A new option for early breast cancer patients previously irradiated for Hodgkin's disease: intraoperative radiotherapy with electrons (ELIOT)

Mattia Intra¹, Oreste Gentilini¹, Paolo Veronesi¹,², Mario Ciocca³, Alberto Luini¹, Roberta Lazzari⁴, Javier Soteldo¹, Gabriel Farante¹, Roberto Orecchia²,⁴ and Umberto Veronesi¹

¹Department of Breast Surgery, European Institute of Oncology, Milan, Italy
²University of Milan, School of Medicine, Milan, Italy
³Medical Physics Unit, European Institute of Oncology, Milan, Italy
⁴Department of Radiotherapy, European Institute of Oncology, Milan, Italy

Introduction

Patients who have undergone mantle radiotherapy for Hodgkin’s disease (HD) are at increased risk of developing breast cancer. In such patients, breast conserving surgery (BCS) followed by breast irradiation is generally considered contraindicated owing to the high cumulative radiation dose. Mastectomy is therefore recommended as the first option treatment in these women.

Methods

Six patients affected by early breast cancer previously treated with mantle radiation for HD underwent BCS associated with full-dose intraoperative radiotherapy with electrons (ELIOT).

Results

A total dose of 21 Gy (prescribed at 90% isodose) in five cases and 17 Gy (at 100% isodose) in one case were delivered directly to the mammary gland without acute complications and with good cosmetic results. After an average of 30.8 months of follow up, no late sequelae were observed and the patients are free of disease.

Conclusion

In patients previously irradiated for HD, ELIOT can avoid repeat irradiation of the whole breast, permit BCS and decrease the number of avoidable mastectomies.
(ELIOT) in women with early breast cancer who had been previously irradiated for HD.

**Materials and methods**

Between July 1999 and April 2005, 756 breast cancer patients who were candidates for BCS received ELIOT as the sole radiation treatment in the European Institute of Oncology in Milan. Of these, 100 patients had been treated in the past within a preliminary validation phase I study [11,12] and 440 patients are currently in an institutional phase III ongoing randomized clinical trial, in which 21 Gy ELIOT (prescribed at 90% isodose) is prospectively compared with external postoperative fractionated radiotherapy (PFR) including elective treatment of the whole breast. Eligibility criteria for the ELIOT randomized trial included patients aged between 48 and 75 years affected by a unicentric breast invasive carcinoma with a maximum diameter of 2.5 cm. Locally advanced tumors (T3 and T4), the presence of a contralateral synchronous or metachronous tumor, non-invasive carcinomas (including Paget’s disease), other breast malignancies different from carcinoma, multifocality or multicentricity of the disease, previous surgical biopsy and previous oncological history are considered exclusion criteria, while a breast thickness superior to 3 cm is considered a technical contraindication, it being impossible to deliver energy of more than 9 mega-electron volts (MeV) with the present ELIOT dedicated linac. No particular tumor breast locations are excluded from ELIOT, but the close proximity of the tumor to the skin and pectoral major muscle infiltration are considered relative contraindication for ELIOT. In fact, in these cases, the irradiation of the entire breast, including skin and pectoral major muscle, is mandatory. Finally, if the tumor is very close to the axilla, ELIOT is avoided due to the risk of irradiating the axillary nerves and vessels.

In a selected group of 216 invasive breast cancer patients who were candidates for BCS, and who had specifically asked for and signed informed consent for ELIOT or in whom PFR was not considered safe or feasible due to clinical reasons (e.g. severe cardiopathy, large scars from skin burns, vitiligo, geographic or social obstacles), ELIOT was performed outside the randomized trial. In this selected group of patients, only the tumor size (larger than 2.5 cm), locally advanced disease, multifocality or multicentricity were considered exclusion criteria. Of these 216 patients, 6 were previously treated for HD and received mantle radiation (Table 1).

The breast cancer presentation of these six patients is described in Table 2. Five patients underwent BCS and radioguided sentinel lymph node biopsy according to the standard technique adopted at the European Institute of Oncology [13].

