Eur J Cancer, Vol. 29A, No. 7, pp. 957–961, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Breast Conserving Therapy in Patients with Relatively Large (T2, T3) Breast Cancers by Preoperative Irradiation and Myocutaneous LD Flap Reconstruction. A New Technique in Breast Conservation

F.A.N. Zoetmulder, J.H. Borger, E.J.Th. Rutgers, R. Bergman, J. Peterse and H. Bartelink

We investigated the feasibility of breast conserving treatment (BCT) in patients with large (T2, T3) breast cancers, by combining preoperative radiotherapy and tissue replacement after wide excision by a myosubcutaneous flap transposition. The treatment consisted of 50 Gy whole breast irradiation followed by a 15–25 Gy iridium implant to the primary tumour with 2 cm margins. Four weeks after completion of the radiotherapy, wide excision of the original tumour area with a 1 cm margin and an axillary dissection was performed. In the same session the breast was reconstructed with an ipsilateral latissimus dorsi transposition flap. The treatment results in the first 6 patients are encouraging with respect to treatment toxicity and cosmetic outcome. The clinical tumour response after radiotherapy was difficult to evaluate. However, microscopic evaluation showed residual tumour in all specimens with (focal) involvement of the surgical margins in two. With a minimum follow-up of over 2.5 years no tumour recurrences in the breast have occurred.
Eur J Cancer, Vol. 29A, No. 7, pp. 957–961, 1993.

INTRODUCTION

BREAST CONSERVING TREATMENT (BCT) for smaller breast cancers measuring up to 5 cm is now widely accepted as a safe treatment option. The results of three large randomised [1–3] and numerous retrospective studies [4–14] justify this approach and provide information on prognostic factors concerning local control. No clear contraindications for BCT have been found although margin involvement, extensive ductal carcinoma *in situ* component and young age are frequently mentioned as adverse factors. Tumour size does not appear to be an independent prognostic criterion for local recurrence. The only study which mentions such an effect awaits further evaluation by multivariate analysis [1]. From pathology studies on the multifocality of breast cancer it has been established that the incidence of additional tumour foci is unrelated to tumour size [15]. Therefore, in terms of local control, a large tumour size alone cannot be considered as a contraindication for BCT.

In terms of cosmetic results, however, tumour size plays the main role in determining the feasibility of BCT. In relation to the size of the breast even relatively small tumours may not be suitable for a conservative approach. The volume reduction associated with a tumourectomy performed with a generally recommended macroscopic tumour-free margin of 1–2 cm is too large in some cases of T2 and almost all cases of T3 breast cancers. For a safe and cosmetically acceptable performance of BCT in such cases one needs to look for ways to reduce the tumour volume and replace the lost tissue volume.

The former aim may be achieved by preoperative radiotherapy, which is an established modality of local therapy in breast cancer. Eradication of T2, T3 tumours would require very high irradiation doses resulting in unacceptable side-effects with regard to cosmetic outcome [16–18]. However, lower doses can be used if radiotherapy is combined with a significant tumour volume reduction by a wide excision of the primary tumour. Based on the pathology data provided by Holland [15] a 4 cm zone around the primary breast tumour may still contain additional (microscopic) tumour foci. By irradiating the whole breast to a dose of 50 Gy and adding a boost up to 70 Gy directed at the primary tumour with a 2 cm margin, eradication of tumour located directly around the primary lesion and elsewhere in the breast can be achieved. This radiation dose combined with excision of the primary tumour with a 1 cm margin around the palpable lesion should result in good local control. However, the resulting defect will be too large for acceptable cosmesis. Replacement of the lost volume can be achieved by transposition of a myocutaneous flap based on the latissimus dorsi, while this technique is simple when combined with an axillary dissection. In order to investigate the feasibility of this approach we performed a pilot study combining preoperative breast irradiation, tumourectomy and axillary dissection and myosubcutaneous latissimus dorsi flap transposition in patients presenting with relatively large T2 tumours in small breasts and those having T3 tumours irrespective of breast size.

Correspondence to F.A.N. Zoetmulder.
F.A.N. Zoetmulder and E.J.Th. Rutgers are at the Department of Surgery; J.H. Borger and H. Bartelink are at the Department of Radiotherapy; R. Bergman is at the Department of Plastic and Reconstructive Surgery; and J. Peterse is at the Department of Pathology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
Revised 1 June 1992; accepted 9 Dec. 1992.

