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Breast conservation treatment in Hong Kong—early results of 203 patients: retrospective study

在香港接受乳房保留治療的203名患者的早期結果：回顧研究

Objective. To study the clinical outcomes of patients with invasive or non-invasive breast cancer after breast conservation treatment.
Design. Retrospective study.
Setting. Clinical oncology department of a public hospital, Hong Kong.
Patients. Two hundred and three patients who received postlumpectomy radiotherapy at the Pamela Youde Nethersole Eastern Hospital between January 1994 and June 1999.
Interventions. Adjuvant radiotherapy with or without systemic adjuvant treatment.
Main outcome measures. Actuarial local control rate, progression-free survival rate, disease-specific survival rate, and cosmetic score.
Results. The median follow-up was 3.5 years. Two of the 25 patients with carcinoma in situ only developed local recurrence; the 5-year actuarial local control rate was 91.3%. Among the 178 patients with invasive cancer, seven had a local recurrence and 12 developed distant metastases without local failure. The 5-year actuarial local control, progression-free survival, and disease-specific survival rates for patients with invasive cancer were 95.5%, 85.8%, and 95.2%, respectively. The risk of local recurrence was significantly increased for younger patients (age <40 years) and those with positive final margins. Cosmetic scores were rated good to excellent by 95.6% of patients.
Conclusions. The early clinical outcomes of these patients are comparable to those in large overseas trials, which have demonstrated the equivalence of mastectomy and breast conservation treatment in terms of survival. In addition to mastectomy, with or without breast reconstruction, breast conservation treatment should be offered as an alternative to suitable Chinese women. To maximise local control, further excision or mastectomy is recommended for patients with positive final margins.

目的：研究侵犯性或非侵犯性乳癌患者在乳房保留治療後的臨床結果。
設計：回顧研究。
安排：香港一所公立醫院的臨床腫瘤科。
患者：1994年1月至1999年6月期間，203名在東區尤德夫人那打素醫院接受局部切除後放射治療的患者。
療法：輔助放射治療；部份患者或配合輔助性全身療法。
主要結果測量：準確局部控制率、癌症無進展存活率、疾病相關存活率、以及外觀評價。
結果：患者的中值隨訪期為3.5年。25名原位癌患者中有2名出現局部復發；5年準確局部控制率是91.3%。在178名侵犯性乳癌患者中有7名局部復發，12名沒有局部復發但腫瘤呈遠處轉移。侵犯性乳癌患者的5年準確局部控制率，癌症無進展存活率，和疾病相關存活率，分別為95.5%、85.8%、和95.2%。局部復發的危險性在年齡小於40歲的年輕患者和最終切除邊沿仍有癌細胞的患者中明顯增加。95.6%患者對患處外觀評為優良。
結論：患者的早期臨床結果與其他大型的外國研究相似，證明乳房切除術和乳房保留治療在存活率方面成效相同。除乳房切除外，乳房保留治療在合適的華人婦女中可作為一種治療的選擇。對於最終切除邊沿仍有癌細胞的患者，為要增加局部控制，我們仍建議作進一步的乳房切除。

Key words:
Breast neoplasms;
Radiotherapy

關鍵詞：
乳房腫瘤；
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Introduction

Breast conservation treatment (BCT), with its cosmetic and psychological advantages, has been increasingly used in the past 20 years. Following the demonstration in the late 1980s of the equivalence of BCT and mastectomy in terms of survival outcome in randomised clinical studies,[1-4] BCT has been widely accepted as one of the standard treatment options for early invasive breast cancer. For stages I and II disease, breast conservation rates in the United States rose from 32.8% in 1985 to 44.1% in 1994. Similarly, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study[5] indicates that local excision and breast irradiation are acceptable alternatives to mastectomy for patients with localised ductal carcinoma in situ (DCIS).

Due to the relatively smaller breast size of Chinese women, BCT has long been considered unsuitable for most patients in Hong Kong.[6] The first large and local series of BCT was reported by Kwan et al[7] in 1996. Fifty-four patients with stage I or II breast cancer were treated with BCT at the Prince of Wales Hospital between 1987 and 1994. At a median follow-up of 1.94 years, one patient developed local recurrence, one had regional relapse, and five developed distant metastases. Various hypofractionated radiotherapy schemes and boosting techniques (electron, iridium implant, and fractionated high-dose rate brachytherapy) were applied to these patients, making interpretation difficult. Cosmetic outcomes were not reported.