### Table 1

**Presentation of and therapy for Hodgkin’s disease**

| Patient no. | Age (years) | Diagnosis | Stage | Therapy |
|-------------|-------------|-----------|-------|---------|
| 1           | 29          | HD, MC    | IIA   | MOPP × 6, Mantle 36 Gy |
| 2           | 28          | HD, NS    | IIB   | MOPP × 4, ABVD × 4, Mantle 20 Gy |
| 3           | 42          | Had       | IIB   | ABVD × 3, Mantle 40 Gy |
| 4           | 38          | HD, MC    | IIA   | MOPP × 6, Mantle 40 Gy |
| 5           | 24          | HD, NS    | IIB   | MOPP × 6, Mantle 40 Gy |
| 6           | 30          | HD, NS    | IIA   | MOPP × 4, ABVD × 4, Mantle 36 Gy |

*a* No histologic subtype determined. ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; HD, Hodgkin’s disease; MC, mixed cellularity; MOPP, nitrogen mustard, vincristine, procarbazine, prednisone; NS, nodular sclerosis.

### Table 2

**Presentation of breast cancer**

| Patient no. | Age (years) | Interval since radiation for HD (years) | ELIOT dose |
|-------------|-------------|----------------------------------------|------------|
| 1           | 35          | 16                                     | 21 Gy (90% isodose), 7 MeV |
| 2           | 42          | 14                                     | 17 Gy (100% isodose), 7 MeV |
| 3           | 50          | 8                                      | 21 Gy (90% isodose), 9 MeV |
| 4           | 50          | 12                                     | 21 Gy (90% isodose), 9 MeV |
| 5           | 34          | 10                                     | 21 Gy (90% isodose), 7 MeV |
| 6           | 39          | 9                                      | 21 Gy (90% isodose), 9 MeV |

*HD, Hodgkin’s disease; MeV, mega electron volts.*
In four out of the five cases, the biopsy showed that the sentinel lymph nodes were free of metastasis, so complete axillary dissection was not performed. In one patient, due to the presence of clinically metastatic axillary nodes, a complete axillary dissection was performed directly.

The radio-surgical technique of the six ELIOT procedures did not differ from the ‘classic’ technique, which has been described previously [14] in patients not previously irradiated for HD.

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 [15] was applied on the first and seventh day of the radio-surgical treatment and every six months during follow up.

Radiation therapy device

The dedicated ELIOT machine (Novac7, Hitesys, Italy) is a miniaturized linear accelerator that can be moved by a robotic arm, docked in the operating room and fulfills the statutory requirements with respect to radiological protection. Additional barriers (from 5 to 15 mm lead) are provided for positioning around the operating table. A lead shield (15 cm thick) is also placed under the surgical bed corresponding to the electron field (beam stopper). ELIOT delivers a single full-dose of radiation directly to the tumor bed after removal of the tumor. Based on the radiobiological models used to predict radiation effects (linear-quadratic surviving fraction or multitarget surviving fraction) [16], 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 $\alpha/\beta$ ratio at 10 Gy, typical for tumors and acute reacting tissues. Using the same equation, but calculating the tolerance of late responding tissues ($\alpha/\beta$ ratio at 3 Gy), this equivalent value increases to at least 110 Gy. The linac does not produce photons, but only delivers electron beams at four different energy levels: 3, 5, 7 and 9 MeV as nominal energies, corresponding to 4.5, 5.2, 6.5 and 7.8 MeV effective energies to the phantom surface, respectively. The depth of 80% isodose ranged between 13 mm (3 MeV, not used in clinical practice) and 24 mm (9 MeV).

In one patient, a total dose of 17 Gy (prescribed at 100% isodose) using electron beams (7 MeV energy) was delivered. In five patients, 21 Gy (prescribed at 90% isodose, 7 or 9 MeV of energy) were administered.

Results

The biological characteristics of the tumors are shown in Table 3. Two patients received adjuvant chemotherapy with cyclophosphamide-methotrexate/5-fluorouracil, followed by tamoxifen 20 mg/day for 5 years associated in one case with LHRH analogue for 2 years. One patient received Adriamycin/cyclophosphamide followed by tamoxifen 20 mg/day for 5 years associated with LHRH analogue for 2 years. Three patients received tamoxifen 20 mg/day for 5 years, associated in two cases with LHRH analogue for 2 years.

