

Conservative surgery and radiotherapy for early-staged breast cancer

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From May 1987 to December 1994, 54 Chinese women with clinical American Joint Committee on Cancer stage I or II breast cancers were treated with breast conservation surgery and radiotherapy at the Prince of Wales Hospital. All patients had invasive carcinoma. Forty-seven patients had pathological axillary lymph node staging. With a median follow up interval of almost two years, the projected five-year actuarial survival and relapse-free survival for the whole group were 75.3% and 79.9%, respectively. The five-year local failure rate, regional failure rate, and distant metastasis rate were 3%, 5%, and 16.5%, respectively, and 83.3% of patients were free of radiation complications. These results compare favourably with other series reported for Caucasians. Careful patient selection and proper integration of the surgical, pathological, and radiotherapeutic aspects of treatment are essential. Breast conserving therapy and radiotherapy should be considered as an alternative to mastectomy in stage I and II breast cancer patients.

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Introduction

Radical irradiation using radium needle implant following limited local resection of early-staged breast cancer was practised as early as 1930. Breast conservation therapy (BCT) and radiotherapy (RT) were more widely practised after 1950 following the introduction of the cobalt teletherapy machine and linear accelerator which made irradiation less cumbersome. Multiple prospective randomised trials comparing BCT and RT with mastectomy began in Europe and the United States in 1970. These studies demonstrated that BCT and RT in selected stage I and II patients could achieve survival outcomes equal to conventional mastectomy, with the additional benefit to the patient

of excellent local and loco-regional control rates and preservation of the treated breast.¹⁻¹¹ The conclusions of these randomised trials were validated at the National Institutes of Health Consensus Conference in June 1990.

Pathological axilla staging is an important component of the overall management of patients with early-staged breast cancer because of its therapeutic and prognostic implications. Multiple studies have demonstrated the prognostic significance of axillary lymph node status and the number of positive axillary lymph nodes.^{12,13} In accordance with the systemic theory of the spread of breast cancer proposed by Fisher, it is widely accepted that some form of adjuvant systemic treatment should be given to patients with axillary lymph node metastasis.¹⁴ Furthermore, because of the low false negative rate of an axillary dissection, a pathologically negative axilla allows the radiotherapist to limit treatment to the breast only, without the additional need to irradiate the axilla and supraclavicular fossa.^{15,16} Hence, pathological axilla staging is recommended together with BCT and RT in the management of early-staged breast cancer.

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Although many studies have evaluated the efficacy of BCT and RT in Caucasians, no information is available in the literature for Chinese patients. This retrospective study was undertaken to evaluate the results of BCT and RT in early-staged Chinese breast cancer patients treated from May 1987 to December 1994 at the Prince of Wales Hospital in Hong Kong.

Subjects and methods

From May 1987 to December 1994, 54 early-staged breast cancer patients were treated with definitive irradiation following breast-conserving surgery (Fig 1). Exclusion criteria included the presence of a multifocal primary (clinical or mammographic evidence), diffuse clustered microcalcification on mammogram, gross residual tumour after local resection, collagen vascular disease, a history of prior irradiation to the breast, and pregnancy. Patients with pathological features of extensive intraductal carcinoma and endolymphatic invasion—which are risk factors known to be associated with treatment failure—were also included unless the microscopic resection margin was involved. All patients were treated uniformly with the departmental treatment protocol, effective since 1993 (Fig 2). Analysis of cases was limited to those who had American Joint Committee on Cancer (AJCC) clinical stage I (T1N0M0) or II (T2N0M0, T1N1M0 or T2N1M0, Table 1).¹⁷

Breast-conserving surgical procedures included lumpectomy, wide local excision, and quadrantectomy. Surgical re-excision was performed in one patient because of a positive initial excision mar-

gin. Forty-seven of 54 patients underwent an axillary surgical staging procedure which included either a sampling (11 patients), level I/II dissection (26 patients) or full axillary clearance (10 patients).