Given that the above series was collected over a 7-year period at a large regional public hospital, BCT was obviously not a common mode of breast cancer management in the early 1990s. Reasons for this included the scarcity of small lesions detected at screening, long waiting times for radiotherapy, and the bias of both surgeons and patients. However, with the increase in number of radiotherapy machines and the promotion of BCT by breast surgeons, oncologists, and patient support groups, the situation has changed considerably, and more and more patients are now treated with breast conservation. In 2000 alone, 56 patients received radiotherapy for BCT in the Department of Clinical Oncology at the Pamela Youde Nethersole Eastern Hospital.

The Department of Clinical Oncology of Pamela Youde Nethersole Eastern Hospital was established in 1994. By examining the clinical outcomes of more than 200 patients treated from 1994 to 1999, we aim to find out whether it is safe to offer BCT as an alternative to mastectomy in our local population, and whether the treatment outcomes of our patients are comparable to those of western countries.

Methods

Patient characteristics and selection

Data analysis was carried out in February 2002. The medical records of all female patients who received post-lumpectomy radiotherapy for BCT at the Pamela Youde Nethersole Eastern Hospital between January 1994 and June 1999 were reviewed, including patients treated for DCIS alone.

In this group of 203 patients, 141 were referred by public hospitals and 62 were referred by private or overseas surgeons. Their ages ranged from 25 to 90 years (median, 44 years). One hundred and ninety-six (96.6%) patients were Chinese, three were other Asians, and four were Caucasians. The median duration of follow-up was 3.5 years (range, 0.2-7.9 years). One patient was followed up for 0.2 years only because she returned to her home country soon after completion of radiotherapy.

Surgical and pathological characteristics

Twenty-five patients had DCIS only. The characteristics of the other 178 patients with invasive carcinoma are listed in Table 1. Ninety-three patients had stage I (T1N0) disease and another five had T1 lesions with unknown axillary status (T1Nx). The remaining 80 patients had stage II disease.

The case selection criteria and treatment largely followed the 1992 Standards for breast conservation treatment jointly developed by the American College of Radiology, American College of Surgeons, College of American Pathologists, and Society of Surgical Oncology.[8] Negative microscopic margins were required before radiotherapy. Patients referred with positive microscopic margins were advised to have further excision before radiotherapy. Indeed, some patients had already had re-excision to achieve negative or wider margins before referral. Overall, 193 patients had negative final microscopic margins, including 44 who had margins that were considered to be close (ie <3 mm). The remaining 10 patients had positive final margins. Further excision or mastectomy was not performed in these patients, either because of refusal by the patient, or because of technical difficulties in further resecting the deep margin close to the chest wall.

Axillary dissection was not done for patients with DCIS only. It was, however, performed for all patients with invasive cancer, except five patients who refused this operation. Since the level of axillary dissection was not clearly stated in many referrals, this factor was not further analysed.

Radiotherapy

All but one patient received whole breast irradiation after breast conserving surgery. The exception was a 74-year-old woman who, on account of her lesion being located high up in the chest wall, received radiotherapy to the tumour bed only (35 Gy in 10 fractions). For all other patients, breast boards were used for the daily treatment. Wedged tangential opposing fields with 6 MV photons (linear accelerators) were used to deliver 50 Gy in 2 Gy daily fractions over 5 weeks. No bolus was used. Electron boost to the tumour bed was routinely given for all patients except

Table 1. Prognostic factors for local and distant/regional failure in patients with invasive cancers