ELIOT was well tolerated in all patients without any unusual acute reactions (grade 0 according to the EORTC/RTOG acute radiation morbidity criteria). In the patients with longer follow up, no late sequelae were observed (grade 0 according to the EORTC/RTOG late radiation morbidity scoring scheme) and all women had an excellent cosmetic result. All the patients are free of disease after 53, 38, 29, 24, 23 and 17 months of follow up (average 30.8).

Discussion

Previous mantle radiotherapy for HD is considered a contraindication to BCS and radiotherapy [17]. This is based on concerns about possible severe sequelae arising from a high total cumulative dose, exceeding normal tissue tolerance, being delivered to the portions of the breast that have presumably already received radiation for the lymphoma, even though modifications of the breast gland over time render the exact calculation of the dose infeasible many years after radiation delivery. Most authors consider these patients at significant risk of complications (fibrosis, skin and soft tissue necrosis, rib

### Table 3

Characteristics of the breast cancer

| Patient no. | Tumor site | T  | N  | G  | ER, PgR | KI67 | PVI |
|------------|-----------|----|----|----|---------|------|-----|
| 1          | UO        | 1c | 0 (sn) | 2 | 15%, 25% | 11% | No  |
| 2          | LI        | 1c | 0 (sn) | 3 | 0%, 0%  | 70% | No  |
| 3          | C         | 1c (is) | 0 (sn) | 1 | 90%, 90% | 13% | No  |
| 4          | S         | 1c | 1a | 2 | 85%, 85% | 25% | No  |
| 5          | UO        | 2  | 1a | 2 | 30%, 0%  | 27% | Yes |
| 6          | UO        | 1b | 0(sn) | 1 | 90%, 90% | 8%  | No  |

T, tumor size; N, axillary lymph nodes; G, tumor grade; ER, estrogen receptors; PgR, progesterone receptors; KI67, proliferative index; C, central; is, extended intraductal component associated; LI, lower inner; PVI, perivascular invasion; S, superior; sn, sentinel node; UO, upper outer.
fractures, potential lung and heart toxicities) [6] and do not
candidate them for BCS and adjuvant radiotherapy. In con-
trast, other reports [18,19] support BCS followed by PFR
when breast cancer develops many years after radiotherapy
for HD. At present, no consensus exists regarding the correct
management of breast cancer after mantle irradiation for HD
and, given the discordant results and the small number of
women treated with BCS, mastectomy continues to be recom-
manded as the standard treatment. To avoid a high total cumu-
lative 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 allow the risk of complications to be
minimized [7-10]. Therefore, over the past decade there has
been increasing interest in a variety of radiation techniques
designed to treat only the portion of the breast deemed to be
at high risk for local recurrence [20]; these include brachyther-
apy implants, MammoSite applicator, intraoperative orthovolt-
age device, and 3D conformal or intensity-modulated external
radiotherapy (partial-breast irradiation (PBI)). All these tech-
niques have similar indications but different applications
[21,22]. In particular, they differ in the source of radiation (for
example, X-ray, iodidum, photons) and the amount of breast vol-
ume treated. Although 5 to 7 year outcome data on patients
with PBI are now becoming available, many issues remain unresolved, including the clinical and pathological
selection criteria of patients, radiation dose and fractionation,
and how these relate to the standard fractionation for whole
breast irradiation, appropriate target volume, local control
within the untreated ipsilateral breast tissue, and overall sur-
vival. With a view to furnishing guidelines and clarifying the
issues of major controversy, a workshop on PBI was held in
Bethesda, in December 2002. The workshop report empha-
sized the importance of education and training with regard to
the results of PBI as it becomes an emerging clinical treatment
[23]. In particular, ELIOT, a new radiotherapeutic technique
that delivers a single dose of radiation directly to the tumor bed
during the conservative surgical treatment of early breast can-
cer, has been proposed for evaluation in randomized clinical
trials as a possible alternative to standard PFR.