Radiation consisted of whole breast irradiation using opposed tangential fields with 6 mV photons. Due to a shortage of radiotherapy machines, a majority of patients in the early part of the study were treated with various hypofractionated regimes. The equivalent conventional dose to the whole breast ranged from 44 Gy to 54.7 Gy. The medial border was set at the patient's midline while the superior, inferior, and lateral borders were 1 to 2 cm beyond palpable breast tissue. No particular effort was made to cover the internal mammary lymphatics. Thirty-nine patients received booster irradiation to the tumour bed using either electrons, iridium implant, or fractionated high dose-rate brachytherapy. The booster radiation dose ranged from 11.5 Gy to 33 Gy. In node-positive patients, those with inadequate axillary sampling (fewer than 6 lymph nodes identified in the pathology report), and those without surgical staging of the axillary nodes, a third field was added to treat the axilla apex and supraclavicular fossa to an equivalent conventional dose of 50 Gy to 57 Gy at a depth of 4.5 cm. A posterior axillary boost was given to increase the midplane axilla dose to the prescribed dose.

Adjuvant systemic treatment was offered to all pathological stage II patients and one pathological stage I patient. The adjuvant chemotherapy regime consisted of either cyclophosphamide, methotrexate, and 5-

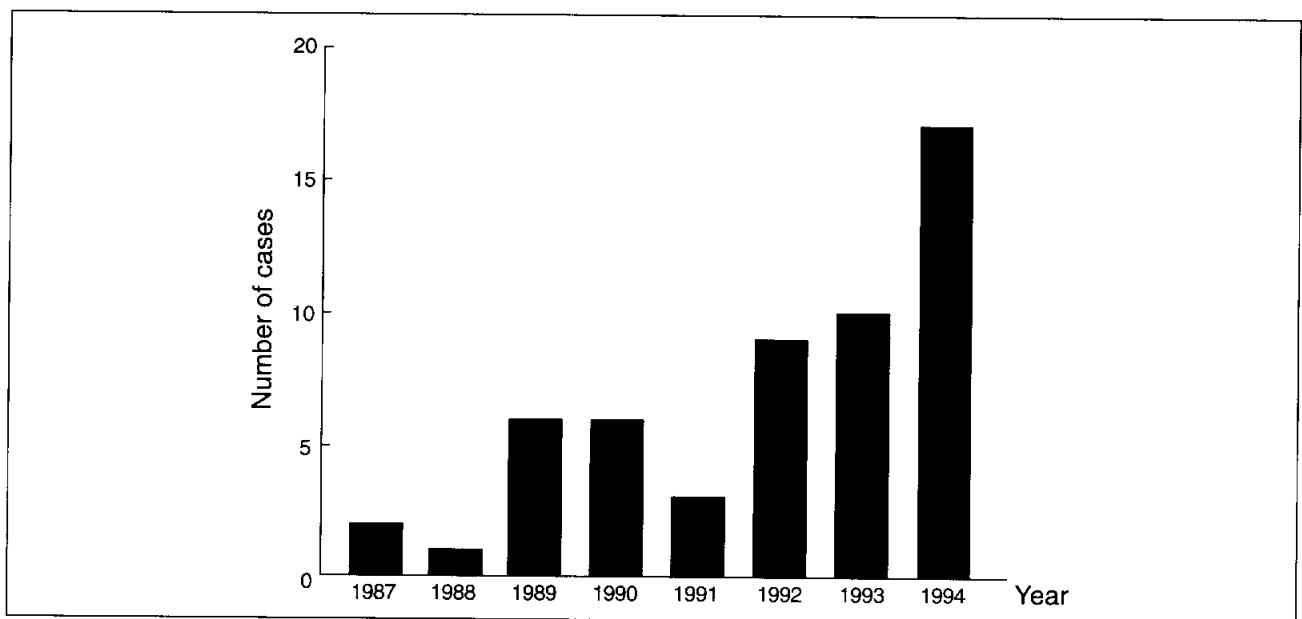


Fig 1. Case distribution from May 1987 to December 1994 for the 54 patients with breast cancer

fluorouracil,¹⁸ or vincristine, epidoxorubicin, and cyclophosphamide. A total of 11 women were treated with chemotherapy of 15 who were pathologically lymph node-positive and two of 41 who were node-negative. Hormonal therapy using tamoxifen was offered to 27 patients. No adjuvant therapy was given to the 14 remaining patients.

