An investigational protocol of intraoperative radiotherapy in the treatment of early-stage breast cancer: partial results from the Hospital Israelita Albert Einstein

Uso da radioterapia intra-operatória (IORT) como protocolo de investigação no tratamento do câncer de mama inicial: resultados parciais do Hospital Israelita Albert Einstein

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ABSTRACT

Objective: To describe and assess the experience of the Hospital Albert Einstein on the treatment of early-stage breast cancer with intraoperative radiotherapy. Methods: Twenty-two patients with invasive breast cancer, older than 45 years, with tumors ≤ 2.5 cm and with clinically normal axillary lymph nodes at intraoperative evaluation, who underwent quadrantectomy with sentinel lymph node biopsy and intraoperative radiotherapy. Clinical characteristics, histological findings and intraoperative radiotherapy technique were assessed. Results: The mean age of patients was 60.4 years and 90.9% of them were post-menopausal. Mean tumor diameter was 1.5 cm, with 81% being of the invasive ductal type; 89% were hormonal receptor positive and Her-2/neu negative. Clinical stage I was found in 86.4%. Sentinel lymph node was negative in 81.8%. The radiation dose was 21 Gy in all patients, with a mean radiation time of 9.65 minutes, mean surgery time of 234 minutes and mean depth of breast tissue irradiated of 1.72 cm. Conclusion: Our preliminary results are similar to those of the literature, demonstrating that intraoperative radiotherapy is a feasible technique in our setting, safe and equivalent to conventional external beam radiotherapy, with potential radiobiological, technical, clinical, psychosocial and economic advantages.

Keywords: Breast neoplasms/surgery; Breast neoplasms/ radiotherapy

RESUMO

Objetivo: Descrever e avaliar a experiência inicial do uso da radioterapia intra-operatória no tratamento do câncer de mama inicial no Hospital Israelita Albert Einstein. Métodos: Foram estudadas 22 pacientes com carcinoma de mama invasivo, idade ≥ 45 anos, tumor ≤ 2,5 cm e axila clinicamente negativa à avaliação intra-operatória, submetidas a cirurgia conservadora com exérese do linfonodo sentinela e radioterapia intra-operatória. As pacientes foram avaliadas quanto às características clínicas, anatomopatológicas e técnicas da radioterapia intra-operatória. Resultados: A média de idade das pacientes foi de 60,4 anos, sendo 90,9% pós-menopausadas. O diâmetro tumoral médio foi 1,5 cm, sendo 81% dos tumores do tipo ductal invasivo. Em 89%, os receptores estrogênicos e/ou progestagênicos foram positivos e o Her-2/neu foi negativo. O estadiamento clínico das pacientes era I em 86,4%. O linfonodo sentinela estava livre de neoplasia em 81,8%. A dose de radiação foi de 21 Gy em todas as pacientes, com tempo médio de irradiiação de 9,65 minutos, tempo médio de cirurgia de 234 minutos e profundidade média de tecido irradiado de 1,72 cm. Conclusão: Nossos dados iniciais são semelhantes aos da literatura, demonstrando que a radioterapia intra-operatória é uma técnica factível em nosso meio, segura e com potencial equivalente à radioterapia externa convencional, com benefícios radiobiológicos, técnicos, clínicos, psicológicos e econômicos.

Descritores: Neoplasias mamárias/cirurgia; Neoplasias mamárias/ radioterapia

INTRODUCTION

The treatment of breast cancer is becoming ever more conservative, and encompasses breast-sparing surgeries (quadrantectomy, segmental mastectomy and lumpectomy) and axillary staging by means of sentinel...
lymph node (SLN) biopsy, with cosmetic benefits and improvement in the quality of life of patients due to the lower risk of major ipsilateral upper limb edema, which is associated to conventional axillary lymphadenectomy.

The rate of cure is also similar to that achieved with radical surgical treatment; however, it is necessary to associate external beam radiation treatment to the breast-sparing surgery for four to six week, in order to achieve such results\(^{(1-4)}\).

In patients who underwent breast-sparing surgery and radiotherapy, 65 to 100% of local tumor recurrences occurred in areas adjacent to the previous segmental excision site, and only few cases showed recurrence in other breast quadrants. Thus, partial breast irradiation may have results equivalent to total external beam irradiation in cases of breast-sparing surgery, with the added benefits of being administered in a single dose, having lower cost and less side effects\(^{(1-4)}\). There are several studies with different partial irradiation modalities of the breast, such as low or high dose brachytherapy, hypo- or hyper-fractioned localized external beam irradiation, all aimed to minimize irradiation time and maintain the historical rates of local recurrence associated to conventional external beam irradiation. Such models of partial treatment are being assessed in a phase III trial, in a joint collaboration of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG), protocol coded as NSABP B-39/RTOG 0413\(^{(6-7)}\).