	Patients No. (%)	Local failure*		Distant/regional failure	
		5-Year actuarial rate (%)	P value	5-Year actuarial rate (%)	P value
Age (years)					
≤40	55	12.0	-	22.0	-
41-60	102	1.0	0.03	4.5	0.09
>61	21	0	-	5.0	-
Pathological stage					
Stage I (T1N0)	**93**	3.0	-	2.5	-
Stage II	**80**	7.0	0.39	21.0	0.01
T1N1	29	-	-	-	-
T2N0	28	-	-	-	-
T2N1	21	-	-	-	-
T2Nx	2	-	-	-	-
T1Nx	**5**	0	-	0	-
Histological grade					
I	34	0	-	0	-
II	54	2.0	0.26	14	0.34
III	60	8.5	-	14	-
NA†	30	5.0	-	10	-
Number of involved nodes					
0	128	4.0	-	6	-
1-3	37	0	0.051	22	0.1
>3	13	23.0	-	31	-
Oestrogen receptor status					
ER+‡ or PR+§	110	5.0	-	4	-
ER-‖ and PR-¶	46	7.0	0.04	30	0.0001
Unknown	22	0	-	5	-
Final margin status					
≥3 mm	130	2.0	-	11	-
>0 but <3 mm	38	10.0	0.01	12	0.91
Positive	10	21.0	-	10	-

* as first site of failure
† NA not applicable or not assessable
‡ ER+ oestrogen receptor–positive
§ PR+ progesterone receptor–positive
‖ ER- oestrogen receptor–negative
¶ PR- progesterone receptor–negative

those with more than 1 cm–free microscopic margins on all sides. The routine boost dose was 10 Gy in five daily fractions. For those with microscopic margins of 1 mm or less, a higher dose of 16 Gy in eight daily fractions was given. Interstitial brachytherapy was not used for boosting. Altogether, 174 patients received electron boost to the tumour bed, including 24 who received the boost dose of 16 Gy.

Regional radiotherapy to the ipsilateral axilla and supraclavicular fossa was offered to those patients with invasive cancer who had more than three positive axillary nodes, gross extranodal extension, or no axillary dissection. A separate anterior field was used to deliver 50 Gy in 2 Gy daily fractions. No posterior axillary field was used. The internal mammary chain (IMC) was not specifically included, although it might have been partially covered by the tangential opposing fields. No separate IMC field was used. Among those 178 patients with invasive cancers, 17 received additional regional irradiation. Another three refused this form of treatment because of concerns over arm lymphoedema.

Radiotherapy was started after a median duration of 5 weeks (range, 2-13 weeks) after surgery unless it had to be deferred until the completion of chemotherapy. The relatively long postsurgical gap (>6 weeks) for some patients was due either to delays in initiating referral or wound healing problems. Patients receiving chemotherapy prior to radiotherapy had a postsurgical gap of 14 to 48 weeks, depending on the chemotherapy regimens used.

Systemic therapies

Patients considered to have an increased risk of distant failure were offered systemic adjuvant therapies. Some patients received such therapies from other public hospitals or private doctors. A total of 149 patients with invasive cancer received additional systemic adjuvant therapy—79 received tamoxifen alone; 40 received both tamoxifen and chemotherapy; and 30 received chemotherapy alone.

Sequencing of chemotherapy with radiotherapy

Patients considered to be at high risk of systemic failure were given chemotherapy within a few weeks of surgery, either concurrent with, or completed before, radiotherapy. Patients at relatively lower risk of systemic failure received chemotherapy after completion of radiotherapy. Among the 70 patients who received chemotherapy, nine were treated preoperatively to downsize the tumour, 21 were treated concurrently with radiotherapy, 15 were treated adjuvantly before radiotherapy, and 25 were treated after the completion of radiotherapy. The impacts of sequencing on local and distant failure rates are reported separately.

Table 2. Scoring system of breast cosmesis

Excellent (9-10)	Treated breast is almost identical to the untreated breast
Good (7-8)	Minimal difference between the treated and untreated breasts
Fair (5-6)	Obvious difference between the treated and untreated breasts
Poor (1-4)	Major functional and aesthetic sequelae in the treated breast

Follow-up and reassessment

Patients were followed up every 2 to 3 months in the first 2 years, and then every 4 to 6 months in the third to fifth years. Annual mammograms were routinely used to detect early recurrence. A 10-point scoring system was used to record the breast cosmesis at follow-up (Table 2). The score was rated as excellent (9-10), good (7-8), fair (5-6), or poor (1-4). The score was given by the patients and by the attending clinical oncologist/trainee. A simple and commonly accepted definition of arm lymphoedema was used, namely, a 2 cm or more difference in mid-arm circumference.