PATIENTS AND METHODS

Patients with T2 breast cancer not amenable for BCT because of relative tumour size and those with a T3 tumour were candidates for this pilot study. Diagnosis was confirmed by cytology. Patients with limited clinical axillary node involvement were also eligible, but required a negative axillary apex biopsy, taken under local anaesthesia, in order to select patients with a relatively good prognosis. There were no restrictions with regard to the site of the primary tumour in the breast. Clinical response to radiotherapy was not a prerequisite in the decision to carry out the procedure. Metastatic disease was excluded by a negative history, physical examination, chest X-ray and blood chemistry results. Additional bone scans and/or liver sonography were performed if indicated.

The pilot study started in March 1988 and 6 patients were entered during the first year. Mean age was 53 years (range 45–59). 2 patients had a T3 tumour and the remaining patients were staged T2. Mean tumour size was 5 cm (range 3.5–6.5). 1 patient had a suspected axillary node metastasis while 4 were considered clinically node-negative. In 1 patient an axillary node was palpable but not considered to be malignant. All patients received whole breast irradiation with 8 MV or cobalt-60 photon beams using a tangential opposing field technique The dose prescribed at the isocentre was 50 Gy in 2 Gy fractions, 5 fractions per week. Patients treated with 8 MV photons had built up material applied for 2 weeks. The extent of the breast tumour was marked by skin tatoos before start of radiotherapy. Three weeks after completion of the external beam irradiation an iridium wire implant using an afterloading technique was given to the original tumour volume with a 2-cm margin. The dose was defined according to the Paris system [28] and 4 patients received a booster dose of 15 Gy and 2 patients received a dose of 25 Gy by this implant (Table 1).

All patients had internal mammary node irradiation to a dose of 50 Gy in 2-Gy fractions given in a mixed MV photon beam and electron or orthovoltage beam technique. The axilla was not irradiated. Surgery was performed 3–4 weeks after the iridium implant and consisted of excision of the original tumour site as marked by the tatoos with a margin of 1 cm. The procedure was performed with the patient in a lateral recumbent position (Fig. 1). A level I and II axillary dissection was performed through a horizontal incision with careful preservation of the thoracodorsal neurovascular trunk.

Based on the tumour location and the necessary pedicle length, the place of the donor site on the latissimus dorsi was chosen. An island of muscle covered with subcutaneous tissue was formed according to the volume required to fill the breast defect. Depending on the extent of skin excision at the tumour site the epidermis on the flap was either removed or left in place.

Table 1. *Tumour and treatment characteristics*

Patient	Clinical staging		Irradiation dose	
	Tumour size (cm)	Node status	Total breast (Gy)	Boost (Gy)
1	4	0	50	15
2	3.5	0	50	15
3	6	1b	50	15
4	4.5	1a	50	15
5	6.5	0	50	25
6	5	0	50	25

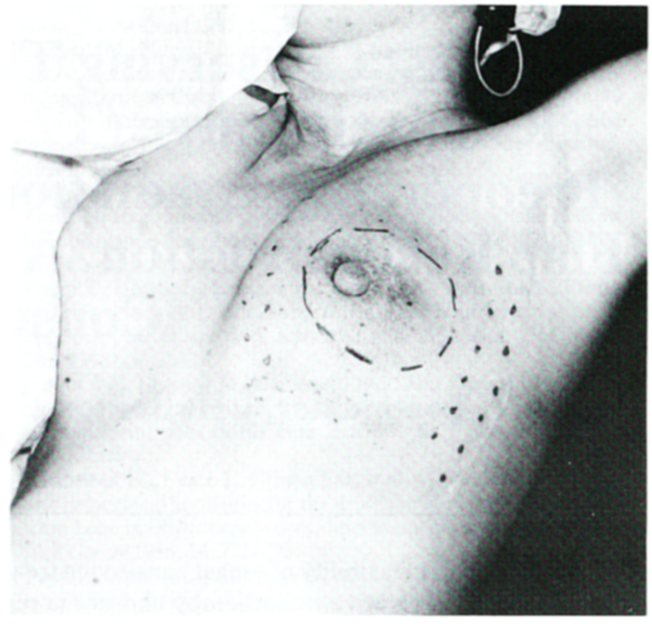

Fig. 1. Patient position at operation.

For transposition of the myosubcutaneous flap a tunnel was made between the axilla and the breast defect. The tissue island was transferred to the tumour excision site and fixed with degradable sutures. All wounds were closed over vacuum drains.

The operation specimen was inkted and microscopically evaluated for tumour excision with special attention to margin involvement. The axillary lymph nodes were routinely examined for lymph node metastases.

