

IORT in breast cancer.

Our experience of the first patients treated



Ann. Ital. Chir., 2017 88, 3: 253-257
pii: S0003469X17026793

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AIM: The aim of this study was to assess the therapeutic effect of intraoperative radiotherapy, describe the method and examine the results of our experience.

BACKGROUND: Breast conserving therapy has recently become a standard treatment modality in patients with early invasive cancer. Radiotherapy, along with surgery, is an integral part of such treatment. The important thing of radiotherapy is to deliver a high dose to the tumour bed. One of the methods is the intraoperative radiotherapy.

MATERIALS AND METHODS: The analysis comprised 41 breast cancer patients treated with breast conserving surgery. Patient's range age was 35-80 years. Cancer type distribution included: 95% ductal carcinoma, 5% other carcinoma. Applicator size: 4 cm. (12%), 5 cm. (64%), 6 cm. (17%), 7 cm. (7%). Electron energies: 6 MeV (22%), 8 MeV (56%), 10 MeV (22%). Intraoperative radiation therapy was delivered in the operating theatre during surgery. After that, all patients were treated with whole breast irradiation.

RESULTS: 41 patients treated with IORT procedures completed. In general there were no severe postoperative complications and we did not detect tumor recurrence in any patient even if the time elapsed from the treatment is still short.

CONCLUSIONS: Due to its exceptional physical and radiobiological properties, intraoperative radiation therapy can be a good alternative to other methods of boosting dose to the postoperative site in management.

KEY WORDS: Breast cancer, IORT, intraoperative radiotherapy, Surgery

Introduction

Breast cancer is the most common malignant neoplasm in women and the third cause of death in Europe. Treatment of early breast cancer consists of breast conserving surgery (BCS), typically in combination with axillary sentinel lymph node biopsy (SNB) followed by external beam whole breast radiotherapy (EBRT). Furthermore, chemotherapy, endocrine and targeted therapies play an important role in the treatment of breast

cancer. The therapeutic approaches chosen depend on the patient, as well as the clinical and pathological parameters of the tumour; such as stage, presence of hormone receptors and other biological characteristics. Intraoperative radiotherapy (IORT) is able to minimise this risk of missing the target and to shorten the interval between tumour excision and the beginning of the adjuvant radiotherapy¹.

Methods

From October 2012 to September 2016, 41 patients with breast cancer were underwent to IORT with mood boost anticipated. From September 2016 we followed the HIOB protocol and others patients were underwent to IORT. The choice of patients were based on internal

Pervenuto in Redazione Novembre 2016. Accettato per la pubblicazione Febbraio 2017

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protocol with eligibility criterias published by a IORT team (radiotherapists, surgeons, radiologists and pathologists) after analysis of national and international guidelines regarding this procedure. Inclusion criteria were T2N1Mmi, G1-G2-G3, unifocal invasive carcinoma (biopsy-proven), size ≤ 3 cm., non-metastatic disease, negative axillary lymphonodes for macro metastasis and age ≥ 35 years old. Neoadjuvant treatments were not allowed before surgery. Patients' range age was 35–80 years. Local evaluation (mammography, breast ultrasound, MRI,) evaluated precisely the diameter of the tumor. Prior to use, mechanical stability, dose rate and homogeneity of the emitted radiation were checked in detail. The patients received a perioperative intravenous single shot antibiotic treatment with 2 g cefazolin. After informed consent was given from every woman in whom radiotherapy was planned, the surgical and radiotherapeutic procedures were performed as a standardized operating procedure. Axillary lymph node dissection was performed using a sentinel lymph node procedure in all cases. Tumor-free margins of at least 2 mm were assessed by frozen sections. Nodes were analyzed by intraoperative imprint cytology and only after negative extemporaneous examination we proceeded in IORT procedure. The tissue surrounding the excision cavity was then mobilized and approximated by sutures to bring it into the radiotherapy planning target volume. Our procedure has provided a first time of IORT with delivery of a single high dose of 10 GY of radiation therapy on



