

Role of Radiotherapy in Patients with Early Breast Cancer

a report by

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Introduction

Numerous studies have shown that radiotherapy (RT) can reduce both tumor burden and the risk of tumor recurrence in various circumstances, and it has played an integral role in the conservative management of early breast cancer. In 1991, the National Institutes of Health (NIH) Consensus Conference recommended the following steps for patients who undergo breast conservation:

- local excision of the primary tumor with clear margins;
- level I-II axillary node dissection; and
- post-operative breast irradiation to 45 to 50 Gy with or without a boost.^{1,2}

For early stage breast cancer, lumpectomy plus sentinel lymph node (SLN) biopsy followed by breast conservation RT (BCR) is a *de facto* standard of care.³⁻⁶

The basis for this standard of care derives from large randomized studies that have demonstrated that the treatment of local breast cancer does not need to be as disfiguring as in the past. The major risk of death continues to lie in our inability to prevent metastatic disease. Breast cancer is a systemic disease which requires a systemic approach. This paper will focus on the use of RT in the treatment of localized breast cancer: when and how should it be delivered, what are the benefits and what are the short- and long-term risks?

Landmark Studies of Radiation Therapy in Early Breast Cancer

For most of the 20th century, all stages of breast cancer were treated mainly by aggressive surgical intervention. In 1894, Halsted et al. presented the first series of radical mastectomy (RM), which was described as *en bloc* removal of the breast, muscles of the chest wall, axillary nodes, and lymphatics. This technique became the standard of care for decades. In 1971, Fisher et al. challenged this standard in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial.⁷

Patients were randomized to undergo RM versus total (simple) mastectomy plus RT to the chest wall, axilla, supraclavicular, and internal mammary lymph node areas. RM had no survival benefit over mastectomy (node negative) or mastectomy with radiation (node positive). The specific aims of this trial were to determine in patients with clinically negative axillary nodes whether total mastectomy (TM) followed by axillary dissection for those patients who subsequently develop positive nodes is as effective a therapy as RM; and whether TM with post-operative regional radiation (TMR) is as effective a treatment as RM or TM with postponement of axillary dissection until positive nodes occur. In patients with clinically positive nodes, the trial confirmed that RM and TMR were equivalent procedures.

Between July 1971 and September 1974, 1,765 women with primary operable breast cancer were randomly assigned to treatment. A total of 1,079 women who were clinically axillary node negative at the time of protocol entry were assigned to receive RM, TMR, or TM with a delayed axillary dissection only if their axillary nodes became clinically positive. A total of 586 women with clinically positive axillary nodes underwent either RM or TMR without axillary dissection. The radiation consisted of 50Gy in 25 fractions delivered by supervoltage equipment to the axilla, and node-positive women received an additional boost of 10–20Gy. The internal mammary nodes and the supraclavicular nodes received a dose of 45Gy in 25 fractions. None of the women received adjuvant systemic therapy. Most women were 50 years of age or older at the time of entry. The mean (\pm SD) tumor diameter for the node-negative group was 3.3 ± 2.0 cm and for the clinically node-positive group, 3.7 ± 2.0 cm. The 25-year follow-up continues to demonstrate no significant differences in long-term outcome either in clinically node-negative patients who underwent RM and those who underwent TMR (Hazard ratio [HR] for death 1.08 (95% confidence interval [CI], 0.91–1.28; $p=0.38$) or TM (HR for death 1.03 (95% CI, 0.87–1.23; $p=0.72$), or in clinically node-positive patients who underwent RM and those who underwent TMR (HR for death 1.06 (95% CI, 0.89–1.27; $p=0.49$). This study also proved that there