The records of these 54 cases were reviewed for histology of primary tumour, breast failure, regional failure, distant metastasis, complications from radiotherapy, and survival. Cosmetic outcome and acceptance by patients and their spouses will be presented in a separate paper. Follow up time ranged from 0.16 to 6.02 years with a median of 1.94 years. Survival curves were calculated using the Kaplan-Meier method with the time period beginning from the date of surgery.

Results

The tumour characteristics for the 54 patients are shown in Table 2. A majority of the patients had invasive ductal carcinoma. Fifty per cent belonged to AJCC clinical stage I and 50% to stage II. For the 47 patients with pathological axillary staging, 46.8% were stage I and 53.2% were stage II. The breakdown by number of positive lymph nodes (one to three vs four or more) is also given. Oestrogen receptor and progesterone receptor status were not analysed because this data was not available in a

significant percentage of the group, particularly those in the earlier years of this study. The median age was 43.5 years (range, 21 to 83 years).

Figure 3a shows that the actuarial overall survival and disease-free survival at five years for the group were 75.3%±18% (95% confidence limits) and 79.9%±15.3%(95% confidence limits), respectively. Also given at yearly intervals are the number of patients at risk. The median follow up time was 1.94 years. The actuarial survival rates of patients with clinical and pathological stage I and II breast cancer were similar (Fig 3b). This is probably related to the small number of patients in our study.

Our present study showed excellent local and regional control. Only one patient relapsed in the breast area and another relapsed in the axilla (Fig 4). The patient who relapsed diffusely in the breast received a total dose of 63 Gy to the tumour bed and adjuvant chemotherapy due to positive nodal status. The patient with axillary relapse had received axillary irradiation because of two metastatic lymph nodes with pathological evidence of extracapsular involvement on full axillary dissection. Because of the small number of patients in the study, the impact of potential risk factors (T stage, N stage, radiation dose, chemotherapy) for local and regional control could not be analysed. Distant metastasis occurred in five patients, four of whom belonged to pathological stage II and were given adjuvant