Fig. 1

tumor bed followed by a treatment of external radiation therapy (RTE) body breast residual (WBI) of 50 GY (200 CGY/fraction). Dose IORT was delivered with LINAC – SORDINA, an accelerator mobile electron and the prescribed dose was of 10 Gy. External radiotherapy was delivered with a LINAC- VARIAN with photon energy 6-15 mv, with total dose of 50-56 Gy and dose fraction of 2 Gy. The technique for planning was 3D conformal through use of two camps bribery isocentric. (Table I, II)

The radiation oncologist identified visually the tumor bed and, together with the surgeon, with multiple measurements by needle millimeter. A semi-conductor detector (PTW) was placed in the middle of the tumor cavity and fixed to proceed to an in vivo dosimetry. The applicator tubes were then placed under visual control. The size of applicator was chosen according to size of clinical T assessed by RMI. (Table III, Fig. 1). Protection radiation disc always was armed and used with diameter of 2 cm. longer respect to the applicator diameter.

The energy has been selected based on the depth of the breast tissue surrounding the resection cavity, mobilized to fill the same. (Table IV) The depth was measured by means of a needle inserted millimeter several times in this tissue until touching the radiation protection disc. The radiation protection disc as stated by the manufacturer is always inserted and used with the diameter of 2 cm. greater than the diameter of the applicator.

TABLE I

Pz	Dose Total RTE	Dose Fraction RTE
40	DT 50 GY	DF 200 CGY
1 *	DT 56 GY	DF 200 CGY

*DT of 56 Gy was necessary for critical study of microscope margins

TABLE II

Pz	Mv RTE
36	6
3	6-15
2	15

TABLE III

Pz	Applicator Size
5	4 cm
26	5 cm
7	6 cm
3	7 cm

TABLE IV

Pz	MeV ENERGY IORT
23	8
10	6
5	10

Results

In general the method was well tolerated, there were no severe postoperative complications and we did not detect tumor recurrence in any patient even if the time elapsed from the treatment is still short. Surgical parameters of the patients are presented in details (Table V, VI, VII).

TABLE V

Pz	Grading
1	G1
29	G2
11	G3

TABLE VI

Pz	Istological Types
37	Ductal Carcinoma
1	Mucinous Carcinoma
1	Duttal And Lobular Carcinoma

TABLE VII

Pz	TNM	
20	T1c NO	IA
4	T1c N1	IJA
1	T1c N1a	IJA
1	T1c N1b	IJA
5	T1c N1mi(sent)	IB
1	T1a N0	IA
5	T1b N0	IA
1	T1b N1mi(sent)	IB
1	T2 N0	IIB
1	T2 N1mi (sent)	IIB
1	T2 N1a	IIB

Discussions

Intraoperative radiotherapy (IORT) is a procedure in which ionising radiation is administered during surgery. The technique involves the precise application of a high dose of radiation to the target volume area or region of interest, with minimal exposure to healthy tissue, which can be displaced and/or protected during the procedure. IORT is driven by a multidisciplinary approach in cancer treatment and emphasises the interaction between

surgery and radiation, thus reducing the chances of a residual tumour, favouring effort at the surgical resection. This implies a minimisation of the tumour burden, maximising the radiobiological effects of a single dose and high irradiation. Its use as a component of treatment in combination with other modalities (radiotherapy, chemotherapy, maximal surgical resection) is feasible and practical if such multidisciplinary cooperation is close and coordinated. The use of IORT is based on the greater radiologic effect of 10Gy administered in a single dose rather than in 5 doses ³.