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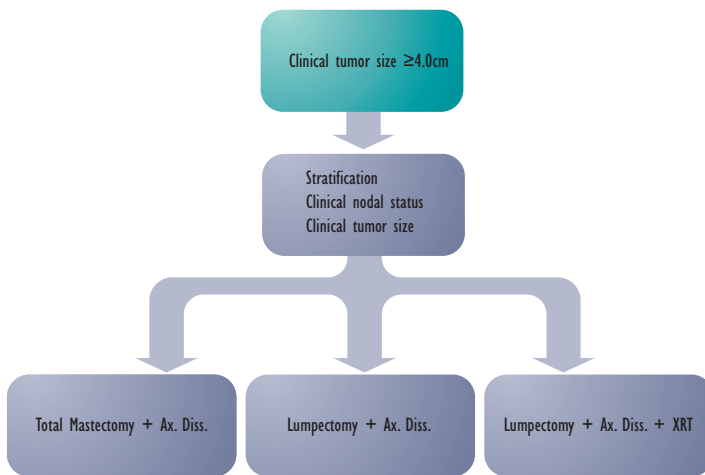
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Figure 1: Schema of the NSABP B-06 Study



All patients with histologically positive axillary nodes receive L-PAM + 5 FU.
Total mastectomy performed in event of ipsilateral breast tumor recurrence.

were no significant survival advantages in removing occult positive nodes at the time of initial surgery or from the addition of loco-regional radiation to TM.

As the concept emerged that less treatment was not detrimental to the overall prognosis of women with breast cancer, studies evaluating the role of surgery were put forth. In 1976, the protocol NSABP B-06 compared segmental mastectomy (SM) and axillary dissection with and without radiation of the breast with TM and axillary dissection (see Figure 1).⁸ The specific aims were to determine, in patients with or without clinical axillary node involvement who may be amenable to SM, whether:

- SM and axillary dissection with or without radiation of the breast is equivalent to TM plus axillary dissection;
- cosmetically acceptable preservation of the breast in a subset of patients with primary cancer can be achieved without unfavorably influencing treatment failure and mortality rates as well as morbidity; and
- evidence could be obtained to indicate the clinical significance of microscopic multi-focal tumor in the breast.

No survival benefit of TM was found.

Between August 1976 and January 1984, a total of 2,163 women were randomized into the trial. Those treated with lumpectomy underwent tumor resection with removal of sufficient normal breast tissue to ensure both tumor-free specimen margins and a satisfactory

cosmetic result. The protocol required that 50Gy of radiation be administered to the breast, but not the axillary or other regional nodes, in women assigned to lumpectomy and breast irradiation. Neither external-beam nor interstitial radiation was used as a supplemental boost. All women with one or more positive axillary nodes received adjuvant systemic therapy with melphalan (L-PAM) and 5-fluorouracil for a two-year period.

After 15 years of follow-up, there was no significant differences in overall survival (OS), disease-free survival (DFS), or distant disease-free survival (DDFS) between the patients randomized to TM versus lumpectomy alone (HR, 1.05 (95% CI, 0.90–1.23; $p = 0.51$) or lumpectomy and breast irradiation (HR, 0.97 (95% CI, 0.83–1.14; $p = 0.74$)).⁹ Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women who underwent post-operative breast irradiation, compared with those who did not, was 0.91 (95% CI, 0.77–1.06; $p = 0.23$). The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3% in women who underwent lumpectomy and breast irradiation compared with 39.2% in women who underwent lumpectomy alone ($P < 0.001$). Radiation was also associated with a small but marginally significant decrease in death due to breast cancer. However, this decrease was partially offset by an increase in deaths from other causes.

Types of Radiation

Modern radiation for early breast cancer is divided into two general approaches, either conventional external beam radiation therapy (EBRT) to the whole breast or partial breast irradiation (PBI) to the portion of the breast deemed to be at high risk for local recurrence. EBRT is delivered to the breast to a dose of approximately 45–50Gy over a five- to six-week period. A boost dose specifically to the tumor bed is sometimes necessary, although it is controversial. For the last ten years, radiation oncologists have been looking at the efficacy and safety of PBI and accelerated PBI (APBI) in the hope of decreasing complications associated with EBRT. Several different APBI techniques have been described in the literature, including interstitial brachytherapy, external beam with three-dimensional conformal (3-D-conformal) radiation therapy/intensity-modulated radiation therapy (IMRT), the MammoSite[®] device and more recently, intra-operative radiation therapy (IORT) with photons or electrons. Many clinicians believe APBI may increase the utilization of radiation therapy by providing better patient acceptance secondary to more rapid and focused treatment. Additionally, the potential for breast preservation after local tumor recurrence,

completion of all local therapy before initiation of systemic therapy and decreased costs are further advantages that APBI may offer.¹⁰

