A Two-step Selection of Breast Cancer Patients Candidates for Exclusive IORT with Electrons: A Mono-institutional Experience

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Abstract. *Aim: To assess the impact of a two-step multiparameter selection on the actual enrollment of women with breast cancer into a prospective intraoperative radiotherapy (IORT) trial. Patients and Methods: From September 2009, a prospective clinical trial was started in order to deliver adjuvant exclusive single -fraction IORT to patients with early breast cancer. To select patients meeting suitable eligibility criteria for the clinical trial, a two-step decision process was developed: at pre-surgical examination (first step) and during surgery (second step). Results: A series of 464 patients with breast cancer was analysed: at the first step, out of 464 patients, 333 (71%) were considered eligible for the IORT protocol; at the second step, out of 333 patients, 199 (60%) met the eligibility criteria and received the IORT fraction according to the criteria of the controlled trial. Conclusion: In our experience, the ultimate rate of patients who enrolled in the IORT clinical trial after the two-step decision process was 43%.*

The standard of care for adjuvant therapy of early breast carcinoma includes whole breast irradiation (WBI) after conserving surgery in order to minimise the risk of local failure and thus ultimately improve disease-specific survival (1, 2). Although new validated hypofractionated schedules have been explored to shorten treatment, the delivery of WBI remains long lasting from three to six weeks, and may affect women's quality of life, whether in active young or in older patients (3-5). The evidence that more than 80% of the breast recurrences after breast irradiation occur mainly in the area of the primary tumour site (1, 2, 6) have led to clinical research to investigate whether it is possible to identify a group of patients that may benefit from tumour-bed radiotherapy alone administered in a few days or even in one day. Thus, over the past several years, the use of accelerated partial-breast irradiation (APBI) as an alternative to WBI has been increasingly explored (7). Intraoperative radiotherapy (IORT) is the only APBI technique that favours the performance of surgery and radiotherapy in the same day, offering a radiobiological advantage, minimizing the risk of repopulation of residual cancer clonogen cells before and during radiotherapy delivery; moreover, it is very convenient for the patients. APBI modalities such as IORT are now unlikely to replace WBI for all patients treated with breast-conserving surgery, it still being necessary to accurately select patient, as indicated by ASTRO and ESTRO recommendations (8, 9).

The purpose of this investigation was to assess the rate of women with early breast cancer who, selected before and during surgery for IORT strategy according to a prospective monoinstitutional protocol, actually received the proposed single-shot radiation treatment. The different decision steps followed to fully assess the eligibility for IORT protocol are described and discussed.

Patients and Methods

In September 2009, we started a prospective pilot study aimed to explore the feasibility of two different single doses of IORT for patients with early breast cancer (NIH trial number: NCT 01276938 registered at www.clinicaltrials.org). IORT with electron beam was delivered by a mobile linear accelerator (LIAC; Sordina s.p.a. Padua, Italy). The prospective trial was started after approval of the Ethical Board Committee at the National Cancer Research Institute, Genoa, Italy. The criteria adopted in this protocol for eligibility are shown in Table I.

According to the pilot study two different IORT doses (18 and 21 Gy) were administered on the basis of primary breast tumor size. According to recent radiobiological data (10), the nominal single dose of 21 Gy in one fraction was proposed for patients at higher risk of

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Key Words: Breast cancer, intraoperative radiation therapy, decision process.

Table I. *Eligibility criteria for Genoa prospective trial of intraoperative radiotherapy.*

Parameter	Favourable condition
Age	>45 years
Histology	Invasive not lobular carcinoma no extensive (<25%) intraductal component
Tumor size	≤2.5 cm
Nodal status	Negative
Surgical margins	Negative (>5 mm)
Follow up	Patient's availability
Radiological examinations	Patient's availability
Informed consent	Obtained

local relapse (high risk: pT2-pT1c), while the lower dose of 18 Gy in one fraction (equivalent to the dose of conventional radiotherapy of 60 Gy in 30 fractions) was investigated to control lesions with a maximum diameter less than or equal to 1 cm (low-risk patients: pT1a-pT1b). The patients treated out of protocol received 21 Gy as standard indicated by others (10, 11). The delivery of IORT technique adopted in our institute has been described in detail by other authors (11, 12).