In the treatment of breast cancer in early stages breast conserving therapy is a generally accepted treatment philosophy: local control and survival data are the same as after mastectomy. The additional aim of breast conserving therapy is to treat patients with breast cancer without mutilation and simultaneously with optimal cosmetic results, as far as possible. Radiation therapy to the whole breast after breast conserving surgery is the standard treatment in the conservative approach and its value has been established in many retrospective studies as well as prospective randomised trials ². Interest in the role of accelerated partial breast irradiation (APBI) in the management of breast cancer has been growing. The rationale behind this approach is that the majority of local recurrences in the breast occur in the index quadrant whether radiotherapy is given or not. Therefore, "occult cancers" in other quadrants are probably not the cause of local recurrence and radiotherapy to the index quadrant alone maybe sufficient. The aim of APBI is to decrease the volume of breast irradiated whilst increasing the dose per fraction (hypofractionation). A number of different techniques can be used for partial breast irradiation, including linear accelerator (LINAC)-based intensity modulated radiotherapy, interstitial brachytherapy, MammoSite and intra-operative radiotherapy (IORT) ⁴.

Veronesi et al. reported the 5.8-year follow-up results of a randomized controlled equivalence trial comparing IORT with electrons and external radiotherapy (EBRT) for early breast cancer (ELIOT) in 1305 patients. They concluded that accelerated partial breast irradiation (APBI) using the IORT technique resulted in a significantly higher ipsilateral breast tumor recurrence (IBRT) of 4.4 % compared to 0.4 % in the whole-breast irradiation group. However, the differences in survival were not reported and the adverse events to the skin were significantly fewer in the IORT group ⁵⁻⁶.

Semiannual or annual diagnostic mammography is routinely utilized to screen for local recurrence of breast cancer after breast-conserving surgery. Since the majority of these recurrences appear within the first 5 years postoperatively, a mammographer's challenge is to distinguish between the seminal parenchymal changes associated with cancer recurrence and the usual treatment-related changes that may evolve in the initial years following breast-conserving therapy. The growing popular-

ity of APBI, in general, and IORT, in particular, has led physicians to question whether administration of focused, high-dose radiation to the tumor bed might produce parenchymal changes that could interfere with mammographic surveillance of cancer recurrence or lead to excessive diagnostic or invasive procedures to evaluate mammographic findings. There are only a few published papers describing the radiographic appearance of the breast following IORT. With each, investigators observed varying degrees of fat necrosis and parenchymal scarring, likely related to the technique of IORT delivery. IORT and WB-EBRT have an almost equivalent potential to affect mammographic interpretation and that IORT does not disproportionately impair mammographic surveillance for breast cancer recurrence ⁷.

External-beam radiotherapy (EBRT) of the breast after breast conserving surgery (BCS) reduces the local breast tumour recurrence rate from 25-30% to less than 10% at 10 years. However, it is still a problem to find the optimal therapy modality for the remaining 10% of breast cancer patients presenting with a tumour recurrence years after BCS and EBRT. The normal tissue tolerance does not allow, even after years, a second full-dose course of radiotherapy to the entire breast after a second BCS. Especially for patients with small, localized recurrences, in whom a local excision would technically be possible, mastectomy is generally preferred over BCS for fear of worse outcome due to omission of radiotherapy. This is particularly unsatisfying, because recurrent breast tumours, with increasing advances in diagnostic modalities and regular follow-up visits, are often diagnosed at a very small tumour size. Furthermore, the most common and survival-limiting problem for these patients is usually not the local situation within the breast, but the increased risk of developing distant metastases. A novel option is to treat these patients after re-resection of the recurrent tumor with partial breast irradiation (PBI). This approach is based on the hypothesis that reirradiation to a limited volume will be effective and result in an acceptable frequency of side effects. Intraoperative radiotherapy is one option to deliver high doses to a restricted area at risk i.e. the adjacent tissue to the tumour cavity after tumour resection. IORT can be delivered with dedicated linear accelerators in the operation room or novel mobile devices using electrons or low-energy x-rays ⁸.