IMRT uses a computer-defined variable intensity pattern to modulate the intensity of the delivered beam over the treated field so that a standardized uniform dose is delivered over the entire breast. Preliminary data using IMRT delivery to the breast and/or chest wall in patients with breast cancer suggest that dose distribution is homogeneous and that IMRT provides a favorable toxicity profile.^{11,12}

The MammoSite brachytherapy system is a novel form of balloon catheter-based intracavitary APBI that allows treatment of a five to seven-day course after breast conserving surgery. Currently, the MammoSite device is one of the most popular techniques for APBI in the US.^{1,2,10,13,14} The MammoSite device is placed at the time of initial lumpectomy, at re-excision, or post-lumpectomy via a percutaneous approach with ultrasound guidance. If the MammoSite is placed intra-operatively, it is inserted into the lumpectomy cavity after being tunneled through a small counter-incision. The balloon is inflated with 30–70ml of a saline-contrast mixture, depending on the size of the resected specimen as determined by the surgeon. Metallic clips are not placed in the lumpectomy cavity. Three to four days after breast conserving surgery, the patient is evaluated by computed tomography (CT) scan. After verifying appropriate dosimetry, minimum skin distance of 5mm, conformance, and absence of an air pocket or seroma, intracavitary APBI is administered twice daily using high-dose rate Ir¹⁹² in fractions of 340cGy given over five days for a total dose of 34Gy. There is a minimum six-hour interval between treatments.

NSABP Protocol B-39 (RTOG Protocol 0413) is an on-going randomized phase III study of conventional whole breast irradiation versus partial breast irradiation for women with stage 0, I, or II breast cancer. The main aim is to evaluate the effectiveness of partial breast irradiation (PBI) compared with whole breast irradiation (WBI) in providing equivalent local tumor control in the breast following lumpectomy for early-stage breast cancer. The study will also compare OS, recurrence-free survival (RFS), and DDFS between women receiving PBI and WBI. It will also look at quality-of-life issues related to cosmesis, fatigue, treatment-related symptoms, and perceived convenience of care. Women enrolled in this trial must have undergone a lumpectomy of a tumor no greater than 3cm with histologically clear margins including DCIS. Sentinel node biopsy is permitted, but patients may not have more than three positive axillary nodes. PBI may be delivered by high-dose rate multi-catheter brachytherapy,

MammoSite, and 3-D-conformal external beam radiation therapy. Ideally, PBI therapy will be given twice daily, with doses at least six hours apart, on five treatment days over a period of five to ten days. This trial will accrue 3,000 patients over a period of two years and five months. Accrual is projected to be approximately 75 patients each month for the first year, increasing to 125 patients each month in subsequent years. The trial is designed to test the equivalency of PBI and WBI with a 85% power to detect as statistically significant a relative hazard of ipsilateral breast cancer recurrence that would be larger than 1.17 or less than 0.86.

Effect of Radiation Therapy on Local Recurrence

Many randomized studies have demonstrated that the rate of local recurrence is significantly decreased after radiation of the breast. In a pooled analysis of 15 randomized trials studying the effect of breast radiation after lumpectomy, recurrence estimates were calculable for a pooled total of 9,528 patients, of whom 9,422 were analyzed resulting in: 4,731 patients of whom 875 had ipsilateral breast tumor recurrence in the no RT arms; and 4,691 patients of whom 279 had ipsilateral breast tumor recurrence in the RT arms.¹⁵ The pooled relative risk of ipsilateral breast tumor recurrence with no RT versus RT based on all 15 trials was 3.00 (95% CI, 2.65–3.40) (see *Figure 2a*). There was a statistically significant heterogeneity across studies, with substantial variations in relative risks. In the 11 studies with a median of more than five years of follow-up, the observed average percentage of local relapse ranged from 1.4% to 5.7% per year when RT was omitted and from 0.4% to 2.1% per year when RT was administered. The individual relative risks estimated in these trials varied from 2.32 (95% CI, 1.56–3.45) to 4.89 (95% CI, 2.45–9.76). In the four studies that had less than five years of follow-up, the percentages of relapse were small. The corresponding relative risks presented more variability, as might be expected from the shorter follow-up.¹⁵ In the recent meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) about three-quarters of the eventual local recurrence risk occurred during the first five years.¹⁶

To reduce the risk of local recurrence and thereby decrease the additional therapies for the management of these recurrences, it is recommended in most instances that RT be used after lumpectomy.

