Breast Preservation Therapy in Stage I and II Carcinoma: Factors Affecting Outcome

Carlos A. Perez

Radiation Oncology Center
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missori 63108
Correspondence to: Carlos A. Perez, M.D.
Director, Radiation Oncology Center 4511
Forest Park - St. Louis, MO 63108

R. Bras. Mast. Vol 2 - nº 3; 1993

Abstract

Records were reviewed of 511 patients with 519 histologically confirmed carcinomas of the breast treated with wide local excision of tumor and irradiation to the breast (4600 to 5000 cGy in 5 weeks) and, in 109 patients, to regional lymphatics. In 271 patients with T_1 and 98 with T_2 tumor, boost to primary tumor site (1000-2000 cGy) was delivered using electrons (9-12 MeV); in 72 patients with T_1 and 34 with T_2 tumors, ^{192}Ir implant was performed. Pathologic staging was T_1 in 373 and T_2 in 146 lesions (1988 AJC). Sixty-seven patients (18%) with T_1 and 46 (32%) with T_2 tumors had microscopically positive axillary lymph nodes.

Actuarial breast relapse rates at 5 years were 5% in T_1 and 10% in T_2 tumors and at 10 years 12% and 18%, respectively. Lymph node recurrenses were noted in 1% of T_1 and 5% of T_2 tumors. Distant metastases were detected in 5% of T_1 and 22% of T_2 tumors. Five-year actuarial breast relapse rates were 10% in T_1 tumors and 18% in T2 ($p = 0.04$). Differences in 5- years breast relapse for patients with extensive intraductal component (EIC) were not statistically significant (7% in T_1 tumors with EIC and 4% without it; 14% in T_2 tumors with EIC and 7% without it). There was minimal correlation of irradiation dose to primary tumor with breast relapse (in T_1 from 2% to 7% and in T_2 from 7% to 9% with doses >5500 cGy in contrast to 20% with 5000 to 5500 cGy). No correlation was noted with either type of boost (electrons or interstitial brachytherapy). Desease-free survival for patients with T_1 tumors was 87% at 5 years and 82% at 10 years; for patients with T_2 tumors, it was 75% at 5 years and 70% at 10 years.

Excellent/good cosmetic results were obtained in 78% of the patients. No difference was observed between the group treated with electrons or ^{192} Ir implant to the boost area.

Better understanding of prognostic factors and refinement of treatment techniques will enhance the results of breast conservation therapy.

Introduction

Combined breast conservation surgery and irradiation is established therapy for many patients with intraductal carcinoma, and stages T_1 and T_2 carcinoma of the breast, yielding tumor control and survival equivalent to modified or radical mastectomy 91-6). Important advantages of breast-conserving therapy are the cosmetic results and psychological benefits that enhance the quality of life in these patients (7-9).

Selection of patients/tumors and refinement in treatment techniques continue to improve the results of this therapy. Criteria for use of breast conservation therapy are (1) tumor less than 5 cm in diameter, (2) relationship of size of tumor to size of breast, (3) absence of unfavorable prognostic factors, (4) clinically negative axilla or low, mobile axillary lymph nodes, (5) psychological attitude of patient, (6) attitude and technical expertise of surgeon, and (7) expertise and resources in radiation therapy.

Numerous reports have described host- and tumor-related (10-17), surgical and irradiation technical factors (4, 18, 19), and the interaction with hormones or cytotoxic agents that may influence therapeutic outcome (20-22). Our experience in the treatment of the patients and analysis of factors affecting therapeutic outcome are reviewed in this manuscript.