Single dose electron beam intraoperative radiotherapy (IORT) was assessed for its radio-bioequivalent dose to the conventional external beam irradiation treatment according to theoretical models of acute and late complications for each tissue (alpha/beta - \(\alpha/\beta\) effect or ratio), and it is currently a therapeutic option in investigation, with phase I and II studies demonstrating its safety for the treatment of breast cancer; however, there is little information comparing the results of external beam radiotherapy with IORT\(^{(8-9)}\).

Orecchia and Veronesi, in Milan, are currently conducting a phase III trial comparing single dose IORT with conventional external beam radiotherapy, according to preliminary results published\(^{(9)}\).

The primary objective of the present study is to describe and to assess the initial experience of implantation and application of IORT in the treatment of early-stage breast cancer at the Hospital Israelita Albert Einstein (HIAE), and the secondary objective is to assess the initial short term results.

**METHODS**

Twenty-two patients with invasive unicentric breast cancer, with tumors with clinical diameter equal to or smaller than 2.5 centimeters, negative axillary clinical staging, and age equal to or greater than 45 years, perimenopausal were selected.

All patients underwent clinical examination, preoperative laboratory tests, systemic clinical staging tests, when appropriate, and breast imaging, encompassing: routinely, palpation, mammography and ultrasonography, and, when appropriate, breast magnetic resonance and PET-CT.

The following patients were excluded from the study: individuals with multicentric tumors at the diagnostic assessment, or confirmed intraoperatively; whose tumor diameter was greater than 2.5 centimeters at surgery; with extensive intraductal component (greater than 20% of tumor volume, by definition); with metastasis to other sites; with active collagen diseases (lupus, scleroderma, dermatomyositis); with life expectancy of less than two years due to co-morbid conditions; and with more than one axillary sentinel lymph node macroscopically involved at surgery.

Conventional conservative surgery was performed, with tumor resection with free margins and sentinel lymph node (SLN) excision, with intraoperative histological examination of the margins and the SLN. All microcalcifications identified by the diagnostic mammography were excised and confirmed at the surgical procedure and prior to the single dose irradiation.

After surgery was performed, a lead disk was placed over the pectoral muscles and under the area of excised parenchyma and the glandular tissue surrounding this area was sutured over the disk (figure 1). The patient was then sent to the radiotherapy room, the collimator, with diameter of at least 45 mm (considering the theoretical recurrence risk radius of 2 cm of the tumor bed), was positioned with measurement and angle appropriate for each case, and radiotherapy was done with electron Figure 1. Inserting a lead disk under glandular tissue
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RESULTS

Twenty-two surgical procedures with intraoperative therapy were performed in 22 patients. Their mean age was 60.4 years. Regarding the menopausal status, 90.9% of patients (n = 20) were post-menopausal and only 9.1% (n = 2) were peri-menopausal (table 1).

Table 1. Characteristics of patients submitted to IORT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean age</td>
<td>60.4 years</td>
</tr>
<tr>
<td>Status</td>
<td>Postmenopausal – 90.9% (n:20)</td>
</tr>
<tr>
<td>Menopausal</td>
<td>Perimenopausal – 9.1% (n:2)</td>
</tr>
<tr>
<td>Mean tumor diameter</td>
<td>1.5 cm (0.8 to 3.5 cm)</td>
</tr>
<tr>
<td>Mean number of sentinel lymph nodes</td>
<td>1.6</td>
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</table>

Mean tumor diameter was 1.5 cm, ranging from 0.8 to 3.5 cm (the tumor with 3.5 cm in diameter corresponded to a 2.5 cm invasive tumor added to an in situ lobular carcinoma, only diagnosed histopathologically). Eighty-one percent of tumors were ductal invasive, 9.5%, lobular invasive, and 9.5%, of other histological types (one tubular carcinoma and one mucinous carcinoma). Regarding tumor localization, 36.4% were in the upper-lateral quadrant, 31.5%, in the lower-lateral quadrant, 31.5%, in quadrant junction; 68.2% of tumors occurred in the left breast and 31.8% in the right breast.