Axillary lymph node metastases were found in 3 patients. 2 patients were premenopausal and received six cycles of adjuvant cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy and two postmenopausal patients received tamoxifen, 30 mg daily at least for 1 year.

Patients remained in follow-up with clinical evaluation every 3 months and annual mammographs. The cosmetic outcome was evaluated annually according to clinical guidelines with special attention to breast appearance (symmetry) and consistency (fibrosis). Annual photographs in three positions were made to follow the cosmetic outcome in time.

RESULTS

All 6 patients completed radiation therapy and surgical procedures according to the protocol. Except for the usual mild early skin reactions (grade 1–2 erythema) no complications occurred from radiotherapy. The clinical response of the primary breast tumour was difficult to establish and palpable tumour was present in all patients at the time of operation. Progression during radiotherapy occurred neither in the breast nor in the axillary or other regional lymph nodes. The macroscopic examination of the tumourectomy specimen showed no signs of tumour in 3 patients and reductions in tumour size of more than 50% compared with the initial clinical measurements in the remaining 3 patients (Table 2).

Microscopic tumour was found in all breast specimens and in 2 cases the resection margins were involved focally. In 2 patients the completeness of excision could not be clearly assessed (Table 2). Lymph node metastases were found in 3 patients during microscopic examination of the axillary specimen, in all cases these were intracapsular.

Table 2. Pathology data

Patient	Specimen weight (g)	Tumour size(cm)*	Microscopic margins
1	70	1	Doubtful
2	140	1	Free
3	155	2.3	Free
4	128	0	Doubtful
5	220	0	Involved
6	95	0	Involved

*Macroscopic examination of breast specimen.

Table 3. Cosmetic evaluation

Patient	Follow-up (months)	Breast symmetry	Breast shape	Fibrosis
1	34	Good	Good	None
2	36	Good	Good	None
3	34	Fair	Good	None
4	37	Good	Good	None
5	24	Fair	Good	None
6	27	Good	Good	None

There were no complications during or after surgery. Wound healing occurred per primam and no infections were seen. The mean weight of the breast specimen was 135 g (range 70–220 g). In 2 patients the skin overlying the tumour had been included in the excision. In these cases the skin defect was replaced by a skin island on the lattissimus dorsi flap. Patients stayed in the hospital for a mean duration of 12 days after surgery.

Early cosmetic evaluation at a median follow-up of 32 months showed good results in all 6 patients (Table 3). Except for 2 cases with slight asymmetry, breast shape and symmetry were scored as good (Fig. 2). There was a remarkable absence of both fibrosis and lymphoedema in all patients. All patients remained free of local, regional and distant recurrence at a median follow-up of 32 months.

DISCUSSION

In conventional breast conservation treatment, surgical excision of the breast tumour followed by breast irradiation result in both acceptable local control rates and cosmetic outcome. In this setting radiotherapy aims at the elimination of microscopic tumour foci left behind the breast. Very often a boost is used to treat the tumour site to higher dose levels. Especially in incompletely or narrowly excised tumours the use of such a boost is tenable. In our experience [4] the use of a 25-Gy boost in incompletely excised breast tumours results in very high local control rates and in fact margin involvement is not an adverse prognostic factor for local control. Obviously, radiation therapy is able to eliminate even macroscopic volumes of breast cancer. This can also be gathered from the large experience of primary radiation therapy of breast cancer published by other authors [18–26].

However, the adverse effects of high-dose radiotherapy on the cosmetic outcome (fibrosis, skin changes) make it less suitable as the sole treatment for BCT. More limited doses of radiotherapy can be used safely when combined with tumour volume reduction by wide surgical excision. To correct for the loss of