Statistical methods

Actuarial local control, progression-free survival, and disease-specific survival rates were estimated using Kaplan-Meier survival curves. The date of last local excision was used as the beginning of the follow-up interval. Using log-rank tests, the following clinical and histopathological factors were analysed for their ability to predict for local failure and distant/regional failure: age, pathological stage, histological grade, number of involved nodes, oestrogen receptor status, and final margin status.

Results

Local and distant failure

Ductal carcinoma in situ

The median follow-up for the 25 patients with DCIS only was 3.4 years (range, 2.6-6.7 years). Two (8.0%) developed in-breast recurrence, one with DCIS only on salvage mastectomy while the other was still being scheduled for operation at the time of the last data entry. The 5-year actuarial local control rate was 91.3%. There was no distant or regional failure in this group.

Invasive breast cancer

The median follow-up for the 178 patients with invasive cancer was 3.6 years (range, 0.2-7.9 years). Seven (3.9%) suffered local recurrence, five with local recurrence only and the other two with regional or distant secondaries simultaneous with the local recurrence. Local recurrences were detected at 12 to 76 months after surgery. All five patients with local recurrence had only undergone salvage mastectomy: three had invasive ductal carcinomas, one had DCIS with micro-invasion, and one had DCIS only.

Of the five patients with local recurrence only, two were detected at a late stage. In one of the patients, gross skin infiltration was detected soon after childbirth. In another patient, there was extensive local recurrence requiring flap reconstruction in salvage surgery. The first patient had a good response to preoperative chemotherapy and remained disease-free after salvage mastectomy. For the second patient, however, salvage surgery was unsuccessful and she developed further local recurrence and lung secondaries 8 months later. Overall, four of the five patients presenting with local failure only remained disease-free after salvage treatment.

The risk of disease failure in relation to the patient and histopathological characteristics are shown in Table 1. Despite the higher boost dose given, patients with positive microscopic margins still had a significantly higher risk of 5-year local failure compared to those with close (<3 mm), but clear, margins, and those with negative margins (21% versus 10% and 2%, respectively; P=0.01).

Our experience is similar to overseas studies[9,10] in that the risk of local recurrence was significantly higher for younger patients. The 5-year actuarial local failure rates for patients aged 40 years or younger, 41 to 60 years, and 61 years or older were 12%, 1%, and 0%, respectively (P=0.03).

Twelve (6.7%) patients developed distant metastases without any signs of local recurrence. As expected, oestrogen receptor–negative tumours had a significantly higher 5-year actuarial distant failure rate compared with oestrogen receptor–positive tumours (30% versus 4%, P=0.0001); the same was true for stage II tumours compared with stage I tumours (21.0% versus 2.5%, P=0.01).

The 5-year actuarial local control and progression-free survival rates for patients with invasive cancer were 95.5% and 85.8%, respectively (Fig). Since most patients with in-breast recurrence only remained disease-free after salvage treatment, the 5-year actuarial disease-specific survival rate remained high at 95.2%.

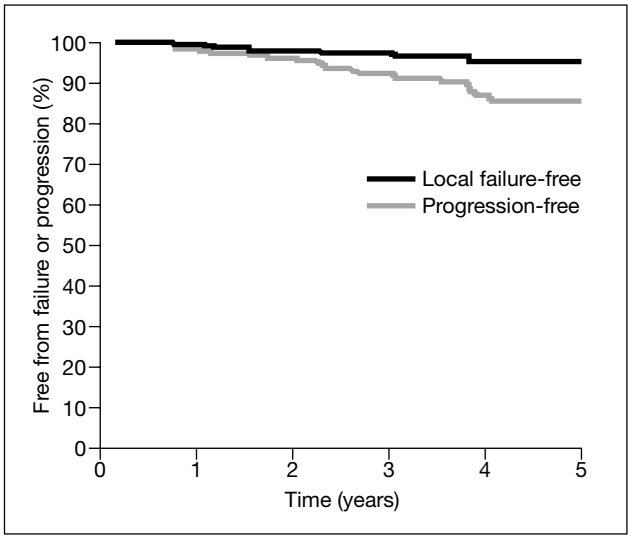

Fig. 5-Year actuarial local control and progression-free survival rates among 178 patients with invasive cancer undergoing breast conservation treatment

