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Original Article

Local therapy for breast cancer in malignant lymphoma survivors

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SUMMARY

Aims: Breast cancer is the most frequent secondary tumor in young women previously treated with mantle radiation for Hodgkin's disease. Prior therapeutic radiation to the breast region is considered an absolute contraindication to breast conservative surgery, and mastectomy is considered the treatment of choice. We performed a retrospective review to assess the potential of performing breast conservative surgery and intraoperative radiotherapy with electrons (ELIOT), in these patients.

Methods and results: Forty-three patients affected by early breast cancer, previously treated with mantle radiation for malignant lymphoma, who underwent breast conservative surgery and ELIOT, were identified in our institution. Median age at diagnosis of lymphoma was 26 years (49% were less than 25). Median interval between lymphoma and breast cancer occurrence was 19 years. A total dose of 21 Gy (prescribed at 90% isodose) in 39 patients (91%), of 17 Gy (prescribed at 100% isodose) in 1 patient and 18 Gy (prescribed at 90% isodose), was delivered. ELIOT was well tolerated in all patients without any unusual acute or late reactions. After a median follow-up of 52 months, local recurrence occurred in 9% of the patients and metastases in 7% patients.

Conclusion: In patients previously treated for lymphoma, partial breast irradiation, and in particular ELIOT, permits breast conservative surgery without acute local complications, decreasing the number of avoidable mastectomies.

Introduction

Before the advances in radiotherapy and chemotherapy, Hodgkin's disease (HD) was a permanent fatal disease. In the 1960s these advances radically changed prognosis of HD, and have resulted in a large number of long-term survivors at risk for the serious late side-effects of therapy and second primary tumors.[1] Breast cancer (BC) accounts for the largest absolute risk of second cancers among female survivors of HD, also exceeding deaths resulting from HD.[2,3] The risk of developing BC after radiotherapy for HD is well documented[4–8] and it is attributed to the incidental inclusion of portions of the breast in the portals used to irradiate the mediastinum with or without infraclavicular/axillary regions. The cumulative incidence of BC increases with young age at initial treatment, radiation dose, radiation therapy field size, and time from treatment. It approaches 25% to 30% in women aged 55 years who were treated for HD at age 25.[9,10] The estimated risk of breast cancer is also affected by the duration of follow up after radiotherapy and the method used to calculate risk.[11] This increased risk emerges approximately 10 years after primary therapy and persists beyond 25 years of follow-up.[5] Comparative studies suggest that the prognosis and pathologic characteristics of breast cancer after lymphoma are similar, stage for stage, to that of primary breast cancer without radiation exposure.[1,12]

When BC occurs, prior therapeutic radiation to the breast region, such as mantle radiation for HD, is considered an absolute contraindication to breast-conserving surgery (BCS), based on concern about possible severe sequelae arising after a high total cumulative dose to the breast.[13] Therefore, several authors[14,15] have suggested mastectomy as the treatment of choice for these patients. Few studies have been published whereby alternative therapies to mastectomy have been employed; they describe local excision alone, or local excision with interstitial brachytherapy or followed by local field external beam radiotherapy.[16–22]

Intraoperative radiation therapy is a special irradiation technique that permits the administration of a high irradiation dose in a single fraction during surgery, alone or as a boost technique.[23] Seeing the target directly, it enables maximum precision in the delivery of the

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dose and, at the same time, reduces the dose to healthy surrounding organs as lung, heart, contralateral breast or skin.[24]

At the European Institute of Oncology (EIO) in Milan, electron intraoperative therapy (ELIOT) has been investigated in breast cancer patients candidates for BCS since July 1999. After a preliminary validation phase I and II study[25,26] patients were recruited in an institutional phase III randomised trial, in which a single dose (21 Gy prescribed at 90% isodose) of intraoperative irradiation on a limited field, was prospectively compared with standard external beam irradiation (50 Gy on the whole breast and 10 Gy boost on tumor bed) in order to evaluate the effectiveness of the new approach in terms of local control, regional control, disease-free, distant metastases and overall survival, cosmetic outcome, and cost. The preliminary results are in the course of analysis and they will be the subject of a future dedicated publication.

