Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1228–1235, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.07.040

**CLINICAL INVESTIGATION** **Breast**

# EARLY SIDE EFFECTS OF THREE-DIMENSIONAL CONFORMAL EXTERNAL BEAM ACCELERATED PARTIAL BREAST IRRADIATION TO A TOTAL DOSE OF 40 GY IN ONE WEEK (A PHASE II TRIAL)

Céline Bourgier, M.D., Ph.D.,* Charlotte Pichenot, Ph.D.,† Rodolfe Verstraet, M.S.,† Mohamed El Nemr, M.D.,* Steve Heymann, M.D.,* Bruno Biron,† Suzette Delaloge, M.D.,‡ Marie-Christine Mathieu, M.D.,¶ Jean-Rémy Garbay, M.D.,§ Jean Bourhis, M.D., Ph.D.,* Alphonse G. Taghian, M.D., Ph.D.,** and Hugo Marsiglia, M.D.*††

*Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; †Department of Physics, Institut Gustave Roussy, Villejuif, France; ‡Department of Breast Oncology, Institut Gustave Roussy, Villejuif, France; ¶Department of Pathology, Institut Gustave Roussy, Villejuif, France; §Department of Breast Surgery, Institut Gustave Roussy, Villejuif, France; **Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and ††Radiotherapy Unit, University of Florence, Florence, Italy

**Purpose: Several accelerated partial breast irradiation (APBI) techniques are described in the literature, and apparently, the three-dimensional (3D)-conformal technique is being used increasingly. Nonetheless, the optimal radiation dose is not yet known. Here, we report feasibility and early toxicities of APBI delivering 40 Gy over 5 days, in a phase II trial.**

**Methods and Materials: From October 2007 to September 2008, 25 patients with pT1N0 cancer received 3D-conformal APBI. The prescribed radiation dose was 40 Gy in 4-Gy fractions given twice daily. This technique used two minitangents and an "en face" electron field. Toxicities were systematically assessed at 1, 2, and 6 months and then once every 6 months.**

**Results: The planning tumor volume for evaluation (PTV_EVAL) coverage was adequate: the mean dose to the PTV_EVAL was 41.8 Gy (range, 41–42.4 Gy). Mean doses to the ipsilateral lung and heart were 1.6 Gy (range, 1.0–2.3 Gy) and 1.2 Gy (range, 1.0–1.6 Gy), respectively. One and two months after completion of APBI, most patients had no or mild erythema ($n$ = 16 patients at 1 month; $n$ = 25 patients at 2 months); none of these patients developed moist desquamation. After a median follow-up of 12 months, only 1 patient had a significant moderate field contracture (grade 2). Other reported late toxicities were grade 1.**

**Conclusions: 3D-conformal APBI (with two minitangents and an "en face" electron field) using a total dose of 40 Gy in 10 fractions twice daily over 5 days achieved appropriate PTV_EVAL coverage and offered significant sparing of normal tissue. Early tolerance was excellent.** © **2011 Elsevier Inc.**

**3D-Conformal accelerated partial breast irradiation, 40 Gy in 1 week, Toxicities.**

## INTRODUCTION

Breast-conserving therapy usually combines conserving surgery and radiotherapy for stage I and II breast cancer (2, 3). Irradiation of early breast cancer delivers 45 to 50 Gy in 23 to 25 fractions over the whole mammary gland and is often followed by a boost of 10 to 16 Gy in 5 to 8 fractions to the tumor bed (4). Thus, standard radiotherapy for early breast cancers is completed within 6 to 7 weeks. Although breast irradiation decreases the risk of local recurrence by 70% to 80%, breast cancer survivors present with late effects such as radiation pneumonitis, cardiac toxicities, rib fractures, and secondary radiation-induced cancers (5).

There have been successful attempts to reduce the overall treatment time for whole breast radiation therapy (6–8) and with accelerated partial breast irradiation (APBI) (1, 9–14), with the main goal of achieving equal efficiency. Recently, analysis of breast-conserving therapy trials suggests that local relapses occur most frequently within the tumor bed, with around 5% to 10% rate of local relapse elsewhere (15). The equivalence of APBI is currently being evaluated through international trials such as National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B39/Radiation Therapy Oncology Group (RTOG) protocol 0423 (16). In addition, the APBI concept has emerged as a method of sparing normal tissues such as lungs and heart and producing

Reprint requests to: C. Bourgier, M.D., Ph.D., Département de Radiothérapie, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94 800 Villejuif, France. Tel: (+33) 1 42.11.49.98. Fax: (+33) 1 42.11.65.06; E-mail: bourgier@igr.fr

Conflict of interest: none.

Received May 6, 2010, and in revised form July 9, 2010. Accepted for publication July 13, 2010.

a good aesthetic outcome owing to confined treatment volumes.

Multiple APBI modalities have been described and could be divided into two groups: invasive (12–14, 17–19) and noninvasive techniques (1, 9, 10, 20–22). However, some questions concerning APBI are still unresolved, such as the optimal total dose, the optimal dose/fraction, the number of fractions, and the optimal technique. NSABP B39/RTOG 0432 have used a three-dimensional (3D) conformal APBI arm to deliver a total dose of 38.5 Gy/10 fractions of 3.85 Gy twice daily in 1 week. This dose has been determined by mathematical and biological modeling without any clinical basis (10, 23). At the Massachusetts General Hospital (MGH) a phase I/II dose escalation trial (clinical trial 03-179) was started in 2003 that uses a total dose of 32 Gy/8 fractions twice daily for 4 days, 36 Gy/9 fractions twice daily for 4.5 days, and 40 Gy/10 fractions for 5 days (A. Taghian, personal communication) (1, 24). That study is still in progress. At the Institut Gustave Roussy, we have begun a collaboration with the MGH and initiated a phase II trial at the dose level of 40 Gy/10 fractions, using the same technique, which consists of two minitangents and an ''en face'' electron field contributing around 20% of the total dose (8 Gy) (1). Here, we report feasibility and early toxicities of a pilot phase II trial at the 40-Gy dose level, using the technique described by Taghian *et al.* (1).