Eligibility criteria for IORT were evaluated at two different decisional steps, at pre-surgery and intrasurgery. The first decisional step was soon after diagnosis and staging in order to consider the potential to enroll the patients in the trial or to treat them off protocol. The second decisional step was during the surgical procedure to confirm the indication for exclusive IORT according to the pathological data about tumor and lymphnode specimens. The patients not included in the pilot study were considered suitable for either exclusive 21 Gy IORT off protocol or 10 Gy IORT boost plus external WBI schedule (36 Gy/12 fractions).

The main aim of this investigation was to evaluate the rates of women who actually received exclusive IORT according to eligibility criteria after the two-step decision process.

Results

From September 2009 to December 2011 at our Radiotherapy Department, a total number of 464 breast cancer patients (age: range 45-89 years) were seen at the first decisional step as candidates for receiving exclusive IORT soon after conservative surgery. The different decisions assessed after the two-step decision-making process are shown in Table II. At the first decisional step, 107 patients (23%) were considered for IORT but not included in the pilot study protocol, either due to not complete meeting the selection criteria (Table IV), or to unsuitability for WBI (Table III). Seven patients (1.5%) submitted to nipple-sparing mastectomy were considered for exclusive IORT with a total single dose of 16 Gy to the nipple areolar complex (NAC) in order to reduce the risk of local recurrence in this area. Seventeen patients (3%) conservatively operated on for local relapse after a previously conservative treatment, including previous radiotherapy, were irradiated with IORT (18 Gy) to the tumour bed to allow physiological anatomy of the breast to be maintained. After the second decisional step, out of the remaining 333 patients who initially met the protocol criteria, only a group of 199 (60%) was indeed included in our pilot study. A subgroup of 50 patients (15%) evidenced poor features on examination of frozen specimen sections and received IORT as boost. Eighty patients (25%) were considered at the second decisional step as being ineligible for exclusive or boost IORT due to technical problems. Out of the remaining 199 patients who fully entered the protocol according to the previously mentioned considerations an exclusive IORT dose of 21 Gy or 18 Gy were delivered, respectively, in 134 (67%) patients with higher (pT1c-pT2) and in 65 (33%) patients with lower (pT1a-pT1b) risk of local relapse. The ultimate rate of patients who enrolled in the IORT clinical trial after the two-step decision process was 43%.

Discussion

IORT with electrons is an innovative strategy for adjuvant radiotherapy based on giving the radiation dose to the surgical field immediately after the breast tumour is removed. This technique has the advantage of the integration of the radiation treatment into the surgical procedure, when the breast tissue still has a rich vascularization that makes it more sensitive to the action of the radiation (oxygen effect) and before tumour stem cells have had a chance to proliferate. Moreover the precise application of one single high dose of irradiation directly to the tumour bed with complete skin sparing has the great advantage of shortening the radiotherapy time from 5-6 weeks to one single fraction. Although advanced results appear promising (11), irradiation using IORT requires careful selection of patient candidates for this technique in order to avoid the risk of local recurrence. The aim of this report was threefold: i: to investigate, among all the women with breast cancer who were possible candidates for IORT, the actual number of women who met the eligibility criteria for a monoinstitutional prospective trial designed to assess the feasibility of two different radiation single doses; ii: to evaluate the groups of patients who did not meet eligibility criteria before and during surgery, by analysing in detail the reasons for ineligibility; iii: to assess the clinical conditions where IORT may be indicated for women who are unsuitable for WBI.

A two-step decision process was designed in order to select patients for adjuvant IORT. The first-step selection was carried out during the first visit of the patients with breast cancer: the parameters considered at this phase were the size of the tumour (at clinical and radiological examination) and other specific features evident from mammography, ultrasound and magnetic resonance imaging; breast size, site of the tumour and technical feasibility of IORT were also considered. On the basis of clinical and histological parameters, a first selection of patients candidate to be enrolled in the prospective protocol was made by carefully considering the adherence to the

Table II. *Different strategies taken after the two-step decisional process for patients candidate for exclusive intraoperative radiotherapy.*

Clinical assessment and strategy	Number of patients (%)	Decisional step
Overall evaluation for IORT	464 (100%)	1
Off protocol IORT as exclusive treatment	107 (23%)	1
IORT for NAC in NSM	7 (1.5%)	1
IORT for re-treatments	17 (3.5%)	1
No IORT (deferral to external WBI)	84 (18%)	2
IORT as boost + WBI	50 (11%)	2
IORT at two different dose levels according to prospective trial	199 (43%)	2

IORT: Intraoperative radiotherapy; NAC: nipple areola complex; NSM: nipple sparing mastectomy; WBI: whole breast irradiation.