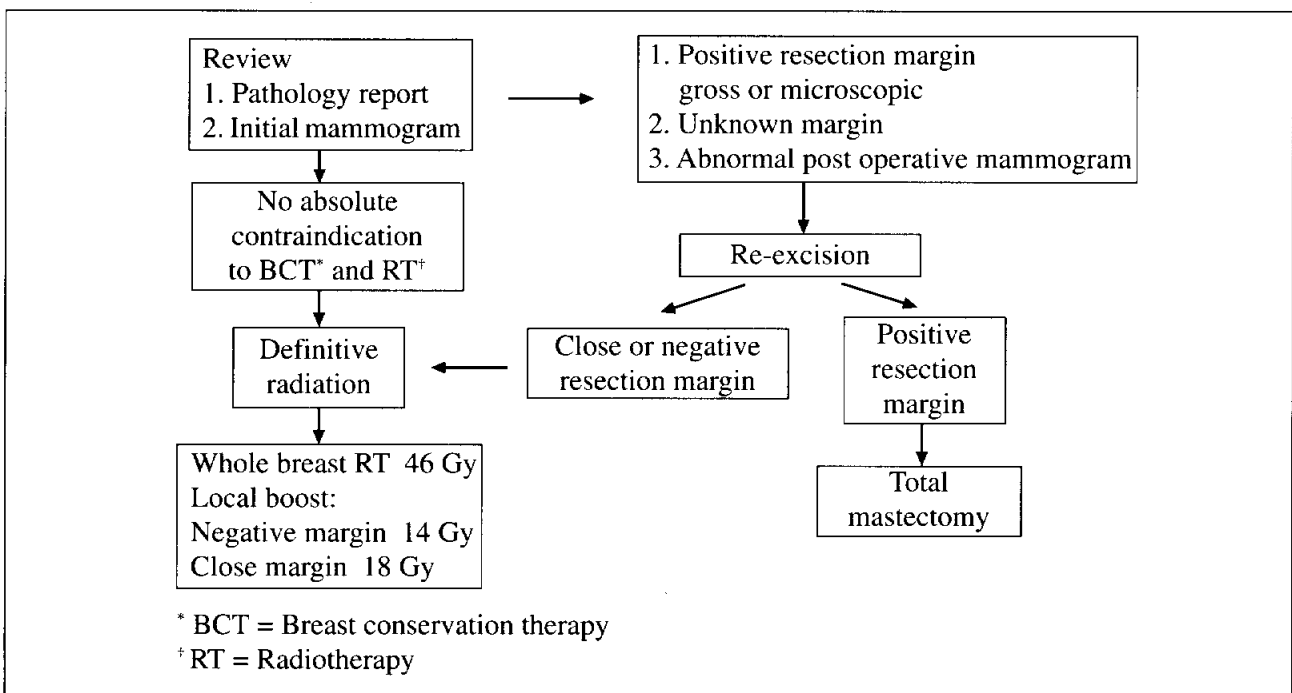


Fig 2. Treatment protocol for breast conservation therapy and radiotherapy used in this study

systemic treatment. The patient with local failure had simultaneous liver and bone secondaries five months after the completion of adjuvant chemotherapy. She rapidly deteriorated and died despite salvage treatment.

Table 3 shows the complications of irradiation which arose. Lymphoedema of the arm, defined as a difference of 2 cm or more in arm circumference, is the most common complication. Four of the five patients who developed lymphoedema had level I/II axillary dissection and post-operative axillary irradiation. The maximum difference in arm circumference in these five patients was 4 cm. None of them were symptomatic or had complications such as ulceration and cellulitis. Of the three patients who developed symptomatic radiation pneumonitis, one had a history of pulmonary tuberculosis and the others had irradiation of both breasts following bilateral breast-conserving surgery. The patient with matchline fibrosis presented with a linear plaque of induration at the upper part of the treated breast 18 months after irradiation. Biopsy showed radiation dermatitis and fibrosis with no evidence of relapse.

Cox regression analysis was performed to assess the influence of T stage (T1 vs T2), N stage (N0 vs N1), age, adjuvant chemotherapy and total radiation

dose to the breast on survival. Except for the marginal significance of N stage on survival ($P=0.07$), all other factors were not statistically significant. The small patient number and the short follow up time probably account for the negative effect of T and N stages on survival.

Discussion

Breast cancer has overtaken bronchogenic carcinoma to become the most common malignancy in women in Hong Kong since 1990.¹⁹ Our department has been treating approximately 150 new cases of breast cancer annually, 75% of which are stage I and II disease (unpublished data). With the increase in public awareness of the disease and the establishment of well-woman clinics by the Department of Health, the proportion of early-staged breast cancers detected is expected to increase. Our study showed that a majority of stage I and II breast cancer patients were being treated with mastectomy, although breast conservation surgery has been used more in recent years.

As one of the major objectives of primary radiation therapy for early-staged breast cancer is breast preservation, local and loco-regional control are important outcome parameters to measure the success of treatment. Our overall projected five-year local con-