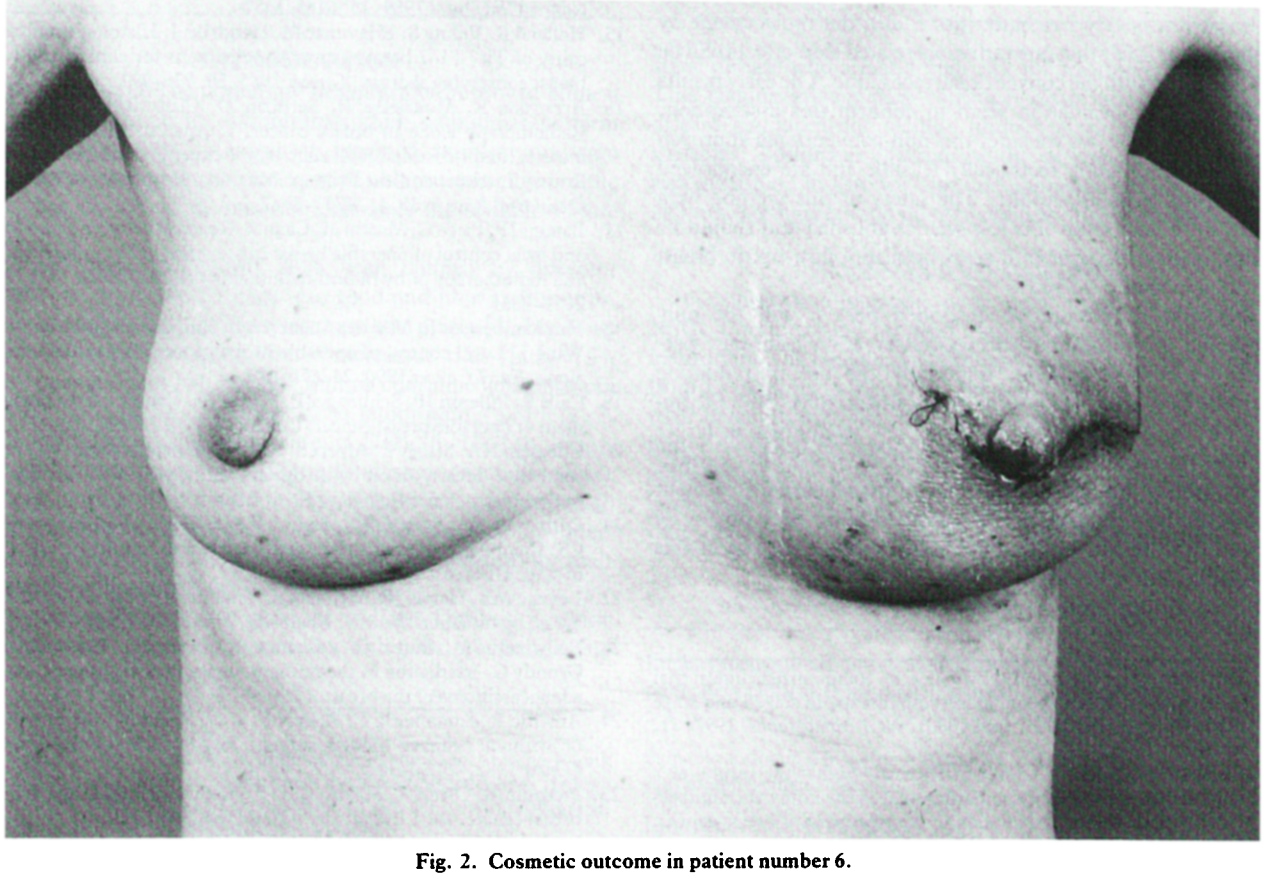

Fig. 2. Cosmetic outcome in patient number 6.

breast volume after surgical excisions of the primary tumour we introduced primary reconstruction using a latissimus dorsi myo(sub)cutaneous flap.

From our limited experience in the 6 patients described here the technical feasibility and good cosmetic outcome of this technique can be concluded. However, the safety of this procedure remains questionable because of the findings at microscopic evaluation. The involvement of surgical margins found in 2 patients raises questions about possible risks of tumour recurrence in the breast. All tumours showed a good response to radiotherapy and this treatment did not aim at a total elimination of all tumour cells. The microscopic evaluation took place only 4 weeks after completion of radiotherapy. It is, therefore, not surprising that tumour cells are found at microscopy. The question is whether these tumour cells can still produce viable offspring. In the absence of a laboratory method to determine the clonogeneity of tumour cells after radiotherapy we can only wait and see whether the patients with involved margins have a higher risk of local recurrence. From our knowledge of the time course of local recurrences in BCT (29) it is to be expected that these recurrences will occur in the early period of follow-up since they are expected to be true or marginal recurrences. The occurrence of incomplete excisions made us raise the dose of the boost implant from 15 to 25 Gy which did not change the findings in the subsequent patients with regard to margin involvement or cosmetic outcome.

