractions of RT are given in 5 wk (one fraction per week), however, this is thought unlikely to represent the "ultimate" hypofractionation. The next step would be to investigate the 30 Gy/5 fractions regime given over a shorter time period.

The same fractionation schedule has also been tested clinically with an overall treatment time of 2 wk[33]. The authors evaluated erythema and moist desquamation in 30 patients receiving 30 Gy in five fractions over 15 d. Grading of skin reactions using RTOG criteria resulted in: 3% grade 0, 67% grade 1, 30% grade 2 and no grade 3 or 4 toxicity. Moist desquamation developed in 4/30 patients (13%). There was some evidence that the risk of acute skin reactions and change in breast appearance (photographically assessed) increased with larger breast size, but the small sample size prevented formal statistical testing. No recurrences were seen after a median follow-up of 3 years. This very short regime showed similar skin toxicity results to the RTOG trial (RTOG 97-13): 7% grade 0, 58% grade 1, 32% grade 2, 3% grade 3 and no grade 4 acute skin toxicity[34]. A correlation between breast size and acute toxicity was reported in the RTOG 97-13 study, with small-breasted women developing 11%-21% grade 2 or higher skin toxicity compared with 43%-50% in large-breasted women.

A further step would be to shorten the RT schedule into 1 wk i.e. to study a 5-fractions RT schedule given over 5 consecutive days. Such a schedule would have significant clinical/practical implications as it would allow RT to be integrated more effectively with surgery and systemic therapies, and it could be used for partial breast RT [see below, Accelerated Partial Breast Radiotherapy (APBI)].

RT EQUIPMENT AND DOSE FRACTIONATION

An important tool in the implementation of hypofractionated RT in early breast cancer is the currently available (in most RT departments in Europe and the US) equipment which obtains a better RT dose distribution i.e. both homogeneous within the planning target volume and sparing neighbouring normal tissues and organs. Three-dimensional treatment planning allows the distribution of the prescribed dose to be evaluated. Dose to the heart and lungs can also be evaluated. This information can be used to optimize the treatment plan accordingly, by the use of techniques such as intensity modulated radiation therapy (IMRT). There is now evidence that such an improvement in dose distribution translates into improved clinical outcome. This improvement in RT planning and delivery would favour hypofractionated RT schedules as it would prevent normal tissues receiving a higher (than the prescribed) dose per fraction and total dose[35,36].

A randomized trial from the Royal Marsden Hospital tested three-dimensional (3D) IMRT against 2D dosimetry using standard wedge compensators, regarding late reactions after whole breast RT. The primary endpoint was change in breast appearance and secondary endpoints were patient self-assessments of breast discomfort, breast hardness, quality of life and physician assessments of breast induration. The 2D-arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT-arm patients (95% CI: 1.2-2.5, $P = 0.008$). Significantly fewer patients in the 3D IMRT group developed palpable breast induration. No significant differences between the treatment groups were found with regard to patient reported breast discomfort, breast hardness or quality of life[36].

Another technique that could make breast RT courses shorter is APBI, which is defined as a radiation technique that employs fractions higher than 1.8-2.0 Gy per day to a partial volume of the breast over a period of less than 5-6 wk[37]. The rationale of this technique is to treat the lumpectomy cavity and an adjacent margin of 1-2 cm as the majority of breast recurrences are diagnosed within this volume. The techniques for APBI include interstitial implantation of radioactive needles, MammoSite (the MammoSite system employs a dual lumen spherical balloon-catheter which is placed in the surgical cavity and filled with water; a high-dose-rate Iridium-192 source in the central lumen delivers the RT in 10 fractions over 5 d), targeted intraoperative therapy, intraoperative electrons and photon beams with 3D conformal/IMRT techniques. Further description of the rationale and techniques of APBI is beyond the scope of the present discussion, however, there are interesting reviews on this method[38,39].

A randomized trial, in progress in the UK, testing intensity modulated RT and partial organ RT following breast-conserving surgery for early breast cancer, is the Intensity Modulated Partial Organ Radiotherapy (IMPORT) trial; the control arm of this trial is: current standard 3-wk RT to the whole breast. Test arm one is: reduced RT to the whole breast (lower-risk areas for recurrence) with standard RT to the partial breast, in the sites of higher risk for recurrence and test arm two: standard RT to the partial breast only (IMPORT Low-risk study). To test dose-escalated IMRT after breast-conserving surgery in women with a higher than average risk of local recurrence, the IMPORT-high trial is also in progress[40,41].

CONCLUSION

In conclusion, hypofractionated RT after breast-conserving surgery for early breast cancer could have a significant

impact in breast oncology and breast cancer patients. Data from randomized trials and the experience from various departments worldwide are encouraging. However, in addition to clinical experience and expertise, appropriate advanced RT equipment and techniques are fundamental in the clinical application of hypofractionated breast RT.

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