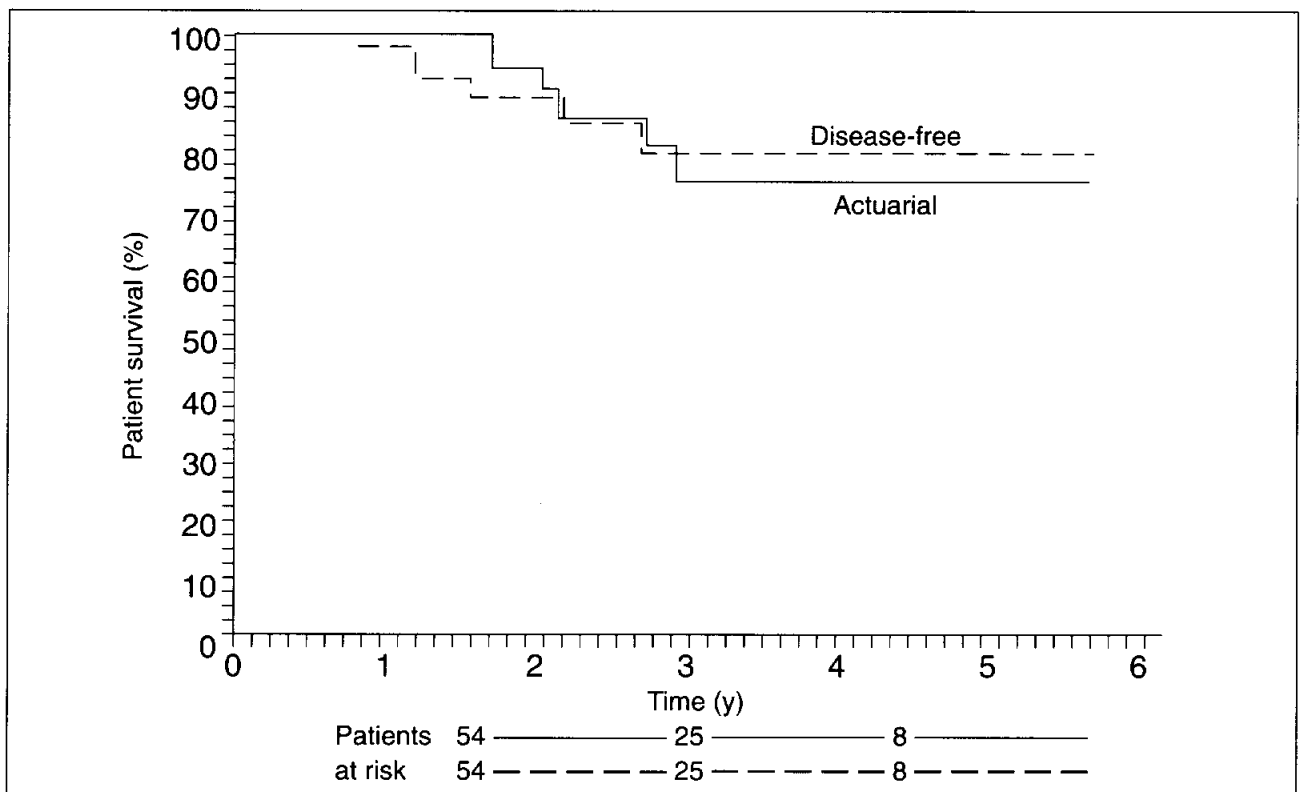


Fig 3a. Actuarial survival and disease-free survival rates over the six years of the study period

trol rates of 97% compare favourably with other reported series. Recht et al, from the Joint Center for Radiation Therapy report a 4% and 10% local recurrence rate at five years for stage I and II patients, respectively, who were treated with excisional biopsy plus a boost dose of more than 6000 rad.²⁰ Solin et al, from the University of Pennsylvania, United States, report a five-year local failure rate of 6% in stage I and II breast cancer patients treated with BCT and RT with boost dose of 60 to 66 Gy.²¹ Five-year results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial reported by Fisher et al, report a 7.7% breast recurrence rate for segmental mastectomy plus breast irradiation but without a breast boost.¹ Although our early local control rate is extremely good, a longer follow up period and more patients included in the study are needed to draw a firm conclusion.

In order to achieve good local control comparable to that achieved with mastectomy, it is necessary to choose patients carefully and to integrate the surgical, pathological, chemotherapeutic, and radiotherapeutic aspects meticulously in the overall treatment programme. The probability of breast relapse is directly related to the microscopic residual tumour burden in the breast and indirectly to the total radiation dose given. In order to achieve a good

cosmetic outcome, it is agreed that the whole breast dose should not exceed 50 Gy, the booster dose should not exceed 16 Gy, and the patient should be treated with conventional 2 Gy fractions.²²