Thus, after a previous study published in 2005,[27] we performed a new retrospective review to assess the potential of performing ELIOT in women with early breast cancer who had been previously irradiated for HD, in order to avoid a dangerously high total cumulative dose of radiotherapy to the whole breast, soft tissues of the thoracic wall, lung and heart, without rejecting the possibility of BCS.

Methods

Between 2000 and 2010, 43 patients previously submitted to mantle radiation therapy for HD and non-Hodgkin's lymphoma (NHL) developed invasive BC and underwent BCS and ELIOT as the sole radiation treatment. The clinical and histological data for BC were fully obtained. However, several parameters for HD and NHL were not exhaustive (stage/treatment details), especially in older cases and for some of the patients treated elsewhere and further referred to our institute only after BC diagnosis.

Mobile accelerator with electron beams

Two mobile linear accelerators a Novac7 (Hitesys Srl, Latina, Italy) and a Liac (Info&Tech, Roma, Italy), installed in two different operating rooms at the IEO were used to deliver electrons. These miniaturized linear accelerators, that can easily be moved near the operating table by means of motors acting on the wheels and a robotic arm that can take the necessary positions for irradiation, deliver electrons at the following different nominal energies: 3–5 – 7–9 MeV (Novac7) corresponding to 4.5, 5.2, 6.5 and 7.8 MeV effective energies to the phantom surface, respectively; and 4–6 – 10 MeV (Liac). The depth of 80% isodose ranged between 13 mm (3 MeV, not used in clinical practice) and 24 mm (9 MeV). The collimation of the beam is achieved by a hard-docking system, consisting of perspex applicators, 5 mm thick. The flat-ended and bevelled (15° up to 45°) round applicators have a diameter ranging from 4 to 12 cm. The nominal source to surface distance (SSD) is 80–100 cm for Novac7 and 60 cm for Liac. Radiation protection is obtained by a primary beam stopper, consisting of a trolley-mounted 1.5 cm thick lead shield and some mobile 1.5 cm thick lead shields (100 cm long, 150 cm high), that are positioned around and beneath the operating table.

Based on the radiobiological models used to predict radiation effects (linear-quadratic surviving fraction or multi-target surviving fraction),[28] we can estimate that a dose of 60 Gy delivered at 2 Gy daily, which is the radiation dose required to control the microscopical residual disease after breast resection, is equivalent to a single fraction of 20 to 22 Gy when using an α/β ratio at 10 Gy, typical for tumors and acute reacting tissues. Using the same equation, but calculating the tolerance of late responding tissues (α/β ratio at 3 Gy), this equivalent value increases to at least 110 Gy. The portion of the breast (CTV, Clinical Target Volume) that needs to be irradiated is generally an area of 4–6 cm in diameter. This field size allows keeping a safe margin around the tumour bed of at least 1–1.5 cm. Other sizes of applicator can be selected based on the breast size, tumour bed site and technical capacity to mobilize the gland. The appropriate electron energy is selected based on the gland thickness measured after the temporary reconstruction of the breast. The dose of 21 Gy is prescribed at the level of 90% of the isodose.

The radio-surgical technique of the 43 ELIOT procedures doesn't differ from the classic technique used in patients not previously irradiated for HD, and it has been previously described.[29]

Results

Out of 43 patients, 35 (81%) presented a previous HD and 8 (19%) a NHL. The median age at diagnosis of HD and NHL was 26 years (range, 14–65 years); globally, 21 women (49%) were 25 years old or less. Main clinico-pathological features of HD and NHL are detailed in Table 1. All patients received radiotherapy (RT) to the upper part of their body, and 34 (79%) also had chemotherapy (CT) for lymphoma. Adriamycin containing regimens like ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and Stanford V for HD or m-ACOD (methotrexate, calcium, leucovorin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) for NHL were the most frequently used (11 patients). These regimens have replaced alkylator-based regimens such as mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) that were used in 6 patients, and are currently the standard CT regimen for limited stage HD. Two patients were treated by other combinations, mainly based on cyclophosphamide

Table 1
Clinico-pathological features for Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Analysis of 43 patients.