Immunohistochemistry of tumor specimens was performed in 18 cases, and in 16 of them (89%), estrogen and/or progesterones receptors were positive and in only 2 cases (11%), hormone receptors were not expressed. Most tumors (89%) did not hyper-express Her-2/neu.

In the cases of invasive ductal carcinoma (n = 18), 50% were of histological grade III, 28%, grade II, and 22%, grade I.

As for clinical staging, 86.4% of patients (n = 19) were stage I and 13.6% (n = 3), stage IIa.

SLN was identified in all cases, and a mean of 1.6 lymph nodes/patient were excised. In 18 patients (81.8%) the SLN was tumor-free and in only 4 patients (18.2%), the SLN was positive for metastasis, when a complete axillary lymphadenectomy was performed. In the positive SLN cases, 2 were isolated macro metastasis, of patients with either a T1c tumor or a T2 tumor, and micrometastasis in other two patients, one with a T1b tumor and another with a T1c tumor. In these four cases in whom complete axillary lymphadenectomy was done, the SLN was the only affected lymph node, and the remaining lymph nodes excised were tumor free. The decision of doing single dose irradiation when the SLN was positive was made due to the prognostic controversy about the detection of micrometastasis, impacting on the indication of adjuvant chemotherapy and complementary axillary dissection, and in those with macrometastasis, the evidence of no additional axillary lymph nodes affected.

In the original protocol of Orecchia and Veronesi, axillary...
irradiation was performed even with up to three lymph nodes affected\(^{(9)}\).

Regarding the technical characteristics of IORT, the radiation dose was of 21 Gy in all patients, with a mean irradiation time of 9.65 minutes, mean surgical time of 234 minutes, mean irradiated tissue depth of 1.72 cm (0.9 to 2.4 cm) and the cone utilized was 4.5 cm in diameter in 50% of cases, 5.1 cm, in 13.6% and 5.7 cm, in 36.4% (table 2).

No short-term complications of surgery or IORT were observed in all cases.

**Table 2.** Technical characteristics of IORT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean irradiation time</td>
<td>9.65 min (7.56 to 11.85 min)</td>
</tr>
<tr>
<td>Mean surgical time</td>
<td>234 min (120 to 330 min)</td>
</tr>
<tr>
<td>Irradiation dose</td>
<td>21 Gy</td>
</tr>
<tr>
<td>Cone (diameter used)</td>
<td>4.5 cm: 50% of cases</td>
</tr>
<tr>
<td></td>
<td>5.1 cm: 13.6% of cases</td>
</tr>
<tr>
<td></td>
<td>5.7 cm: 36.4% of cases</td>
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**DISCUSSION**

Supported by the results of the NSABP – B06 and Milan I, II and III trials, breast-sparing surgery has become the treatment of choice for early-stage breast cancer. Such studies demonstrated promising outcomes when conservative surgery was followed by external beam irradiation. The cure rate was similar to that of radical surgery\(^{(2,3,10-11)}\).

The need for complementary radiotherapy associated to breast-sparing surgery was emphasized in some studies, such as the NSABP B21, the Milan III and others, because the local recurrence rate was significantly higher in patients who did not undergo irradiation\(^{(11-12)}\). The importance of radiotherapy in reducing local recurrences is due to the elimination of residual malignant foci adjacent to the main focus, as proven by the studies by Rosen et al. and Holland et al.\(^{(13-14)}\).

Other studies showed that over 80% of local recurrences after breast-sparing surgery and radiotherapy occurred in the original tumor site, and segmental irradiation has become an alternative for the treatment of these patients\(^{(10,15-17)}\).

The likelihood of tumor control at a certain dose of absorbed radiation decreases with increased number of tumor cells, thus partial intraoperative radiation poses the advantage of being performed immediately after cytoreduction, requiring smaller radiation dose with higher biological efficiency. A single 21 Gy dose in IORT shows similar theoretical results in local control, the radiation biological equivalence adjusted by the dose, than the conventional fractioned 56 Gy dose.\(^{(9)}\)

Moreover, the tissue treated at surgery is richly vascular and oxygenated, which should render it more sensitive to the cytotoxic effects of radiotherapy, when compared to the irradiated scar tissue in postoperative external beam radiotherapy and, occasionally, after months of chemotherapy.