The excellent local control in our series is partly related to the high radiation dose employed in the initial years of the study when cosmetic outcome was sacrificed and is partly related to the short median follow up. Our careful patient selection should also have helped. Multifocal tumour, a positive resection margin, and mammographic evidence of diffuse clustered microcalcifications, which are known to indicate significant residual microscopic disease in the breast, were excluded. For those patients with microcalcifications suggestive of tumour on their mammogram, a specimen radiograph is mandatory to ensure complete removal of the entire lesion. Re-excision should be advised for all patients with a positive initial resection and this has not been reported to result in a worse cosmetic outcome. Fowble et al, at the University of Pennsylvania, United States, and the NSABP-B06 trial report that patients with pathological risk factors, such as extensive intraductal carcinoma and endolymphatic invasion, can be safely included for BCT and RT if the microscopic resection margin is clear.²³ Our

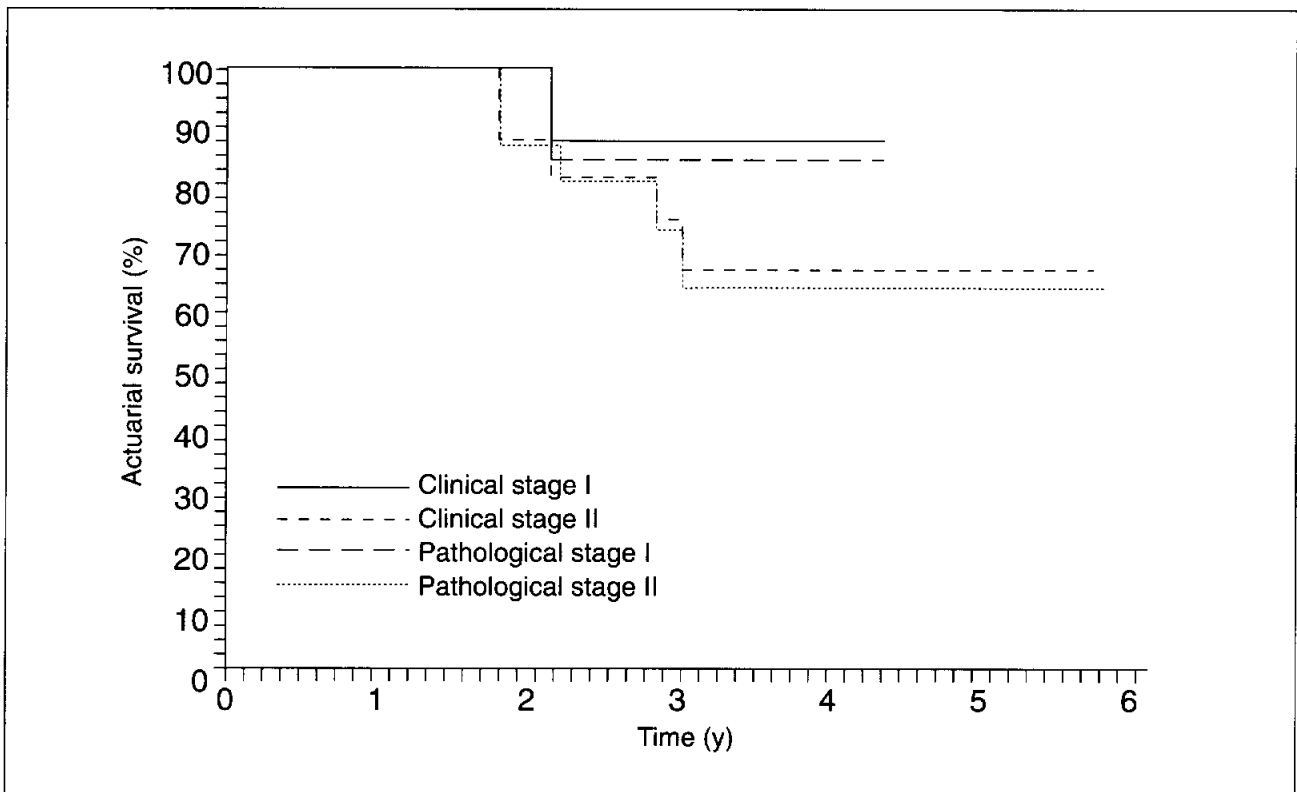


Fig 3b. Actuarial survival comparing clinical stage I and II breast cancer patients with pathological stage I and II breast cancer patients