	No. of patients	%
Treatment period		
<1970	1	2.3
1970–1980	11	25.6
1981–1990	15	34.9
>1990	16	37.2
Age at diagnosis		
<20 years	13	30.2
20–30 years	17	39.5
>30 years	13	30.2
Ann Arbor stage (n = 19)		
I	5	11.6
II	13	30.2
III	–	
IV	1	2.3
Treatment (n = 43)		
RT alone	9	20.9
CT alone	–	
RT + CT	34	79.1
RT technique (n = 29)		
Mantle	15	34.9
Involved fields	14	32.6

RT: radiotherapy; CT: chemotherapy.

Table 2
Interval between Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) treatment and BC occurrence. Analysis of 43 patients.

Interval lymphoma and BC (years)	No. of patients	%	RT + CT	RT alone
>1 and ≤5	3	7	2	1
HD	2		2	–
NHL	1		–	1
>5 and ≤10	6	14	6	–
HD	4		4	–
NHL	2		2	–
>10 and ≤15	7	16.2	5	2
HD	6		5	1
NHL	1		–	1
>15 and ≤20	8	18.6	7	1
HD	6		6	–
NHL	2		1	1
>20 and ≤25	7	16.3	6	1
HD	6		5	1
NHL	1		1	–
>25 and ≤30	6	14	3	3
HD	5		2	3
NHL	1		1	–
>30	6	14	5	1
HD	6		5	1
NHL	–		–	–

BC: breast cancer; RT: radiotherapy; CT: chemotherapy; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma.

and vinblastine (CEOP and CVPP). We have no information about the CT regimen in 15 patients. One patient with NHL relapsed after 4 years of RT (40 Gy) for B Cell NHL, and was treated with CT.

The median interval between lymphoma treatment and BC occurrence was 19 years (range, 2–36 years) with no significant differences according to initial HD and NHL treatment: 20 years in case of RT alone and 19 years in case of CT + RT. BC occurred after 20 years of lymphoma diagnosis in 44% of the patients, between 10 and 20 years in 35% and within 10 years in 21% (Table 2). Median age of patients at diagnosis of the first BC was 46 years (range, 33–70 years).

According to the TNM classification,[30] we found 14 (33%) T1b, 24 (55%) T1c and 5 (12%) T2. The median tumor size was 1.5 cm. Two tumors were multifocal and 1 patient had a bilateral BC at diagnosis (invasive in one side and in situ in the contralateral breast, this last not being included in our analysis). Thirty-six tumors (84%) were invasive ductal carcinoma, 1 patient had invasive lobular carcinoma and 6 (14%) were other invasive subtypes. None of the patients had metastasis at first diagnosis.

According to the Elston–Ellis classification,[31] of 42 evaluable invasive carcinomas, 9 (21%) were grade I, 18 (42%) grade 2 and 15 (35%) grade 3. Estrogen (ER) and progesterone (PR) receptors were positive in 35 patients (81%). Her2 overexpression was found in 4 out of 43 patients (9%). Ki-67 labeling index was less than 20% in half of the patients (49%). Peritumoral vascular invasion was absent in 35 (81%) patients.