Table 3. Cosmetic scores in 203 breast conservation treatment patients

Cosmetic score	Self-assessment by patient No. (%)	Assessment by clinical oncologist No. (%)
10	9 (4.4)	7 (3.4)
9	52 (25.6)	54 (26.6)
8	76 (37.4)	77 (37.9)
7	38 (18.7)	40 (19.7)
6	5 (2.5)	4 (2.0)
5	2 (1.0)	3 (1.5)
4	1 (0.5)	1 (0.5)
1-3	0 (0)	0 (0)
Not recorded	20 (9.9)	17 (8.4)
Median cosmetic score*	8	8
Average cosmetic score*	8.07	8.04

* of patients with known scores

Treatment complications

Radiotherapy was well tolerated and completed uneventfully in all but two patients, one stopped radiotherapy prematurely at 56 Gy for personal reasons and the other stopped prematurely at 46 Gy after developing a breast abscess. Transient grade 1 to 2 skin reactions were common, but there were no other significant acute side-effects. There were no cases of radiation pneumonitis, rib fractures, matchline fibrosis, or brachial plexopathy.

Arm lymphoedema developed and persisted in three (17.6%) of the 17 patients who received additional regional irradiation. Three (1.6%) of the remaining 186 patients who did not receive additional regional irradiation also developed mild and transient arm lymphoedema. In other words, arm lymphoedema developed in only six (3.0%) patients.

Cosmesis

The cosmetic scores are shown in Table 3. Seventeen patients did not have any cosmetic assessment recorded and three had scores given by doctors only. The average (out of 10) cosmetic scores given by patients and doctors were 8.07 and 8.04, respectively. The cosmetic results were rated as either good or excellent by 95.6% of patients. Eight patients rated their cosmetic results as either poor or fair.

Discussion

Options for the surgical management of primary breast tumours include breast conserving surgery plus radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Despite recent advances in reconstructive techniques, BCT is still more widely used to preserve the body contour. For example, throughout the study period, only 21 patients referred for systemic treatment or radiotherapy had breast reconstruction performed. Preferences on the part of the patient and/or the surgeon, and the limited availability of experienced plastic surgeons might all be contributing factors.

For invasive breast cancer, radiotherapy is widely accepted as one of the essential component in BCT.[8,11] Breast conserving surgery without radiation therapy has been compared with breast conserving surgery followed by radiation therapy in four prospective randomised trials,[2,12-14] all of which demonstrated a higher in-breast recurrence rate with breast conserving surgery alone. Thus far, we still cannot reliably identify a subgroup of patients that do not require radiotherapy. The recently reported results of the NSABP B-21 study[15] also support the belief that even small tumours with clear resection margins require radiotherapy.

Similarly, for DCIS after lumpectomy, the NSABP B-17 study[5] showed that the occurrence of invasive cancer decreased from 13.4% to 3.9% with the addition of radiation, and that of recurrent DCIS was reduced from 13.4% to 8.2%. Only 1% of patients in the NSABP study died from breast cancer, which was similar to the historical control rate (after mastectomy). This trial indicates, therefore, that local excision, together with breast irradiation, is an acceptable therapy for localised DCIS. It did not identify any subset of patients that did not benefit from the addition of radiation therapy.

The 5-year actuarial local control and disease-specific survival rates in our patients are comparable to those reported in large overseas studies.[2,3,5] In a series from the Netherlands consisting of 1360 patients with invasive cancer, the 5- and 10-year local recurrence risks were 8% and 12%, respectively.[9] Young age (<45 years) is a major risk factor and there is a gradual, but significant, decrease in local recurrence with advancing age. Local relapse rates of 15% to 20% after 15 years have been reported in a series with extended follow-up, and the annual rate of local relapse was generally estimated to be 1%.[16]

With careful planning of radiotherapy and restriction on the volume of lung tissues irradiated, none of our patients developed clinical radiation pneumonitis, brachial plexopathy, or matchline fibrosis. In addition, the overall incidence of arm lymphoedema in this series (3%) is lower than that reported in overseas series of BCT that have used a similar definition for lymphoedema (3% versus 14% to 16%, respectively).[17,18] More than half of the patients in the overseas studies did not receive regional irradiation. Although reports relate the occurrence of arm lymphoedema to older age, obesity, and surgical techniques, axillary irradiation is still the most important predictor.[19,20] We

believe that our strict selection criteria for axillary radiotherapy contributed to the low rate of arm lymphoedema. However, since late radiation damage and carcinogenesis may take years to develop, longer follow-up is required to conclusively report on the radiotherapy-related side-effects in these patients.