Conclusions

Intraoperative radiotherapy can replace other methods of boost in breast conserving therapy. This method is safe and leads to the shortening of therapy time as compared to electron or photon boost. Radiotherapy boost during surgery not only enables good local control without geographic miss of the tumour, but also delivers good cosmetic effect after therapy

Riassunto

Il trattamento di scelta del carcinoma mammario non avanzato si fonda sull'associazione tra chirurgia conservativa e radioterapia (QUART); quest'ultima ha lo scopo di sterilizzare eventuali focolai neoplastici subclinici della mammella operata o residui neoplastici subclinici del letto operatorio. L'efficacia della radioterapia è dimostrata dal fatto che l'omissione del trattamento adiuvante dopo l'intervento si correla con recidive locali frequenti (17-39%) mentre dopo radioterapia le recidive locali non superano il 7%.

La radioterapia a tutta la mammella dopo chirurgia conservativa rappresenta il trattamento standard e il suo valore è stato stabilito in molti studi retrospettivi e studi prospettici randomizzati. L'interesse per il ruolo di irradiazione parziale della mammella (PBI) nella gestione del carcinoma mammario è in crescita. La logica alla base di questo approccio è che la maggior parte delle recidive locali nel seno si verificano nel quadrante operato. Lo scopo di PBI è quello di diminuire il volume del seno irradiato ed aumentare la dose per frazione (ipofrazionamento). Un certo numero di tecniche può essere utilizzato per l'irradiazione parziale della mammella; tra queste la radioterapia intraoperatoria (IORT). Questa è una procedura in cui le radiazioni ionizzanti sono somministrate durante l'intervento chirurgico. La procedura consiste nell'escissione del nodulo neoplastico e nello scollamento dalla cute e dal muscolo pettorale di un ampio tratto di parenchima mammario circostante al cavo chirurgico, che poi viene provvisoriamente riaccollato, in modo da favorire l'irradiazione radiale dell'area prossima alla sede della neoplasia. Per proteggere gli organi critici sottostanti (pleura, polmone e cuore) viene provvisoriamente collocato, tra muscolo pettorale e tessuto ghiandolare, un disco di piombo in grado di attenuare l'assorbimento degli elettroni. La breccia chirurgica viene quindi chiusa per ricostruire temporaneamente l'integrità della ghiandola mammaria e misurarne lo spessore tramite un ago millimetrato al fine di selezionare l'energia di elettroni ottimale da erogare. A questo punto della procedura l'applicatore selezionato viene inserito nella breccia chirurgica e viene somministrata la radiazione programmata.

Da ottobre 2012 a settembre 2016, 41 pazienti con carcinoma mammario sono stati sottoposti a IORT con boost anticipato. I criteri di inclusione individuati sono stati: T2N1Mmi, G1-G2-G3, carcinoma invasivo unifocale, dimensioni ≤ 3 centimetri, malattia non metastatica, linfonodi ascellari negativi per macrometastasi ed età ≥ 35 anni. Le pazienti sottoposte a trattamenti neoadiuvanti non sono state arruolate. La nostra procedura ha previsto in un primo momento la erogazione di una singola dose elevata di 10 Gy di terapia radiante sul letto tumorale mediante IORT, seguito da un trattamento di irradiazione esterna (RTE) della mammella residua (WBI) di 50 Gy (200 CGY / frazione). Nella nostra

esperienza il metodo è stato ben tollerato, non ci sono state gravi complicanze postoperatorie e non abbiamo rilevato recidive tumorali in tutte le pazienti, anche se il tempo trascorso dal trattamento è ancora breve.

In conclusione si può affermare che i vantaggi della metodica IORT siano soprattutto: visualizzazione diretta ed accurata determinazione dell'area da irradiare; aumento dell'indice terapeutico locoregionale, cioè del rapporto fra dose tollerata dai tessuti sani e dose letale per il tumore, erogando al tumore la maggior dose curativa e ai tessuti sani quella minima possibile; brevità del tempo di trattamento; maggior effetto radiobiologico somministrando un'alta quantità di energia in una singola dose piuttosto che in molte dosi.

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