Effect of Radiation Therapy on Survival

A review by Whelan et al. addressed possible survival differences between patients receiving RT and those not receiving it. No difference in survival was detected

Figure 2a

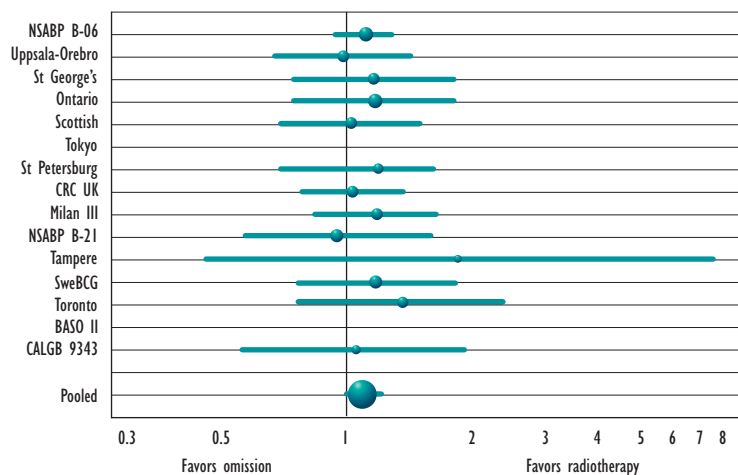


Figure 2b

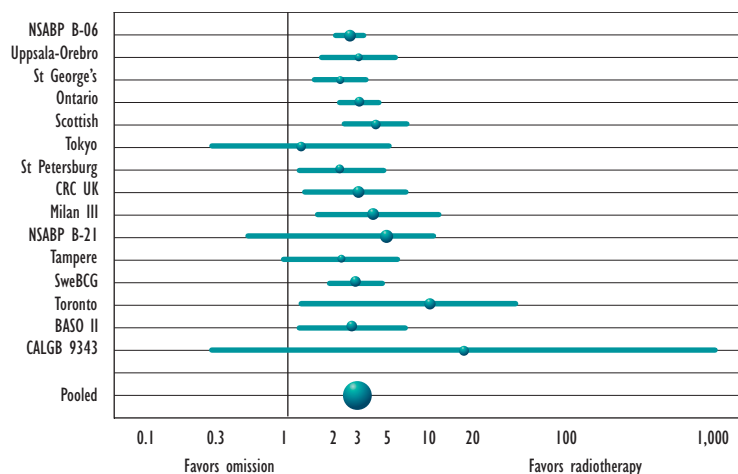


Figure 2a: Omission versus administration of radiotherapy (RT) after breast conserving surgery. Plot of relative risk of death from any cause ($1 =$ no difference) and 95% confidence intervals;

Figure 2b: Omission versus administration of radiotherapy (RT) after breast conserving surgery. Plot of relative risk of ipsilateral breast tumor recurrence ($1 =$ no difference) and 95% confidence intervals.

in any of five randomized clinical trials comparing patients receiving breast irradiation with those receiving no breast irradiation following breast-conserving surgery.¹³ In another review focusing on long-term results of RT, no statistically significant difference in the annual death rates was shown among six trials comparing use of RT versus no RT.¹⁷ These results may suggest that the omission of RT may not have an effect on patient survival. However, a study of the Surveillance, Epidemiology and End Results (SEER) Program database found that, among women who underwent axillary lymph node dissection, breast-

conserving surgery with RT was associated with a reduced mortality HR of 0.728 compared with TM, whereas breast-conserving surgery without RT was associated with an increased mortality HR of 1.105 when compared with TM. This implies a substantial survival disadvantage in patients who did not receive RT.¹⁸ A subsequent study directly comparing the omission of RT with the delivery of RT after breast-conserving surgery in patients aged 40–69 years found a 35% excess in relative mortality associated with the omission of RT.¹⁹ In our own pooled analysis of 15 randomized clinical trials testing the use of breast irradiation, patients who did not receive radiation experienced an increase of 8.6% in the RR of all-cause mortality (see Figure 2b).^{15,20-22}