The role of boost dose to the tumour bed remains controversial. The results of a randomised French study suggest that a 10 Gy boost (with electron beam in four fractions) after whole breast irradiation (50 Gy in 2.5 fractions) may significantly reduce the 5-year local recurrence rate from 4.5% to 3.6%.[21] The boost group had a higher rate of grades 1 and 2 telangiectasia (12.4% versus 5.9%), but no difference was seen in the patient-assessed cosmetic score. Similarly, the European Organisation for the Research and Treatment of Cancer (EORTC) randomised trial presented at the Second European Breast Cancer Conference (Brussels, 2000) showed that a boost dose significantly reduced the 5-year local recurrence rate for patients with negative margins from 6.8% to 4.3% ($P<0.0001$).[22] As the surgical margins in many Chinese patients are quite close, we advocate routine boosting except for those with microscopic margins of more than 1 cm. Electron boosting is simple, non-invasive, and effective.

In this study, final resection margin status correlated with the risk of local recurrence. This finding is consistent with that reported by other studies. For example, a recent retrospective study from France found a high 5-year local recurrence rate of 20% in 152 node-negative patients with positive margins after conservative surgery who received radiotherapy without chemotherapy (which might have reduced the local recurrence rate).[23] This study confirmed that positive margins increased the risk of local recurrence. The risk was increased regardless of the extent (single or multiple) and histology (infiltrating or intraductal carcinoma) of the positive margins. Although 64% of patients in this series received doses ≥70 Gy, no dose effect was observed on the local control rate. The authors concluded that radiotherapy could not be considered as an alternative to re-excision for these patients.

Likewise, Wazer et al[10] showed that dose escalation of breast conserving irradiation yielded low local recurrence rates for close (>0 to ≤2 mm) and intermediate (2.1 to 5 mm) margins, but not for positive margins. The overall mean annual local failure rate in the first 4 years was exceptionally low at 0.25%, but it rose to a mean of 1.1% in subsequent years. There was a significant increase in the relative risk of local failure at age 45 years or below (range, 11.1-17.4 years), irrespective of final margin status. These investigators concluded that although graded dose escalation according to final margin status resulted in a low risk of early local recurrence within the first 5 years, this strategy was unable to completely overcome the long-term adverse influence of young age and positive margins.

As to whether the adverse effect of positive margins can be overcome with a higher boost dose delivered by brachytherapy, excellent local control and acceptable cosmetic outcomes have been reported with fractionated interstitial high dose rate brachytherapy boost.[24] However, only six of the 18 patients in this small series had focally positive final margins; the remainder had close, but clear, margins.

In contrast with the previous belief that patients with focal margin involvement and no extensive intraductal carcinoma might reasonably be considered for BCT, we strongly recommend patients with positive margins to have further excision or mastectomy if possible. Further dose escalation, even with interstitial brachytherapy, is likely to be inadequate, and local recurrence is associated with a higher risk of distant metastasis and death.[9]

Should re-excision be performed for patients with close, but clear, margins? Despite years of discussion, the question of what is an acceptable margin status has not been resolved yet. In our series, patients with close (<3 mm), but clear, margins also had an increased risk of local recurrence (10% at 5 years). The closest margins in Chinese women are frequently the deep ones, and re-excision, or even mastectomy, might not help these patients. For some patients, re-excision for wider margins would likely have an adverse effect on the cosmesis. Patient preference, potential impact on the cosmesis, and technical feasibility (especially for close deep margins) are all important considerations in deciding whether or not these patients should undergo re-excision. A more generous initial excision to avoid the need for a re-excision for positive or close margins is advised.

Conclusion

The early clinical outcomes of these patients are comparable to those in large overseas trials that have demonstrated the equivalence of mastectomy and BCT in terms of survival outcomes. In addition to mastectomy, with or without breast reconstruction, BCT should be offered as an alternative to suitable Chinese women. To maximise the local control, further excision or mastectomy is recommended for patients with positive final margins.

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