There were no technical or medical problems with the surgical procedures and wound healing was uneventful in all cases. The use of a latissimus dorsi flap reconstruction was also carried out without problems. The surgical technique of latissimus transposition is relatively easy in this situation as the thorocodorsal neurovascular pedicle feeding the muscle has already been isolated as part of the axillary dissection. With the excision of the most intensively irradiated tissue and the replacement by fresh tissue it is felt that late radiation-related side-effects will be less compared with the conventional technique. The early results of the cosmetic evaluation seem to confirm this assumption. Given these results we consider this non-conventional approach to breast conservation technically feasible and are encouraged by the good cosmetic results. The safety of this method with regard to tumour control is less well established and should be further studied. At almost 3 years median follow-up no breast recurrences have occurred.

Of course the technique described here is not the only adaptation of the standard breast conservation technique presently under investigation. Especially the use of induction chemotherapy has shown some promising results [30]. At present, the long-term results of these new techniques in larger tumours with regard to local control and survival are not known. Further study towards the objective of breast cancer treatment with optimum tumour control and cosmetic outcome is obviously needed. The results of this pilot study support the use of this technique in future studies.

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Eur J Cancer, Vol. 29A, No. 7, pp. 961–965, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Prognostic Implications of Tumour Marker Analysis in Non-seminomatous Germ Cell Tumours with Poor Prognosis Metastatic Disease

Arthur Gerl, Christoph Clemm, Rolf Lamerz, Klaus Mann and Wolfgang Wilmanns

86 unselected patients with poor risk metastatic non-seminomatous germ cell tumours (NSGCT) treated from 1979 to 1990 at a single institution were reviewed with regard to the prognostic relevance of tumour marker analysis. The number of elevated tumour markers was not able to distinguish patients into prognostic subgroups. Pretreatment levels of human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) did not have a significant influence on clinical outcome. HCG and AFP half-life analysis during the first chemotherapy cycles also failed to define prognostic subgroups. If early deaths within 90 days after the onset of chemotherapy were excluded, patients with a half-life of HCG decline greater than 3.5 days tended to have a poorer prognosis which did not reach significance.
Eur J Cancer, Vol. 29A, No. 7, pp. 961–965, 1993.

INTRODUCTION

CISPLATIN-BASED chemotherapy dramatically improved clinical outcome of patients with disseminated non-seminomatous germ cell tumours (NSGCT). However, reported complete remission (CR) rates greater than 90% for good risk patients obscure the fact that 20–30% of all patients ultimately die of their disease [1].

Some prognostic factors have been defined by different authors to subdivide patients into good and poor risk groups. Age of patient [2, 3], primary extragonadal origin [4], histology [2, 4, 5], number and location of metastatic sites [1, 2, 6, 7], performance status [8], baseline human chorionic gonadotropin (HCG) [2–7, 9, 10], baseline alpha-fetoprotein (AFP) [2, 3, 5, 7, 10], lactate dehydrogenase (LDH) [6, 11, 12], lactate dehydrogenase isoenzyme I [13] and the rates of tumour marker decline during chemotherapy [9, 14] have been identified to influence prognosis. Since some of these variables are interrelated, multivariate analyses were performed to determine their relative prognostic importance [1, 2, 5–7].

A staging system developed at Indiana University allows identification of a group of patients with poor prognosis metastatic disease who are at a high risk for treatment failure [15]. This staging system only considers distribution and bulk of disease and does not include tumour markers as prognostic variables. To further characterise the patient group with poor risk metastatic disease we used complementary studies of baseline tumour markers and marker changes during chemotherapy.

PATIENTS AND METHODS

86 consecutive patients with poor prognosis metastatic NSGCT were treated between May 1979 and June 1990 at our institution. The median age of patients was 27 years with a range from 17 to 65 years. Poor risk metastatic disease was consistent with advanced status of the Indiana staging system except for a minor modification: abdominal bulky disease was defined as a palpable mass or a mass greater than 10 cm at computerised tomography (CT) (Table 1). The records, X-rays and CT scans were reviewed by one investigator, and all patients treated at

Table 1. Definition of poor-prognosis metastatic disease

Primary mediastinal non-seminomatous germ cell tumour or >10 pulmonary metastases per lung field or multiple lung metastases >3 cm
Palpable abdominal mass (or >10 cm at CT scan) with supradiaphragmatic disease
Liver, bone or brain metastases

Correspondence to A. Gerl.
A. Gerl, C. Clemm and W. Wilmanns are at the Medizinische Klinik III; and R. Lamerz and K. Mann are at the Medizinische Klinik II of the Klinikum Großhadern der Ludwig-Maximilians-Universität München, Marchioninistraße 15, 8000 München 70 F.R.G.
Revised 9 July 1992; accepted 21 Sep. 1992.