The 2000 EBCTCG suggested that with longer follow-up late lethal toxicity might reduce the OS benefits of RT.¹⁷ In this review, RT produced a reduction of about two-thirds in local recurrence, largely irrespective of the type of patients or treatments. Women with node-negative disease after mastectomy and axillary node dissection were at low risk of local recurrence, hence, the large relative risk reduction translated into only a small absolute reduction in local recurrence and an even smaller reduction in overall recurrence. Although breast cancer mortality did not appear to be reduced by RT during the first two years after treatment; thereafter, the annual death rate from breast cancer was lower by approximately 13% in women who had been allocated RT. However, since the absolute breast cancer death rate is smaller in the second than in the first decade, the absolute benefit is also likely to be smaller. Women in whom isolated local recurrence was prevented were unlikely to develop any recurrence within 10 years. This substantial improvement in local disease control must have been largely or wholly responsible for the moderate, but statically definite, reduction in breast cancer mortality. The favorable effect on mortality from breast cancer was, however, offset by a statically definite increase in the annual death rate from other causes, which were primarily due to excess of vascular deaths, perhaps from inadvertent irradiation of the coronary, carotid, or other major arteries. The underlying mortality rate from breast cancer depends strongly on nodal status and not on age, whereas that from other causes depends strongly on age and not on nodal status. Moreover, with longer follow-up the ratio of breast cancer deaths to other deaths decreases substantially. Age, nodal status and duration of follow-up will substantially influence the absolute magnitude of benefits and toxicities of treatment. For older women and for women at low risk of local recurrence the toxicities may exceed the estimated benefits, but for younger women at high risk of local recurrence the gains would still significantly exceed the risks associated with therapy. For 20-year

survival, the overall balance of benefits and risks with the main types of RT in these trials is likely to be unfavorable for older women and for women of any age at particularly low risk of local recurrence, e.g. those with small screen detected cancers or with no evidence of nodal involvement after mastectomy with axillary clearance, and favorable only for younger women with a relatively high risk of local recurrence. However, if a particular RT regimen, e.g. one of those that strictly limit carotid and intrathoracic exposure, can be shown to yield maximal benefit while avoiding most of the cardiovascular and pulmonary toxicities, survival may be improved in a wider range of patients.¹⁷

The EBCTCG overviews, published in 1987, 1990, 1995, and 2000 compared the benefits of adjuvant RT in the early publications with the more mature data of the same trials. Statistical significance for the odds ratios—death from any cause—were calculated following logrank statistics. The comparison of odds ratios of RT plus surgery with surgery only, was done for the whole group of trials—older trials (patient accrual started in 1970 or earlier), more recent ones (patient accrual started after 1970), large trials (>600 patients), and small trials (<600 patients). Comparison of early with more mature data reveals that the odds ratios for OS remain stable as data become more mature. The analyses of trial age and trial size as predictors of OS benefit indicated that these factors become statistically more significant with increasing maturity of the trials. In the large recent trials an OS benefit due to RT (odds reduction) was found in the successive EBCTCG publications to be 10%, 10%, 12%, and 13% ($p < 0.3$, 0.2, 0.005, and 0.00005), respectively. The difference in survival benefit of RT between the group of large recent trials and group of old or small trials becomes more significant at the successive updates: 10%, 9%, 12%, and 13% (odds reductions), with, respectively, $p = 0.2$, 0.2, 0.004, and 0.00005. These results support the hypothesis that the survival benefit in the recent trials is an inherent characteristic of the recent and large trials, not influenced by follow-up duration. The effect of RT as performed in the large recent trials is clinically and statistically significantly different from the effect of RT in the old or small trials. As a consequence, predictions based on pooled data including old RT trials should not be extrapolated to modern RT. This analysis was confirmed in the latest EBCTCG publication in 2005.¹⁶ Collaborative meta-analyses were conducted based on individual patient data of the relevant randomized trials that began by 1995. Information was available on 42,000 women in 78 randomized treatment comparisons: RT versus no RT—23,500; more versus less surgery—9,300; more surgery versus RT—9,300. Twenty-four types of local treatment comparison were identified. In the comparisons that involved little