Material And Methods

Between January 1969 and December 1988, 511 patients presenting with 519 histologically confirmed stage I and II carcinomas of the breast were treated with wide local excision of the tumor (occasionally quadrantectomy) and irradiation to the breast and, in 109 patients, to the regional lymphatics. All patients have been followed up for a minimum follow-up, 22 years, and median follow-up, 5 years). All patients underwent routine workup, including mammograms and when necessary needle localization, followed by excisional biopsy of the tumor (lumpectomy, tylectomy, or quadrantectomy). The aim of the surgical procedure was to remove all gross and microscopic evidence of tumor with a 1 to 2 cm margin of normal adjacent breast tissue. Tumors were staged according to the clinical and pathological classification described by the American Joint Commitee in 1988 (23); 375 lesions were classified as T_1 and 146 as T_2. In 155 (42%) patients with T_1 and 60 (41%) patients with T_2 tumors a re-excision was performed, ei-

ther because the initial resection had been done outside the Washington University Medical Center and affiliated hospitals or because of microscopic evidence of positive margins in the initial excision specimen. The incidence of residual tumor in the re-excision specimen eas 50% in T_1 and 68% in T_2 tumors. In 86 (80%) premenopausal patients with T_1 T_1 and 45 (80%) with T_2 and in 199 (75%) postmenopausal patients with T_1 and 58 (64%) with T2 tumors, axillary dissection was carried out (usually levels I and II). Adjuvant chemotherapy was administrated to 28 premenopausal patients with T_1 and to 24 patients with T_2 tumors; hormonal therapy alone or combined with cytotoxic agents was administrated to 53 patients with T_1 and 20 patients with T_2 tumors.

Patients were followed up periodically during and after therapy or until death by the staff of the Radiation Oncology Center, the referring surgeon, or other physicians. Occasionally, when the information was not available, contact was made directly with the patient or a relative. Follow-up was obtained in 99.6% of the patients; the few lost to follow-up were considered dead with tumor.

The information was coded on computer-compatible forms and analysed on a computer program + with multiple cross-reference checks to ensure reliability of the data (24). A biomedical statistical program (BMDP)* was used for computation of the data (25,26). All survival and disease-free survival data, as well as some of the local recurrence and morbidity data, utilize actuarial lifetable computations as described by Cutler and Ederer (27). Test and statistical validity were carried out using the generalized Wilcoxon, generalized Savage, (Mantle-Cox), and Tarone-Ware methods (28,29). Multivariate analysis was performed by the Tarone method (30), and the Mantle-Cox was used to test potential significant factors affecting survival.

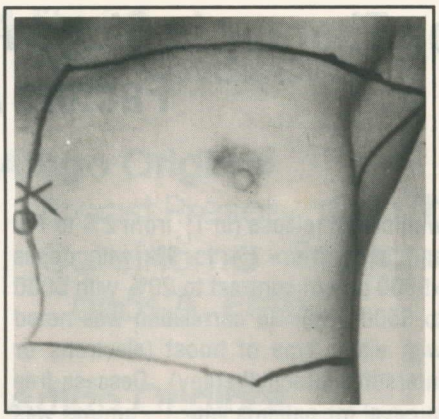


Figure 1 - (A) AP photoghaph of patient with carcinoma of the breast illustrating the treatment portals for the breast only, without fields for irradiation of peripheral lymphatics.

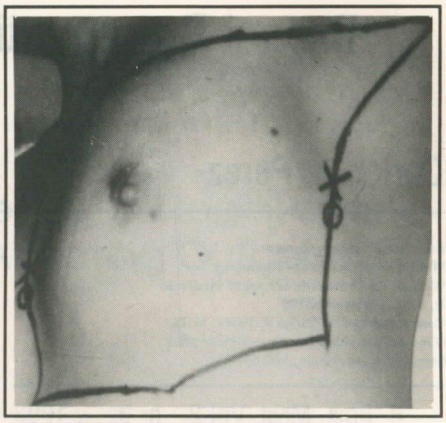
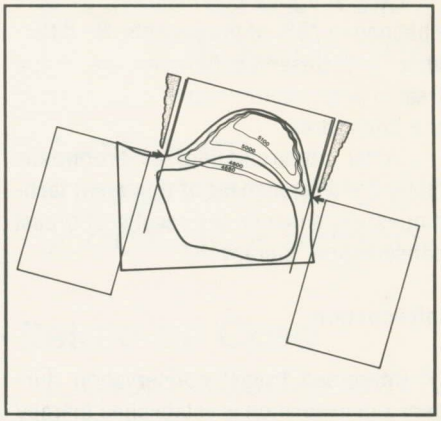


Figure 1(B) Tangential photograph of the same patient. (Perez CA, Garcia DM, Kuske RR, Levitt SH: Breast: Stage T1 and T2 tumors. In Perez CA, Brady LW (eds): Principles and Practice of Radiation Oncology, 2 ed. Philadelphia, JB Lippincott, 1992) (31).