Among 43 breast conservative surgeries, the evaluation of regional lymph nodes was performed in 41 (95%) patients with radioguided sentinel lymph node biopsy according to the standard technique adopted at the EIO.[32] In 30 patients, the biopsy showed that the sentinel lymph nodes (SLN) were free of metastasis, so complete axillary dissection was not performed. In 11 patients (26%), the SLN resulted metastatic at frozen section and axillary dissection was performed. In two patients, due to the presence of clinically metastatic axillary nodes, complete axillary dissection was performed directly. Among 41 patients for which sentinel lymph node biopsy was performed, 30 (70%) had no axillary involvement (pN0), 10 (23%) had 1–3 involved nodes (pN1) and 1 had more than 3 involved nodes (pN2). The two patients with direct axillary lymph node dissection were classified as pN2.

After BCS in all the patients partial breast irradiation with ELIOT, was delivered. We treated one patient with a total dose of 17 Gy (prescribed at 100% isodose) and 3 patients with 18 Gy (prescribed at 90% isodose) as part of the initial dose-finding study. The remaining 39 patients (91%) received 21 Gy (prescribed at 90% isodose).

Hormonal treatment (HT) was prescribed in 28 cases (65%). CT was delivered in 7 patients (14%). CT and HT were both used in 6 patients (16%).

To evaluate acute and late radiation morbidity, the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) scoring scheme[33] was applied on the first and seventh day of the radio-surgical treatment and every six months during follow up. ELIOT was well tolerated in all patients without any unusual acute reactions. Side effects directly attributable to ELIOT were acute haematoma in 2 patients, postoperative infection in 1 patient, and seroma in the treated part of the breast in 5 patients with. After a median time of 52 months (range, 6–132 months) of follow-up, we evaluated intermediate-late side effects using the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. Two patients developed slight induration (fibrosis) in the irradiated area (grade 1 subcutaneous tissue) and 2 other patients had moderate slight field contracture (grade 2 subcutaneous tissue).

Four (9%) out of 43 patients underwent local recurrence (LR). Three (7%) further developed metastases, 2 patients after LR and 1 patient after a contralateral carcinoma. One patient developed secondary lung cancer. Recently, 4 patients died and 39 were still alive. The 4 deaths were due to breast cancer in 3 patients (6.9%) and second lung cancer in 1 patient (2.3%).

Discussion

Since many lymphoma patients have become long-term survivors, attention has shifted to the effects of treatment, including secondary solid malignancies such as BC, the largely most common second primary tumor in women previously irradiated for HD or NHL. According to the American College of Radiology appropriateness criteria on conservative surgery and radiation,[34] the history of RT (e.g., for the treatment of Hodgkin's disease), that delivered a significant dose to the breast and for which re-treatment would result in an excessively high total radiation dose to the breast tissue, is a contraindication for a breast-conserving approach. High radiation doses to the breast result in unacceptable long-term toxicity and poor cosmesis rates. And indeed, most authors consider these patients at significant risk of complications (fibrosis, skin and soft tissue necrosis, rib fractures, potential lung and heart toxicities)[15,35–37] and do not candidate them for BCS and adjuvant radiotherapy. The study from Stanford[15] reported one of two women, who underwent lumpectomy and breast RT, and had a severe tissue necrosis developed in her lateral breast and chest wall at the area of overlap with the previous mantle field. In contrast, other reports[18,20,22,38,39] support BCS followed by external beam radiation when breast cancer develops many years after radiotherapy for HD. In the latest international retrospective multicentric study,[39] 79 out of 203 (39%) patients underwent BCS with whole breast irradiation in 56 (71%). The LR rate was 13.7% versus 21% among 19 patients without

RT after conservative surgery. No unfavorable side-effects of this treatment were observed. At present, no consensus exists regarding the correct management of BC after mantle irradiation for HD and, given the discordant results and the small number of women treated with BCS, mastectomy continues to be recommended as the standard treatment.