With IORT, some potential side effects associated to conventional radiotherapy may be minimized, such as those due to irradiation of the skin, subcutaneous tissue, lungs and heart. Other relevant advantage of IORT is to avoid the delay of local treatment (radiotherapy) because of systemic therapy or vice-versa. The IORT complication rate is low, and the adverse effects reported up to the present time, are fat necrosis, mild to severe fibrosis, which may need surgery, and transient pain. In the cases reported, the incidence was less than 3% and temporary, resolving spontaneously within 36 months, in the worst situation. There is also a potential reduction of noticing a second cancer induced by radiation, due to the smaller tissue volume irradiated, as well as the possibility of a new conservative approach in the case of recurrence\(^{(9,18)}\).

The adverse effects of external beam irradiation on the breast are known and include from a loss of about 6% of ipsilateral pulmonary function, residual skin hyperpigmentation, persistent edema requiring continuous physiotherapy and breast hypersensitivity, in addition to occasional treatment interruption in voluminous breasts and obese patients. Heart toxicity in the left breast external irradiation is a controversial issue, and it correlates only with obsolete breast irradiation techniques. In the present study, no remarkable adverse effects were identified with IORT and no patient needed surgical reintervention. IORT was easily performed in the group studied, with no intraoperative problems, requiring longer surgical times because of moving the patient to the linear accelerator room and proper collimator positioning for treatment. Irradiation time itself was short, not amounting significantly to the total surgical time.

The patients undergoing this treatment were similar to the patients reported in the literature, that is, women with early-stage tumors, clinical stage I in 86.4%, with mean tumor diameter of 1.5 cm and negative SLN (except in the cases discussed previously, which was also similar to the literature). Moreover, they were at low risk for recurrence, age over 45 years, most post-menopausal, with tumors smaller than 3 cm, most of which were ductal, with free margins, free SLN and positive hormone receptors.

Despite the theoretical and practical benefits, the available studies still do not clearly demonstrate which patients would benefit more from IORT, since there are no long-term follow-up data comparing it to conventional radiotherapy, showing similar results regarding global survival and disease-free survival. Other benefits worth...
mentioning include the lower cost of the procedure compared to conventional external beam radiotherapy (approximately three-quarters the price of conventional therapy); feasibility in elderly patients; irradiation of those who live far from the referral centers, unable to travel daily for about 45-day treatment; and thus abolishing treatment dropouts for those reasons, technical contra-indication due to impossibility of lying on their back for a long time when awaken (claustrophobia, painful or deforming arthritis, etc). Setting up an intraoperative radiotherapy program is moderately expensive compared to the costs of setting up conventional radiotherapy and requires greater dedication in multidisciplinary organization (integration among radiology, breast specialist, radiotherapy, pathology, anesthesiology, nursing, and medical engineering teams) in order to achieve the expected results, so that potential failures in either of these steps are minimized.

IORT has, thus, some advantages compared to conventional external beam radiotherapy in patients with early-stage breast cancer. Such advantages are radiobiological (equivalent single dose, execution immediately after cytoreduction, application in highly vascular tissue), technical (improved localization of the excision site, homogeneously distributed dose, in a single dose), clinical (avoids delaying the start of systemic treatment for performing local irradiation and vice-versa), allows similar treatment in patients with unfavorable physical conditions – voluminous breasts, non-tolerated prolonged positioning while awake), psychological (avoids weekly radiotherapy sessions and exposure to patients in terminal clinical situation or with moral impact) and economical (shorter treatment, less expensive than conventional treatment, earlier resumption of work and daily activities, as well as not requiring company for transportation for about 45-days of treatment and, thus, minimizing treatment dropout).

However, the profile of the patients who benefit more by IORT is not well defined yet and there are no long-term follow up data demonstrating similar global survival and disease-free survival results when compared to conventional radiotherapy. Therefore, IORT is an available technique strictly investigational, radiobiologically effective, and comparable to conventional external beam radiotherapy in theoretical models, of easy performance, with potential social and economical benefits compared to external beam radiotherapy in cases of early-stage breast cancer.

The costs of setting up intraoperative radiotherapy is not exorbitant, it might also be utilized for the treatment of other malignancies (retroperitoneal sarcomas, pancreatic, gastric, rectal and other tumors)\(^{(19)}\), but it requires a perfectly integrated multidisciplinary team in order to avoid failures in a disease potentially controlled by conventional techniques, as is early-stage breast cancer.

CONCLUSION

The preliminary data of the present study are similar to those of the literature, demonstrating that IORT is a technique feasible in our setting, equivalent to conventional external beam radiotherapy, with radiobiological, technical, clinical, psychological and economical benefits.

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REFERENCES