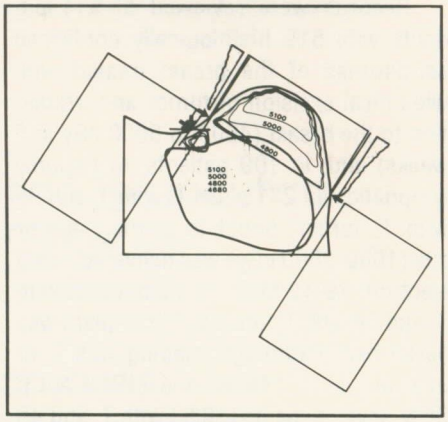


Figure 1 (C) Isodone curves for irradiation of the breast only. Figure 1(D) Isodone curves for irradiation of the breast and internal mammary lymph nodes.

Irradition Techniques

All patients were treated to the entire breast and adjacent chest wall with tangential fields, including up to 2.5 cm of underlying lung, using ^{60} Co, 4 or 6 MV photons to deliver a dose of 4600 to 5000 cGy in 180 to 200 cGy fractions over a period of 5 weeks (Figure 1). Use of compensators or wedges ensures a more homogeous dose distribution in the breast. Bolus should not be used because it interfers with satisfactory cosmesis. In 271 patients with T_1 and 98 with T_2 tumors, a boost to the primary tumor excision site was delivered, using 9 to 12 MeV electrons, while in 72 patients with T_1 and 34 with T_2 an interstitial ^{192}Ir implant as performed. In 29 patients with T_1 and 12 with T2 tumors, no boost was delivered, usually because the surgical procedure was a quadrantectomy and the margins were negative on pathological examination.

In 131 patients who had no axillary dissection, supraclavicular and axillary lymph node irradiation was administered to 94 patients (4600 cGy calculated at 3 cm with occasional boost to the axillary lymph nodes with a posterior portal). In patients with inner quadrant tumors the internal mammary lymph nodes are irradiated with separate portals, delivering 1400 to 1600 cGy with 4-6 MV photons and additional 3200 to 3000 cGy, respec-

tively, with 12-15 MeV electrons (31).

Adjuvant Therapy

Chemotherapy, usually CMF (cyclophosphamide, 100 mg/m² PO on days 1 through 14; methotrexate, 40 mg/m² IV on days 1 and 8; and 5FU, 600 mg/m² IV on days 1 and 8) was administered every 28 days for a total of 6 to 9 cycles. Of the patients with positive axillary nodes, 36 with T_1 tumors and 30 with T_2 tumors received adjuvant chemoherapy; in the patients with negative lymph nodes, 12 with T_1 and 8 with T_2 tumors received adjuvant chemotherapy because they were judged to have high-risk tumor features. Chemotherapy was initiated after completion of radiation therapy in most patients. Tamoxifen (10 mg bid) was administered to 53 patients with T_1 and 20 with T_2 tumors (usually postmenopausal); these include 11 patients with T_1 and 7 with T2 tumors who also received chemotherapy.

Results

Histological type of the primary tumor was invasive ductal carcinoma in 427 patients (82%) and infiltrating lobular carcinoma in 26 (5%) (24). In 5% of patients with T_1 and 12% with T_2 tumors, extensive intraductal carcinoma as defined by Harris et al (32) was noted. Sixty-seven patients (18%) with T_1 and 46 (32%) with T_2 tumors were reported to have microscopically positive axillary lymph nodes.