To avoid a high total cumulative dose to portions of the breast or soft tissues of the thoracic wall, one of the conservative options is to treat just the tumor bed. The irradiation of a small volume of the breast and adjacent structures could minimise the risk of complications.[16,17,19,21] Therefore, over the past decade there has been increasing interest in alternative delivery strategies, partial breast irradiation techniques designed to treat only the portion of the breast deemed to be at high risk for LR,[40] such as interstitial or intracavitary brachytherapy (MammoSite applicator), intraoperative radiotherapy with electrons, intraoperative orthovoltage device (Intrabeam), and 3-D conformal or intensity-modulated external beam radiotherapy. All of these techniques have similar indications but different applications.[41] In particular, they differ in the source of radiation (e.g. X-ray, iridium-192, photons) and the amount of breast volume treated.[42–49] When in July 1999 we focused our interest on the use of intraoperative radiotherapy as an exclusive treatment in small unifocal invasive breast carcinomas, we considered that ELIOT could be specifically applied in all those special situations in which external beam radiotherapy was not considered safe or feasible for various reasons and, in particular, in patients irradiated for HD.[50] In our first report,[27] six patients, previously irradiated for HD, underwent breast conservative surgery followed by ELIOT. The LR rate was 8%. ELIOT was well tolerated without any unusual acute reactions despite previous breast irradiation. Other teams reported a similar number of cases treated by various partial breast irradiation techniques, as well as brachytherapy or MammoSite applicator,[51–54] with excellent outcomes and local control in carefully selected patients. The possibility of a new breast treatment by photons, electrons or brachytherapy was already confirmed by other studies in small and late LR after a first radiosurgical breast conserving treatment.[55,56] The present study confirms these findings, with 43 patients who underwent ELIOT after BCS. After a median follow up of 52 months, the LR rate was 9%, according to the rates observed in young patients in general statistics.[57,58] We did not observe any ischemia or necrosis on the skin flap due to the careful sparing of the subcutaneous vessels during the mobilisation of residual breast around the tumor bed. No increased post-operative complications (pain, seroma, haematoma, infection) were observed in these patients when compared to the overall group of ELIOT patients. The length of hospital stay was therefore not prolonged. The cosmetic outcome was also very good in all patients: no skin erythema was observed as a result of the complete removal of the skin from the radiation beam.

Young age seems to be the most important risk factor for BC occurrence in patients previously irradiated for lymphoma, especially under 30 years, corresponding to the highest breast radio-sensitivity period. The median age at diagnosis of lymphoma in our series was 26 years; almost half of the patients were less than 25 years old. The latency interval is quite long, approximately 15 years, as in our report; the median interval after lymphoma treatment and BC occurrence was 19 years with a median age of 46 years at diagnosis of BC. Similarly to other series such as that of Cutuli et al.,[39] the median age at diagnosis of HD and BC was 25 and 42 years, respectively and the median interval to develop BC was 18.6 years.

Because of the long latency required to observe second solid cancers after RT for HD and the rapid evolution of RT techniques for HD, many estimates of radiation-related second cancer risk reflect outcomes of treatment no longer in use.[59] Published risk estimates are largely based on patients treated with 35 Gy to mantle, extended-field, or subtotal nodal RT fields in the 1960s through the 1980s. Since that time, HD treatment has progressed to the use of smaller involved radiation therapy fields. Recent clinical trial results suggest that low-dose (20 Gy) RT may emerge as standard treatment for adult HD,[60–62] and these new effective RT techniques probably will reduce in the future the absolute risk of secondary BC expected.

In conclusion, intraoperative radiotherapy with electrons (ELIOT) dramatically reduces the radiation exposure of the normal tissues and, in particular, of the previously irradiated breast, avoiding a high total cumulative dose to the gland and to the soft tissues of the thoracic wall. In patients previously treated for HD who develop breast cancer, ELIOT permits breast conservative surgery, independently of the interval between mantle radiotherapy and breast surgery, without acute, intermediate and late side effects, so decreasing the number of avoidable mastectomies, and achieving a good local control of the disease.

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Conflict of interest statement

G. Viale: Consultancy: Roche, GSK; Travel expenses: Novartis. M. Intra, V. Galimberti, P. Veronesi, M. Colleoni, R. Orecchia and U. Veronesi have no conflict of interest to declare.

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