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Review

Clinical and technological transition in breast cancer

Philip Poortmans[a], *Hugo Marsiglia*[b], *Manuel De las Heras*[c], *Manuel Algara*[d,*]

[a] *Radiotherapy Department, Institute Verbeeten, Tilburg, The Netherlands*
[b] *Radiotherapy Department, Instituve Gustave Roussy, Villejuif, France*
[c] *Radiotherapy Department, Hospital Clínico San Carlos, Madrid, Spain*
[d] *Radiotherapy Department, Parc de Salut Mar, Barcelona, Spain*

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ABSTRACT

This article is a summary of the conference "Clinical and technological transition in breast cancer" that took place in the Congress of the Spanish Society of Radiation Oncology, placed in Vigo (Spain) on June 21, 2013. Hugo Marsiglia and Philip Poortmanns were the speakers, the first discussed about "Clinical and technological transition" and the second about "EORTC clinical trials and protocols".

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1. Introduction

Technological advances lived in the field of radiation therapy (RT), over the last decades have led us to have volume delineation, dose calculation and treatment units toward much more accurate treatment. With them we get more appropriate radiation dose to the level we want to treat. This unquestioned fact has caused that these new technologies will be adopted as standard without demonstrating their superiority in clinical trials. On the other hand, for the advance in knowledge of volumes that should be treated, which dose should receive or the best suitable fractionation, we need to have sufficient scientific evidence to support our treatment protocols. In this article we review the introduction of new technologies and most relevant clinical trials that are changing clinical practice in irradiation of breast cancer patients.

2. Clinical and technological transition

Radiation oncology is a field that has rapidly advanced over the last century. It holds a rich tradition of clinical care and evidence-based practice, and more recently has advanced with revolutionary innovations in technology and computer science [1]. Perhaps the most attractive feature of recent technological advances is the ability to approach any complex tumor geometry, regardless of shape, with an enhanced ability to optimize the dose distribution.

* *Corresponding author at*: Radiation Oncology Department, Hospital de la Esperanza, San Jose de la Montana, 12 08024 Barcelona, Spain. Tel.: +34 933674144; fax: +34 933674271.
E-mail address: malgara@parcdesalutmar.cat (M. Algara).

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2.1. *Accelerated partial breast irradiation*

APBI can be successfully delivered using different radiation techniques (IMRT, brachytherapy, arc therapy, etc.) [2]. For instance, the University of Florence [3] evaluated with a randomized clinical trial the possibility of treating the index quadrant with IMRT in a selected group of patients with early-stage breast cancer. From 2005 to 2008, 259 patients were randomized and treated. The mean value of the ratio between the planning target volume and the ipsilateral breast volume was 21%. The rate of grade 1 acute skin toxicity was 22% and grade 2 was 19%.

Recent reports from the American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) have suggested selection criteria for "suitable patients" who could receive APBI outside of clinical trials [4]. Currently, there are 6 ongoing phase III trials. All are characterized by a significant heterogeneity regarding inclusion criteria and stratification factors. The French UNICANCER trial (SHARE; ClinicalTrials.gov identifier NCT01247233) will randomize 2800 patients in 3 arms: APBI (1 week) using 3-dimensional (3D) conformal radiotherapy, standard radiotherapy (6.5 weeks), and hypofractionated radiotherapy (3 weeks).

2.2. *Arc dynamic therapy*

Tomotherapy is a technique capable of delivering a well tolerated treatment with high homogeneity and coverage indexes and high capabilities for sparing the organs at risk [5,6], especially in patients with anatomically complex breast cancer, bilateral breast cancer or indication for internal mammary chain node irradiation. A Spanish report [7] described early clinical results of tomotherapy treatment in patients with breast cancer and complex treatment volumes. Ten patients were treated with tomotherapy between January 2009 and March 2010. All treatments included daily CT/megavoltage image guidance. The median homogeneity index was 1.09; and the median coverage index 0.81. Median V20 Gy and V10 Gy for ipsilateral lung was 20% and 37.1% respectively. Median V25 and V35 for heart was 15% and 4% respectively. Median dose for contralateral breast was 7 Gy. Skin acute toxicity was grade 1 in 41.7% and grade 2 in 58.3%.