The overall local recurrence rate was 5% in the T_1 and 10% in the T_2 tumor groups, alone or combined with other failures. Regional lymph node recurrences were rare (1% in T_1 and 5% in T_2 patients). Distant metastases were noted in 5% of the T_1 and 23% of the T_2 groups (24).

The actuarial disease-free survival rates for patients with T_1 lesions were 87% at 5 years and 82% at 10 years, whereas for the patients with T_2 tumors they were 75% at 5 years and 70% at 10 years. The overall survival rate at 5 years was 90% for T_1 group and 80% for T_2; the 10-year survival rates were 80% for the former and 60% for the latter group (Figure 2A and B).

Breast Relapses

The actuarial breast relapse rate at 5 years after treatment was 5% in patients

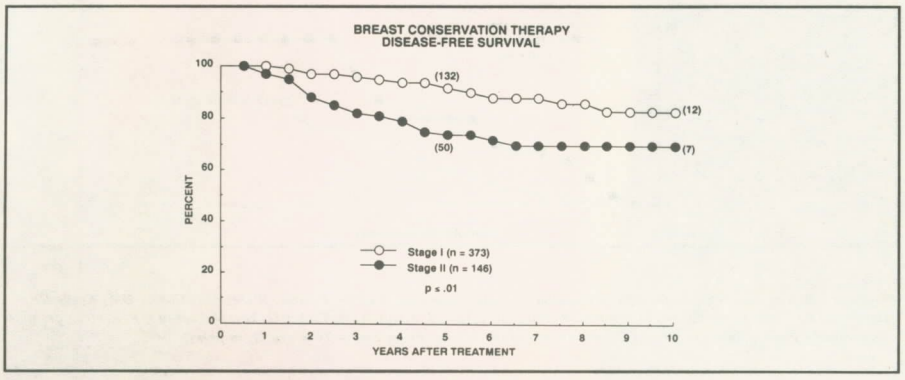


Fig. 2A

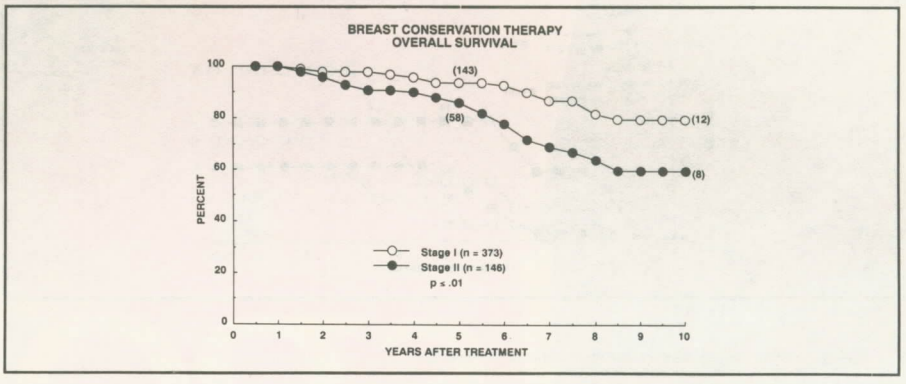


Fig. 2 Breast conservation therapy: (A) Disease-free survival. (B) Overall survival. (Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C; Organ preservation therapy in stage T_1 and T_2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).

with T_1 and 10% with T_2 tumors, and at 10 years 12% with T_1 and 18% with T_2 tumors (Figure 3).
The location of the breast relapse was at or near the primary tumor site in 58% of the patients with T_1 and 67% of the patients with T_2 tumors. The incidence of breast relapse was similar in the various histological tumor types; in the T1 invasive ductal lesions it was 5% (16/309), the same as in the invasive lobular lesions (1/18); for T_2 tumors the incidence was 11% (13/118) NS 12% (1/8), respectively. In patients with T_1 tumors, the 5 year actuarial breast relapse rate was 7% when extensive intraductal component was reported in comparison with 4% when it was absent. The corresponding values for the T_2 tumors are 14% and 7%, respectively (Figure 4).
The differences are not statistically significant.