When in July 1999 we focused our interest on the use of intra-
operative radiotherapy as an exclusive treatment in small uni-
focal infiltrating breast carcinomas, we considered that ELIOT
could be specifically applied in all those situations in which
PFR was not considered safe or feasible for various reasons
(for example, severe cardiopathy, large hypertrophic scarring
from skin burns, vitiligo, geographic or social obstacles) [24]
and, in particular, in patients irradiated for HD. After our first
preliminary report [25], ELIOT was proposed in six patients
previously irradiated for HD. In all cases, the dose delivered
and the energy of electron beams from ELIOT did not differ
from those in the other 549 patients submitted to ELIOT; in
one patient a total dose of 17 Gy (prescribed at 100% isod-
dose) using electron beams at 7 MeV energy and in five patients
doses of 21 Gy (90% isodose, 7 and 9 MeV of energy) were
delivered. The different electron energies administrated (7 or
9 MeV) are related to the different breast gland thickness.

The radio-surgical technique of the six ELIOT procedures did
not differ from the 'classic' technique used for previously non-
irradiated patients [14]. In particular, to ensure a good coverage
of the target by the radiation dose and maximal protection
of the normal tissues in the operative area, adequate prepara-
tion for irradiation of the portion of breast gland to undergo
ELIOT is necessary. Protective devices are placed between
the gland and the pectoral muscle; a dedicated lead disk 5 mm
thick and an aluminium disk 4 mm thick, available in various
diameters (4, 5, 6, 8, 10 cm) are commonly used. The wall pro-
tection is guaranteed both by the absorption properties of the
lead and aluminium and the 9 mm outdistance created by the
disks.

We scored the radiation morbidity according to the RTOG/
EORTC criteria [15]. ELIOT was well tolerated without any
unusual acute reactions despite previous breast irradiation.
We did not observe any ischemic or necrotic problems of the
skin flap due to the careful sparing of the subcutaneous ves-
sels during the mobilization of the residual breast around the
tumor bed. No increased post-operative complications (pain,
seroma, emathoma, infection) were observed in these six
patients when compared to the overall group of ELIOT
patients. The length of hospital stay was therefore not pro-
longed. 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.

The follow up is too short (average 30.8 months) to evaluate
late sequelae in these six re-irradiated patients but no compli-
cations were observed in the four patients with more than 2
years of follow up.

Conclusion
ELIOT dramatically reduces the radiation exposure of the nor-
tal 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, ELIOT permits BCS independently of the inter-
val between mantle radiotherapy and breast surgery, without
acute local complications, decreasing the number of avoidable
mastectomies. A longer follow up is necessary to evaluate the
incidence of radiation-induced sequelae and the local recur-
rence rate.

Competing interests
The author(s) declare that they have no competing interests.

Authors' contributions
MI conceived the study, and participated in its design and
coordination and drafted the manuscript, OG helped to draft
the manuscript, PV participated in the coordination of the study, MC participated in the coordination of the study, AL participated in the design of the study, JS carried out patient follow up, GF carried out patient follow up, and RO and UV participated in the design of the study. All authors read and approved the final manuscript.

Acknowledgements
The authors wish to acknowledge the AIRC (Italian Association for Cancer Research) and the AICF (American Italian Cancer Foundation), which partially funded this research project.

