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Original article

Accelerated partial breast irradiation using 3D conformal radiotherapy: Toxicity and cosmetic outcome

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ABSTRACT

Purpose: The aim of this paper is to analyze the incidence of acute and late toxicity and cosmetic outcome in breast cancer patients submitted to breast conserving surgery and three-dimensional conformal radiotherapy (3D-CRT) to deliver accelerated partial breast irradiation (APBI).
Methods and materials: 84 patients were treated with 3D-CRT for APBI. This technique was assessed in patients with low risk stage I breast cancer enrolled from September 2005 to July 2011. The prescribed dose was 34/38.5 Gy delivered in 10 fractions twice daily over 5 consecutive days. Four to five non-coplanar 6 MV beams were used. In all CT scans Gross Tumor Volume (GTV) was defined around the surgical clips. A 1.5 cm margin was added by defining a Clinical Target Volume (CTV). A margin of 1 cm was added to CTV to define the planning target volume (PTV). The dose–volume constraints were followed in accordance with the NSABP/RTOG protocol. Late toxicity was evaluated according to the RTOG grading schema. The cosmetic assessment was performed using the Harvard scale.
Results: Median patient age was 66 years (range 51–87). Median follow-up was 36.5 months (range 13–83). The overall incidence of acute skin toxicities was 46.4% for grade 1 and 1% for grade 2. The incidence of late toxicity was 16.7% for grade 1, 2.4% for grade 2 and 3.6% for grade 3. No grade 4 toxicity was observed. The most pronounced grade 2 late toxicity was telangiectasia, developed in three patients. Cosmetics results were excellent for 52%, good for 42%, fair for 5% and poor for 1% of the patients. There was no statistical correlation between toxicity rates and prescribed doses ($p = 0.33$) or irradiated volume ($p = 0.45$).
Conclusions: APBI using 3D-CRT is technically feasible with very low acute and late toxicity. Long-term results are needed to assess its efficacy in reducing the incidence of breast relapse.

Introduction

Whole breast irradiation (WBI) is the standard of care for early breast cancer patients who receive breast conserving therapy (BCT). With classic WBI schedules, a dose of 50 gray (Gy) in 25 fractions, 5 days per week, for 5 weeks is delivered to the mammary gland. An additional boost of 10–16 Gy to the tumor bed is often prescribed and loco-regional lymph nodes can also be irradiated in selected patients. This approach minimizes the risk of local failure and improves disease-specific survival with acceptable heart, lung and skin toxicity. Its safety has been demonstrated by several meta-analyses, with local failure rates of 0.5–1% per year of follow-up [1].

It has been reported that only the minority of North-American patients who were potential candidates for BCT actually received it [2], although this trend is changing [3]. Many factors contributed to the underutilization of BCT; however, the logistic problem of undergoing 5–7 weeks of daily radiation certainly played a major role, particularly for elderly patients and for those who live at long distances from radiation facilities [4]. Over a 5-year period spanning from 2000 to 2004, patients from Northern Italy faced a reduced probability of receiving a mastectomy [odds ratio (OR)

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0.70; confidence interval (CI) 0.56–0.88]; nevertheless, radiotherapy was not administered in 20.3% of those submitted to breast conserving surgery, with distance from radiotherapy facilities being the most important factor for radiotherapy omission (OR: 1.75; CI: 1.39–2.20 for those at a travel distance of >45 min) [5]. An epidemiological study from our region confirmed these results in 2007 [6].

The possibility to deliver adjuvant radiotherapy either intra-operatively or as a shorter course post-operatively has certainly the potential to increase the acceptance of BCT. Furthermore, the majority of ipsi-lateral breast relapses after BCT occur in close proximity to the lumpectomy cavity. Given these considerations, many clinicians started to question the opportunity of WBI and accelerated partial breast irradiation (APBI) was developed as a possible alternative for patients with early-stage breast cancer.

Several single-institution experiences, phase I/II trials, and, more recently, prospective randomized studies have been conducted to determine the safety and efficacy of APBI [7]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/Radiation Therapy Oncology Group (RTOG) 0432 trial, a three-dimensional (3D) conformal APBI arm has been used to deliver a total dose of 38.5 Gy in 10 fractions, twice daily, over 1 week [8]. This dose has been determined by mathematical and biological modeling [9]. In the present study, the preliminary results of a mono-institutional series of early breast cancer patients treated with a similar conformal ABPI will be reported.