The breast relapse rate was not correlated with the performance of a re-excision of the primary site margins. Likewise, the status of the surgical margins did not affect the incidence of breast relapses (Figure 5A and B). The breast relapse rate was comparable for patients who received a boost to the primary site by electrons or by interstitial brachytherapy (Figure 6A and B).

As reported by other authors, patients receiving adjuvant chemotherapy or hormonal therapy have a lower incidencé of breast relapses than those not treated with an adjuvant (in patients with T_1 tumors none versus 15% and in the T_2 group 10% versus 23%, respectively). Differences, however, are not statistically significant (p = .22 and .76, respectively).

A total of 16 patients (4%) in the T_1 and 10 (7%) in the T_2 group have developed a clinically detected carcinoma of the contralateral breast.

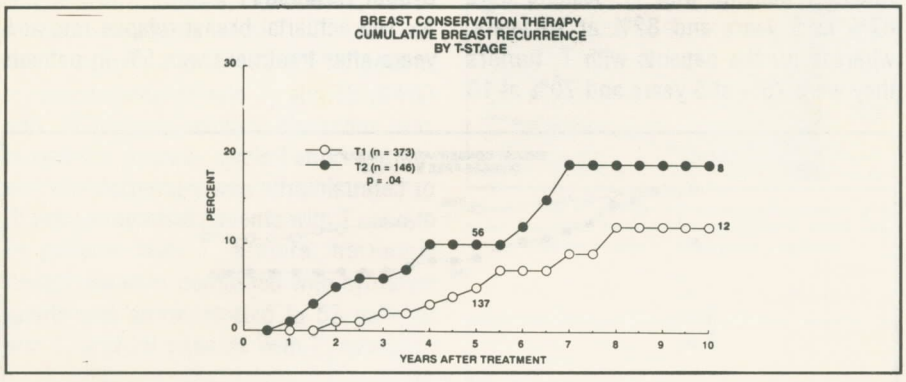


Figure 3 - Breast conservation therapy: Cumulatuive breast recurrence rate by T stage. (Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M,Lockett MA, Rush C: organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).

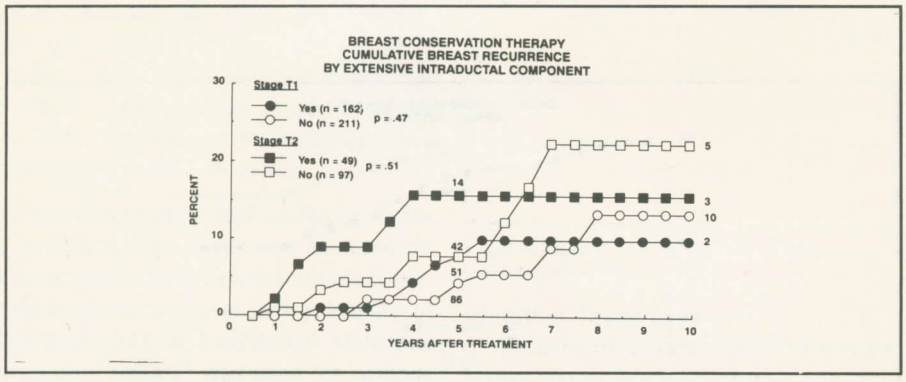


Figure 4 - Breast conservation extensive intraductal component.

Treatment of Breast Relapses

For patients who developed a recurrence in the breast (18 T_1 and 15 T_2 tumors) after initial therapy, 25 were treated with a mastectomy; a repeat wide local excision was performed in 3 patients. Of these 28 patients, 10 received adjuvant chemotherapy. The actuarial cause-specific 5-year survival from time of failure for these patients was 72% for those with T_1 and only 25% for those with T_2 tumors, and from the initial treatment the cause-specific 5-year survival rate was 80% for the patients with T_1 and 35% with T_2 tumors (Figure 7).