References
1. Boivin JF, O’Brien K: Solid cancer risk after treatment of Hodgkin’s disease. Cancer 1988, 61:2541-2546.
2. Tucker MA, Coleman CN, Cox RS: Risk of second cancers after treatment for Hodgkin’s disease. N Engl J Med 1988, 318:76-81.
3. Tinga A, Wasserman TH, Klein EE, Miller EA, Roberts T, Pieploff JV, Kucik NA: The incidence of breast cancer following mantle field radiation therapy as a function of dose and technique. Int J Radiat Oncol Biol Phys 1997, 37:865-870.
4. Wolden SL, Lamborn KR, Cleary SF, Tate DJ, Donaldson SS: Second cancers following pediatric Hodgkin’s disease. J Clin Oncol 1998, 16:536-544.
5. American College of Radiology, American College of Surgeons, College of American Pathologists, Society of Surgical Oncology, Winchester DP, Cox JD: Standards for breast-conservation treatment. CA Cancer J Clin 1992, 42:134-162.
6. Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT: Management of breast cancer after Hodgkin’s disease. J Clin Oncol 2000, 18:765-772.
7. Krishnan L, Jewell WR, Tawfik OW, Krishnan EC: Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. Breast J 2001, 7:91-96.
8. Perera F, Engel J, Holliday R, Scott L, Girotti M, Girvan D, Chisela 6. Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT: Management of breast cancer after Hodgkin’s disease. J Clin Oncol 2000, 18:765-772.
9. Baglan KL, Martinez AA, Frazier RC, Kini VR, Kestin LL, Chen PY, Edmundson G, Goldstein N, McCarthy K, Martinez A: Accelerated partial breast irradiation: A dosimetric comparison of three different techniques. Brachytherapy 2005, 4:121-129.
10. Veronesi U, Orecchia R, Luini A, Gatti G, Venture A, Gniadecki R, Bassani G, Dos Santos GR, Rodriguez J, Luini A, et al.: Intraoperative radiotherapy during breast conserving surgery for early stage breast cancer: long-term results of a randomized trial. Ann Oncol 2001, 12:997-1003.
11. Tucker SS, Thames HD, Taylor JM: How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics. Radiat Res 1990, 124:273-282.
12. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer: Breast radiotherapy after breast-conserving surgery. CMAJ 1998, 158(Suppl 3):S35-42.
13. Deutsch M, Genszen K, Bloomer W, Avisar E: Lymphedema and breast irradiation for breast cancer arising after previous radiotherapy for Hodgkin’s disease. Br J Radiol 2000, 73:905-906.
14. Vicini F, Kini VR, Chen P, Horwitz E, Gustafson G, Benitez P, Salvadori B, Zucali R: Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 2001, 12:997-1003.
15. Intra M, Orecchia R, Veronesi U: Intraoperative radiotherapy: the debate continues. Lancet Oncol 2004, 5:340.
16. Tucker SS, Thames HD, Taylor JM: How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics. Radiat Res 1990, 124:273-282.
17. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer: Breast radiotherapy after breast-conserving surgery. CMAJ 1998, 158(Suppl 3):S35-42.
18. Aref I, Cross P: Conservative surgery and radiation therapy for early stage breast cancer after previous mantle radiation for Hodgkin’s disease. Br J Radiol 2000, 73:905-906.
19. Deutsch M, Genszen K, Bloomer W, Avisar E: Lymphedema and breast irradiation for breast cancer arising after previous radiotherapy for Hodgkin’s disease. Am J Clin Oncol 2001, 24:33-34.
20. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, Salvadori B, Zucali R: Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 2001, 12:997-1003.
21. Dickler A, Kirk MC, Chu J, Nguyen C: The MammoSite trade mark breast brachytherapy applicator: A review of technique and outcomes. Brachytherapy 2005, 4:130-136.
22. Weed DW, Edmundson GK, Vicini FA, Chen PY, Martinez AA: accelerated partial breast irradiation: A dosimetric comparison of three different techniques. Brachytherapy 2005, 4:121-129.
23. Wallner P, Arthur D, Bartelink H, Connolly J, Edmundson G, Giuliano A, Goldstein N, Hevezi J, Julian T, Kuske R, et al.: workshop on partial breast irradiation: state of the art and the science, Bethesda, MD, December 8–10, 2002. J Natl Cancer Inst 2004, 96:175-184.
24. Intra M, Orecchia R, Veronesi U: Intraoperative radiotherapy: the debate continues. Lancet Oncol 2004, 5:340.
25. Intra M, Leonardi MC, Gatti G, Venture A, Gniadecki R, Bassani G, Dos Santos GR, Rodriguez J, Luini A, et al.: Intraoperative radiotherapy during breast conserving surgery in patients previously treated with radiotherapy for Hodgkin’s disease. Tumori 2004, 90:13-18.

Available online http://breast-cancer-research.com/content/7/5/R828