## METHODS AND MATERIALS

### *Study population*

The study population consisted of 25 women referred for adjuvant radiation therapy (RT) and treated with APBI between October 2007 and September 2008. All patients were prospectively enrolled in an institutional and national review board-approved phase II trial. All patients had undergone surgical excision (surgical margins greater than 2 mm) of stage pT1N0 unifocal tumors. Eligibility criteria included (*i*) postmenopausal patients, (*ii*) unicentric, histologically confirmed invasive carcinoma (ductal, tubular, mucinous, or medullary carcinoma) or ductal carcinoma *in situ*, and (*iii*) the following histological characteristics: tumor size less than 20 mm, negative axillary nodes, positive hormonal receptors, and no Her2 overexpression. Patients with histologic evidence of lymphovascular invasion, extensive intraductal component, lobular or papillary carcinoma, insufficient surgical margins (<2 mm), premenopausal patients, and BRCA1/2 carriers were excluded. APBI was initiated within 4 to 12 weeks after definitive surgery. Of the total, 25 patients were accrued from Institut Gustave Roussy; all patients consented to the treatment. Median age was 65 years old (range, 53-78 years). Median time from surgery to radiotherapy was 7.7 weeks (range, 4-10 weeks).

### *Simulation, treatment planning, and treatment*

Simulation and treatment planning have been described previously (25). Briefly, all patients underwent computed tomography (CT) breast simulation scanning, where clinical target volume (CTV) was defined as the delineation of the visible lumpectomy cavity and the surgical clips placed inside the lumpectomy cavity, in conformity with our surgeons' process (four clips upper, inner, outer, and lower surgical margins); planning target volume (PTV) was defined as the uniform expansion of the CTV by 1.5 to 2.0 cm to adapt margins according to tumor size and to margins which were taken by surgery. This contour was expanded by another 0.8 cm to account for the penumbra and the set-up uncertainty. Skin (first 5 mm beneath the epidermis) and anterior chest wall/pectoralis muscles were excluded from the PTV for evaluation (PTV_EVAL) (according to the definition by Vicini *et al.* [26]). Beam arrangements were left to the discretion of the treating physician and usually consisted of a combination of photon beams of 6 MV and electrons of 6 to 22 MeV with Dosigray 4.1.2.50 TPS (Dosisoft). Wedges were used as needed to improve PTV_EVAL coverage and dose homogeneity. The maximum dose could not exceed 115% of the prescribed dose. Normal tissue dose–volume constraints were defined as follows: 50% of the nontargeted breast volume had be less than 50% of the prescribed dose; the PTV_EVAL-to-whole breast ratio had to be less than 25%; and a limited dose was to be received by heart and lungs. The lung volume dose constraints used were as follows: <3% at 20 Gy, <10% at 10 Gy, and <20% at 5 Gy, according to the study by Recht *et al.* (27). Dose inhomogeneity should be less than 15%. The prescribed dose was 40 Gy in 4-Gy fractions twice daily, with a minimum interfraction interval of 6 hours over a maximum elapsed time of 1 week. All fields, photons, and electron beams were treated with each fraction.

### *Toxicities assessment*

Graded evaluations of early toxicities were systematically performed at several planned time points: before APBI, immediately after completion of APBI (day 5), and 3 to 4 weeks (at 1 month) and 6 to 8 weeks (at 2 months) after completion of APBI. Then, late toxicities were assessed by independent physicians at 6 months and then at every 6 months. After a median follow-up of 12 months (minimum-maximum range, 300–634 days), 1-, 2-, 6-, and 12-month evaluations were completed for all 25 patients. Toxicities were assessed as grade 0 for none; grade 1 for mild; grade 2 for moderate; grade 3 for severe; and grade 4 for fatal toxicities.

## RESULTS

### *Treatment planning*

The mean and median volumes of the CTV at the time of treatment planning were 15.1 cc and 13.9 cc, respectively (range, 5.2–28.7 cc). The mean and median PTV volumes were 117 cc and 113 cc, respectively (range, 52–185 cc). The PTV/whole breast ratio determined the percentage of the volume of APBI (mean and median values for PTV/whole breast at 17.2% and 17.9% [range, 10.2%–24.3%], respectively).

### *Planning target volume and normal tissue dosimetry*

PTV_EVAL coverage was adequate, with at least a mean of 99% of the volume encompassed by the isodose of 40 Gy (Table 1). Mean dose to the PTV_EVAL was 41.8 Gy (range, 41–42.4 Gy). To evaluate the radiation dose to nontarget breast tissue, the ipsilateral breast volume excluding the PTV_EVAL was considered. Mean breast V20 Gy was at 44.1% (range, 22.8%– 55.3%). Mean nontarget breast V40 Gy and V20 Gy were at 8.8% (range, 2.9%–18.4%) and 33.1% (range, 7.7%–45.4%), respectively. Mean ipsilateral lung dose was 1.6 Gy (range, 1.0–2.3 Gy), and the V20 Gy was 0.4% (range, 0.0%– 1.3%). The mean heart dose was 1.2 Gy (range, 1.0–1.6 Gy).