Table III. *Patients unsuitable for (WBI) who were considered at the first decisional step as being suitable for exclusive IORT outside of the prospective clinical trial.*

Criteria	Number of patients
Elderly >85 years	8
Concomitant metastatic disease	5
Severe concomitant disease	9
Concomitant neurological disease (difficulties in keeping the set-up position)	3
Psychiatric disease (exempli gratia: schizophrenia, psychosis)	4
Presence of clinical devices affecting WBI delivery (exempli gratia: cardiac pacemaker, deep neurostimulatory devices)	3
Total	32

eligibility criteria. A group of patients who did not meet the eligibility criteria (due to age, co-morbidity, psychiatric and neurological disease) were equally considered for IORT in an off protocol setting if some contraindications (age, suboptimal performance status, distance between home and radiotherapy centre) for WBI were assessed. The second decisional step was performed during the surgery soon after excision of the primary breast tumour. The histological examination of frozen specimen sections provides additional data for suitability of IORT delivery: histology not lobular without extensive intraductal carcinoma (EIC), not ductal carcinoma in situ (DCIS), negative margins of resection (at least 5 mm free margins) and negative node status.

Our analysis showed interesting results. As shown in Table II, after the two-step decision process, ot the 464 patients submitted to our Department for adjuvant IORT, only 199 (43%) were included in a prospective controlled clinical trial by indeed meeting the eligibility criteria. At the first step decisional process, out of 464 patients, 333 (71%) were considered eligible for IORT protocol. The remaining 131(29%) patients were excluded from the protocol but were submitted to IORT due to different indications: 107 were considered unsuitable for WBI, 7 patients were treated in a nipple-sparing mastectomy procedure and 17 patients were selected for IORT after a previous radiotherapy delivered to the ipsilateral breast. At the second step decisional process, out of 333 patients, 199 (60%) met all the eligibility criteria and received the IORT at one of two different doses according to the pilot trial. Fifty patients (15%) received IORT boost and were then planned for hypofractionated WBI according to institutional protocol. The remaining 84 (25%) patients did not receive exclusive IORT nor IORT boost since unexpected surgical and histological features were assessed at surgery.

Table IV. *Patients considered for exclusive (IORT) at the first decisional step although not eligible for Genoa prospective trial of IORT.*

Criteria	Number of patients
Second primary breast cancer	32
Previous or synchronous secondary cancer	22
Lobular histology	3
Bilateral breast cancer	1
Positive clinical nodes	9
DCIS histology or DCIS >25%	3
Uncertain histology	3
Multifocality	2
Second surgery for previous positive margins	2
Total	77

DCIS: Ductal carcinoma *in situ*.

Our results, although preliminary, allow us to discuss some issues strictly related to the more appropriate use of IORT in clinics. The first issue is the need to clearly identify patients

who are unsuitable for IORT, according to ASTRO and ESTRO consensus (8, 9), considering also that basing the decision on histological features is not applicable for the IORT procedure because of the lack of biological parameters, unless a biopsy is performed before surgery. However, out of the 333 patients selected for the IORT protocol after the first decision of step, 134 (40%) were excluded at the second step because of the evidence of adverse prognostic parameters for this radiation technique. This means that our procedures may be useful to further select patients who may fully benefit from exclusive IORT. A longer follow-up will permit the actual clinical efficacy of our procedure to be assessed in the patients enrolled in the prospective protocol. In the meantime, in our experience, IORT appeared to play an interesting role in women in whom WBI appears to be difficult or not convenient. Moreover, the IORT option appears to be applicable for women previously irradiated to the same breast who are willing to be treated with a conservative surgical approach. The indications of IORT for nipple-sparing mastectomy are too preliminary in our experience to be discussed. We believe that a two-step decision process may be useful for carefully selecting patients for exclusive IORT. In our experience, among all the women candidates for IORT, the rates of patients who met the eligibility criteria for exclusive IORT prospective trial after the first pre-surgical decisional step and the second intrasurgical decisional step were 71% and 60% respectively. Therefore, the ultimate rate of patients who enrolled in the controlled clinical trial was 43%.

In conclusion, an accurate selection of patients with breast cancer as candidates for exclusive IORT is strongly needed. An advanced multistepdecision process including the analysis of biological or molecular parameters affecting prognosis after surgery and IORT is hopefully warranted.

Conflict of Interest

None.

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Received February 9, 2012
Revised March 12, 2012
Accepted March 13, 2012