Impact of Adjuvant Chemotherapy on Survival

In patients with T_1 tumors and negative axillary nodes, the 10-year disease-free survival rate for patients who received adjuvant chemotherapy or hormones was 90% compared with 80% for patients who did not receive it (Figure 8A) (p = 0.96). Patients with T_1 tumors and positive nodes treated with adjuvant hormones alone or combined with chemotherapy had a 100% survival rate compared with 80% for those receiving chemotherapy or no adjuvant therapy (Figure 8B) (p = 0.55). In patients with T_2 tumors and negative axillary lymph nodes, 100% of the treated with either hormones alone or hormones combined with chemotherapy and 82% of those who received adjuvant therapy exhibited 5 - and 10-

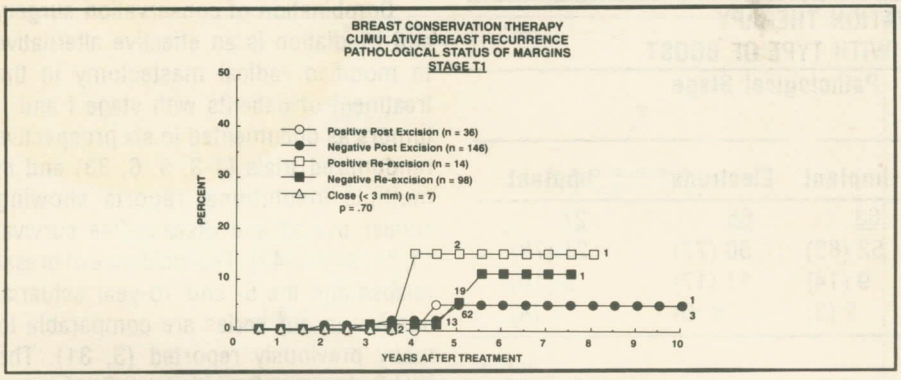


Figure 5 A- Breast conservation therapy: Cumulative breast recurrence rate correlated with pathological status of margins. (A) T1.

year disease-free survival rates compared with 70% in those not receiving chemotherapy (Figure 9A) (p = 0.57).

Patients with T_2 primary tumors and positive axillary lymph nodes who received adjuvant chemotherapy had a 70% 5- and 10-year survival rate, in contrast to 54% and 32%, respectively, for those not treated with adjuvant chemotherapy (p = .29); for a small group treated with hormones alone or hormones combined with chemotherapy the 5- and 10-year survival rate was 100% (Figure 9B).

Morbidity of Therapy

The most frequent moderate/severe side effects of therapy were breast edema, which was noted in 4.8% of the patients with T_1 and 3% of patients with T_2 tumors, and moderate to severe arm edema, which occured in 2.7% of the patients with T_1 and 2% of the patients with T_2 tumors. Only 2% of the patients developed rib fracture, and one patients who received concomitant CMF-prednisone and irradiation for a left breast carcicoma developed paricarditis requiring a pericardial window. Sequelae are shown in Tables 1 and 2.

There was an 8% incidence of arm edema in 291 patients who had axillary dissection compared with none in 131 on whom this procedure was not performed. Moreover, in 97 patients on whom both axillary dissection and lymphatic irradiation were administered, there was further increase in the incidence of arm edema to 14%. The differences, however, are not statistically significant (p = .11). Similar correlation was observed with regard to incidence of breast edema (p = .36).

BREAST CONSERVATION THERAPY
TREATMENT SEQUELAE STAGE T-1
(n = 373)

	Grade 1	Grade 2	Grade 3
Breast Fibrosis	16 (4)	17 (5)	4 (1)
Breast Edema	20 (5)	16 (4)	2 (.5)
Arm Edema	19 (5)	7 (2)	3 (.8)
Soft Tissue Necrosis	3 (1)	1 (.3)	1 (.3)
Rib or Bone Necrosis	1 (.3)	5 (1)	
Pneumonitis	5 (1)	4 (1)	1 (.3)
Pericarditis			1 (.3)
Telangiectasia	9 (2)	0	2 (.5)