Versmessen et al. [8] compared Health-related quality of life (HRQOL) in stage I–II breast cancer patients who were randomized to receive either conventional radiotherapy or hypofractionated tomotherapy. A total of 121 stage I–II breast cancer patients who had undergone breast conserving surgery or mastectomy were randomly assigned to receive either conventional radiotherapy or hypofractionated tomotherapy. Conventional radiotherapy patients received 25×2 Gy over 5 weeks, and breast conserving surgery patients also received a sequential boost of 8×2 Gy over 2 weeks. Hypofractionated tomotherapy patients received 15×2.8 Gy over 3 weeks, and breast conserving surgery patients also received a simultaneous integrated boost of 15×0.6 Gy over 3 weeks. Patients completed the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 and BR23 questionnaires. Hypofractionated tomotherapy patients had a better improvement in global health status and role- and cognitive-functioning, and a faster recovery from fatigue, than conventional radiotherapy patients. These results suggested that a shorter fractionation schedule may reduce the adverse effects of treatment.

2.3. *Intensity-modulated radiation therapy*

Intensity-modulated radiation therapy can reduce radiation dose exposure to normal tissues while maintaining reasonable target homogeneity [9]. Jin et al. [10] compared the dosimetry for the left-sided breast cancer treatment using different radiotherapy techniques. Twenty patients with left sided breast cancer were planned using five different radiotherapy techniques, including: 1) conventional tangential wedge-based fields (TW); 2) field-in-field (FIF) technique; 3) tangential inverse planning intensity-modulated radiation therapy (T-IMRT); 4) multi-field IMRT (M-IMRT); and 5) volumetric modulated arc therapy (VMAT). The planning tumor volume dose prescribed was 50 Gy and V47.5 $\geqq$ 95%. The same dose constraints were used for all five plans. The planned volumetric dose of PTV and organ at risk volumes (OARVs) were compared and analyzed. T-IMRT plan improved the PTV dose homogeneity index (HI) by 0.02 and 0.03 when compared to TW plan and VMAT plan, and decreased the V5, V10 and V20 of all OARVs. However, the high dose volume ($\geqq$30 Gy) of the OARVs in T-IMRT plan had no statistically significant difference compared with the other two inverse plans. In all five plans, the dose volume of coronary artery area showed a strong correlation to the dose volume of the heart (the correlation coefficients were 0.993, 0.996, 1.000, 0.995 and 0.986 respectively).

In order to increase the workload efficiency, a Canadian group [11] developed a template-based breast IMRT technique (TB-IMRT). TB- IMRT provided reduction of planning time compared with conventional breast radiation (14.0 vs 39.0 min, $p < 0.001$) and minimized the use of high energy beams, while providing similar treatment times and equal plans compared to conventional breast radiation.

2.4. *Brachytherapy*

The different indications of breast brachytherapy include all the breast irradiations focusing on the initial tumor bed (partial irradiation of the breast), such as boost, APBI and second conservative radiosurgical treatment in case of ipsilateral in-breast recurrence. Interstitial breast brachytherapy, performed according with the standard rules, remains a major technique for breast cancer treatment [12].

Partial breast brachytherapy and whole breast irradiation (WBI) has shown similar recurrence-free and overall survival rates in elderly breast cancer patients [13], even after adjustment for potential confusing factors. A sample of 29,647 female patients diagnosed with nonmetastatic breast cancer in 2002–2007 treated with breast-conserving surgery and radiotherapy was identified in the Surveillance, Epidemiology, and End Results Program-Medicare data set [13]. Recurrence-free survival and overall survival rates did not differ significantly between the two radiation modalities. After accounting for tumor characteristics, patient characteristics,

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