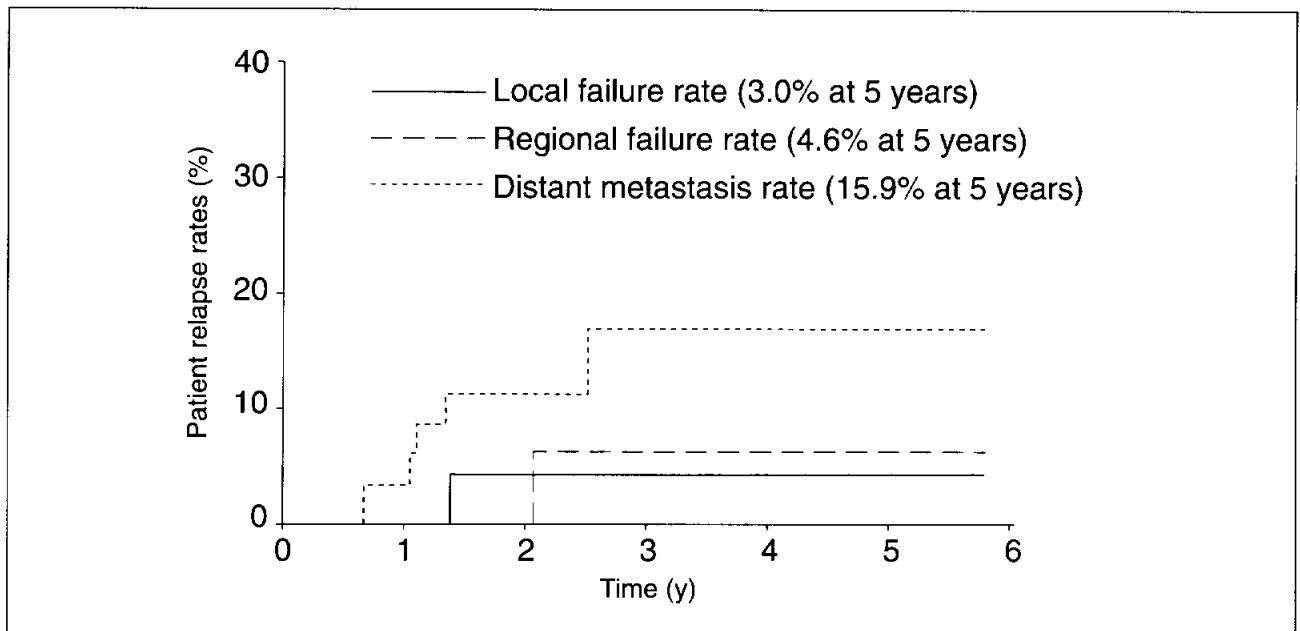


Fig 4. Local failure and regional failure and distant metastasis rates of study patients

Table 1. Stage grouping of breast cancer using the American Joint Committee on Cancer criteria

Stage 0	TIS	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

small study failed to demonstrate the impact of chemotherapy, which is generally considered to improve local control.¹

We were giving axillary irradiation with moderate doses quite liberally in the early part of the study. Since 1993, almost all patients were staged pathologically with either level I or II dissection or full axillary dissection. Regional radiotherapy was only given if there were four or more lymph nodes involved or extra-

capsular invasion. Our study showed excellent regional control with only one patient having axillary relapse. Adjuvant systemic treatment was offered to all pathological stage II patients. Distant metastasis occurred in 16.5% of the patients, which is comparable with other reported series.

Many studies have demonstrated that breast cancer patients treated with BCT and RT have a breast failure rate of approximately 1% to 2% annually, reaching a plateau of 15% to 20% at 15 years.²⁴ Fowble et al, report that 65% of breast recurrences are in the vicinity of the original primary, 26% are in a quadrant distinct from the initial tumour, and the remainder show diffuse involvement of the breast.²⁵ The median interval to relapse is 34 months.²⁵ The prognosis of patients with local relapse after BCT and RT was much better than those with chest wall recurrence following mastectomy. Approximately 90% of patients with breast relapse can be salvaged with mastectomy, having a subsequent disease-free survival rate of 60% at five years. The remaining patients present with inoperable advanced local disease with concomitant or antecedent systemic relapse.²⁵ Unfortunately, our patient who had a diffuse recurrence in the breast with a short disease-free interval belonged to the latter group.