(<10%) difference in five-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25,000 women in the comparisons that involved substantial (>10%) differences, there was an absolute reduction (19%) of the recurrence risk with RT with an absolute mortality reduction of 5%, SE 0.8, $p < 0.00001$). Similar reductions were observed in a subset of 7,300 patients treated with breast-conserving surgery where a 15-year breast cancer mortality risk of 30.5% versus 35.9% was observed (reduction 5.4%, SE 1.7, $p = 0.0002$).¹⁶

Adverse Effects of Radiation Therapy for Patients with Early Breast Cancer

Possible chronic adverse effects include poor cosmetic results and increased risks of arm dysfunction and lymphedema in conjunction with extensive axillary lymph node dissection. These adverse effects can be mild and transient—such as skin redness, or late appearing and more severe—such as secondary lymphedema, fibrosis, pneumonitis, rib fractures, brachial plexopathy, secondary malignancies, or cardiac and vascular damage. Secondary lymphedema can occur in 14–28% of cases after breast cancer treatment, especially after lymphadenectomy. The number of axillary nodes removed and RT especially to axillary nodes are the main risk factors.²³ Long-term toxic effects may include carcinogenesis and cardiac or lung damage. It has been shown that lung and cardiac toxicities could be detected six months after treatment, or even earlier at six weeks post-RT, and that these changes predicted long-term impairment.^{24–26} The estimated incidence of detectable any-grade lung toxicity was 23% and cardiac toxicity was 5–7%.^{24,25,27} Although rare, contralateral breast cancers, sarcomas, lung cancers, esophageal cancer, and leukemias can occur after RT to the breast. RT also prolongs the treatment duration, which could result in loss of income and additional costs that have to be borne by the patient or by the public health system.

The effect on lung carcinogenesis was carefully studied in the NSABP B-04 and B-06 trials.²⁸ For the 1,665 evaluable patients on the NSABP B-04 trial, there was a total of 23 subsequent confirmed and probable ipsilateral or contralateral primary lung carcinomas. Fourteen were among patients who had been allocated to receive RT, and nine were among patients who did not receive RT. The difference was statistically significant. For the 1,850 evaluable patients on the NSABP trial B-06, there was a total of 30 second primary lung carcinomas but no increase in either ipsilateral or contralateral primary tumors of the lung in those patients who had received RT. As recalled earlier, in the NSABP B-04 trial extensive radiation was delivered to the chest wall, axilla, and supraclavicular

and internal mammary lymph node areas. In the NSABP B-06 trial radiation was delivered to the breast only, but neither a supplemental boost nor regional lymph node irradiation was permitted.

To help assess the life-threatening side-effects of RT, the EBCTCG reviewed the trials of RT versus no RT or more surgery. There was, at least with some of the older RT regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1.18, SE 0.06, 2p=0.002) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1.12, SE 0.04, 2p=0.001). Both were slight during the first five years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1.27, SE 0.07, 2p=0.0001) and lung cancer (rate ratio 1.78, SE 0.22, 2p=0.0004).¹⁶

More recently, modeling studies and randomized clinical trials indicate that chemotherapy and concurrent RT

might enhance all types of toxicities.²⁹⁻³² This is an emerging issue that will require close monitoring.

Conclusion

Caution in administering RT to patients with early breast cancer is essential as the potential for cure in this population is excellent. Current trials of PBI will mature soon. The current evidence suggests that it might again demonstrate the paradox that less may be better in the local treatment of breast cancer.

RT is thus recommended after breast conserving surgery for early stage breast cancer, except for medical contraindications such as systemic vascular disease or a previous history of irradiation.¹³ Decision-making requires the evaluation of several factors including patient's comorbidities, histopathologic characteristics of the tumor, prognostic factors, and more importantly, risks and benefits of each possible RT procedure. ■

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