Methods

A phase II trial of APBI was approved by one internal and one external Ethical Committee in 2005. Primary objective of this study was to determine the feasibility, reproducibility, side effects and cosmetics results of the technique. The study population consisted of 84 patients recruited between September 2005 and July 2011 (Table 1). Eligibility criteria were similar to those of the protocol by Vicini et al. [10] and included post-menopausal women (defined as follows: prior bilateral oophorectomy, more than 12 months since last menstrual period with no prior hysterectomy, at least 55 years of age with prior hysterectomy, under 55 years of age with a prior hysterectomy without oophorectomy and with estradiol and follicle-stimulating hormone levels consistent with menopause), with a ≤3 cm invasive ductal carcinoma, absence of an extensive intraductal component (EIC), no skin involvement, and no Paget's disease of the nipple, surgery consisting of a wide local excision with negative surgical margins by at least 2 mm, negative sentinel node biopsy and/or axillary dissection. These clinical and pathologic features where chosen to select patients at low risk of local relapse and are also suggested by the American Society for Therapeutic Radiology and Oncology (ASTRO) [9]. The placement of radiopaque surgical clips delineating the extent of the lumpectomy cavity was mandatory for study entry. A total of 6 clips were positioned after tumor removal delineating the planes of an ideal cube representing the surgical cavity.

3D-conformal radiotherapy (3D-CRT) was performed in accordance with the technique and dose–volume constraints specified in the NSABP/RTOG protocol. Computed tomography-based 3D planning was performed for all patients. CT images were then acquired at 3 mm thick intervals from the level of the mandible through the lung bases. The following structures were outlined: tumor bed, clinical target volume (CTV), planning target volume (PTV), and PTV for evaluation (PTV_Eval). The tumor bed was contoured by means of computed tomography, taking into account postoperative changes and location of surgical clips. The clinical target volume (CTV) was defined as the tumor bed with a 1.5 cm margin, while the minimum distance from skin and chest wall was set at 0.5 cm. The planning target volume (PTV) was defined as the clinical target volume with a 1.0 cm margin. The copied contouring of the PTV was modified to create PTV_eval, which included the PTV but excluded the first 5 mm below the skin surface. The PTV-Eval was used to evaluate the appropriate target coverage.

Table 1
Baseline patient characteristics ($n = 84$).

Variable	Number (%)
Age (years)	
Median	66
Range	51–87
Follow-up (months)	
Median	36.5
Range	13–83
Breast side	
Left	37 (44)
Right	46 (55)
Bilateral	1 (1)
pT Stage	
pT1mi	4 (4.8)
pT1a	9 (11)
pT1b	32 (38.1)
pT1c	38 (45.2)
pT2	1 (1.2)
Histology	
Ductal N.O.S.[a]	72 (85.7)
Mucinous	7 (8.3)
Tubular	3 (3.6)
Intracystic papillary	2 (2.4)
Grading	
1	30 (35.7)
2	34 (40.5)
3	18 (21.4)
n.e.[b]	2 (2.4)
Tumor estrogen receptor status	
Negative[c]	0
Positive[c]	84 (100)
Radiation dose	
34 Gy	60 (71.4)
38.5 Gy	24 (28.6)
Endocrine therapy[d]	83(98.8)
Chemotherapy	0

[a] N.O.S.: Not otherwise specified.
[b] n.e.: Not evaluated.
[c] Negative: <1%, positive ≥1%.
[d] Tamoxifen (3.7%) or aromatase inhibitor (96.4%).

Four to five no-coplanar 6 MV beams arranged tangentially to the breast were used, five fields for the left and four for right breasts respectively. Field arrangements generally approximated breast tangents with a 10°–20° steeper gantry angle for the medial beams to spare breast tissue maximally and couch angles of 15°–70°. The irradiation was performed by Linac Clinac 600 (Varian@), that is equipped with 6 mm micro-multileaf, which provides excellent conformation to the target.

The initial prescription dose was 3.4 Gy twice daily, to reach a total dose of 34 Gy delivered within 1 week. Once acquired sufficient expertise with the technique, after the first 60 patients, we escalated the total dose to 38.5 Gy, at 3.85 Gy per fraction. The fractions were separated by 6 h interval. Plans were evaluated both quantitatively (dose–volume histograms) and qualitatively (isodose curves). Plans were checked for radiation conformity and dose homogeneity indices. The dose–volume constraints were followed in accordance with the specifications dictated in the NSABP/RTOG protocol. In brief, <50% of the whole breast reference volume should receive ≥50% of the prescribed dose and <25% of the whole breast reference volume should receive the prescribed dose. The contralateral breast reference volume should receive <3% of the prescribed dose to any point. Less than 10% of the ipsilateral lung should receive 30% of the prescribed dose and <10% of the contralateral lung should receive 5% of the prescribed dose. For right-sided lesions, <5% of the heart should receive 5% of the

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