The most common complication in our series was lymphoedema of the arm, which occurred in 9.3% of our patients. This was slightly more than the 1% to 7% reported incidence in other series of definitively irradiated patients.²⁶⁻²⁸ However, the definition of arm oedema used by other authors is variable. We take a

Table 2. Patient tumour characteristics

	No. of patients	%
Pathology		
Invasive ductal Ca* grade 1	8	14.8
Invasive ductal Ca grade 2	26	48.1
Invasive ductal Ca grade 3	10	18.5
Mucinous Ca	2	3.7
Medullary Ca	4	7.4
Colloid Ca	1	1.9
Undifferentiated Ca	1	1.9
Infiltrative lobular Ca	2	3.7
Clinical AJCC stage		
Stage I	27	50
Stage II	27	50
Pathological AJCC stage[†]		
Stage I	22	46.8
Stage II	25	53.2
T2N0M0	10	
T1N1M0	10	
T2N1M0	5	
No. of positive lymph nodes[†]		
0	32	68.0
1-3	10	21.4
4 or more	5	10.6
* Ca = Carcinoma		
† Analysed in 47 patients with axillary surgery		

Table 3. Complications of irradiation encountered

Complication	No. of patients	%
Lymphoedema	5	9.3
Radiation pneumonitis	3	5.6
Matchline fibrosis	1	1.9
Without complication	45	83.3

difference of 2 cm in arm circumference as lymphoedema, whereas Danforth et al, use a difference of 4 cm.²⁹ Hence, some of our patients with mild arm swelling might not be considered as a complication in other reported series. Nevertheless, three of the five patients who developed arm oedema had received axillary irradiation of more than 55 Gy and four of the five patients had level I or II axillary dissection plus post-operative irradiation. Both of these factors might contribute to the development of arm swelling. With reduction of the radiation dose to the axilla to

50 Gy and the use of conventional fractionation, the lymphoedema rate is expected to decrease.

With effect from 1993, post-operative axillary and supraclavicular irradiation will only be given to patients with four or more lymph nodes involved or pathological evidence of multifocal extracapsular nodal disease on level I or II, or full axillary dissection. Matchline fibrosis occurred in one patient who was treated in the early days of the study when no particular attention was paid to matching the breast tangential field with the axilla and supraclavicular field. The incidence of symptomatic radiation pneumonitis was 5.6%, which was comparable to the 2% to 9% reported in other series.^{27,28,30,31} One of the three patients who developed radiation pneumonitis had bilateral breast irradiation following BCT. The increase in total volume of lung irradiated probably accounts for the pneumonitis. The upper limit of the thickness of lung allowed in the breast tangents was 3 cm. It was further reduced to 2.5 cm when patients were receiving concurrent chemotherapy and radiotherapy.

We have not observed any patient with rib fracture, fat necrosis, chest wall pain, brachial plexopathy, or pericarditis despite the relatively high radiation dose to both the breast and axilla in our series. Nevertheless, in order to further improve the cosmetic outcome, the total dose to the tumour bed in the breast and to the axilla were reduced to 60 to 64 Gy and 50 Gy, respectively, using conventional fractionation in our current treatment protocol.

Our retrospective study has shown that BCT and RT in a series of Chinese patients showed excellent local and regional control with acceptable complications compared with other studies. With further dose reduction, as suggested in our new treatment protocol, increase in fractionation, and refinement of radiotherapy technique, there should be further improvement in the cosmetic outcome without sacrificing local and regional control. Surgical axillary staging should be incorporated into the management programme because of its prognostic and therapeutic implication. Breast conservation therapy and RT should be offered as an alternative treatment to mastectomy in properly selected early-staged breast cancer patients.

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