( ) Percent

Ration Oncology Center
Mallinckrodt Institute of Radiolgy

BREAST CONSERVATION THERAPY
TREATMENT SEQUELAE STAGE T-2
(n = 373)

	Grade 1	Grade 2	Grade 3
Breast Edema	10 (7)	3 (2)	1 (.7)
Breast Fibrosis	7 (5)	8 (5)	6 (4)
Arm Edema	11 (8)	3 (2)	0
Soft Tissue Necrosis	1 (.7)	2 (1)	0
Rib or Bone Necrosis	0	1(.7)	0
Pneumonitis	2 (1)	2 (1)	0
Fibrosis Other Sites	4 (3)	2 (1)	1 (.7)
Telangiectasia	3 (2)	1 .7)	3 (2)

( ) Percent

Ration Oncology Center
Mallinckrodt Institute of Radiolgy

Cosmesis

Assessment of cosmetics results at any time after treatment was judged to be good to excellent in 316 (80%) of the patients, fair in 62 (16%), and poor in 16 (4%) of the patients (24). There was no significant difference in cosmetics re-

BREAST CONSERVATION THERAPY
COSMESIS CORRELATED WITH TYPE OF BOOST

	Pathological Stage			
	T_1		T_2	
Cosmesis	**Electrons**	**Implant**	**Electrons**	**Implant**
Number of Patients	208	63	65	27
Excellent/good	173 (83)	52 (83)	50 (77)	21 (78)
Fair	29 (14)	9 (14)	11 (17)	5 (19)
Poor	6 (3)	2 (3)	4 (6)	1 (4)

( ) Percent

Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucher G, Vest M, Lockett MA, Rush C: Organ preservation therapy in stage T_1 and T_2 carcinoma of the breast. Front Radiat Ther Oncol, in press (24).

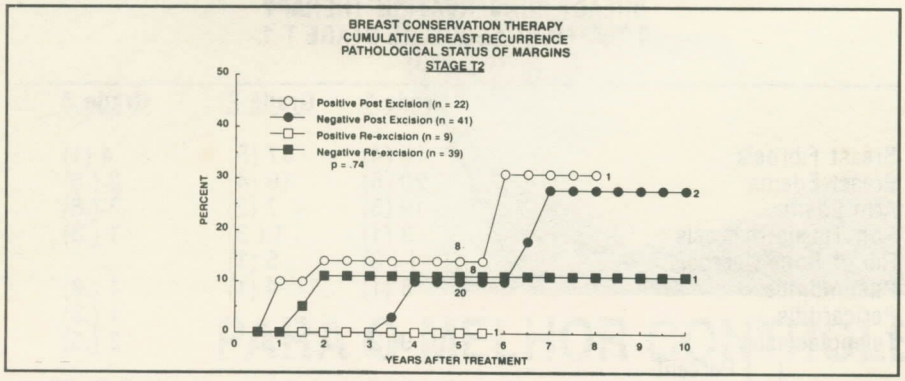


Figure 5(B) T2. (Perez CA, Garcia DM, Kuske RR, halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levry J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C: Organ preservation therapy in stage and T1 and T2 carcinoma of the breas. Front Radiat Ther Oncol, in press) (24).

sults in the patients with T_1 or T_2 tumors. Also, no difference was observed in the cosmetic results of the patients treated to the local tumor site with either electrons or interstitial implant (Table 3). Administration of sequential adjuvant chemotherapy did not have a significant impact on our cosmetic results, probably because chemotherapy was delivered in most patients following completion of irradiation (24).

Discussion

Combination of conservation surgery and irradiation is an effective alternative to modified radical mastectomy in the treatment of patients with stage I and II tumors as documented in six prospective randomized trials (1-3, 5, 6, 33) and in multiple institutional reports showing similar overall and disease-free survival (3, 31, 34, 35-43). The incidence of breast relapse and the 5- and 10-year actuarial survival in our series are comparable to many previously reported (3, 31). The NIH Consensus Development Conference on early stage breast cancer (44) concluded that breast preservation therapy is preferable to mastectomy in appropriately selected patients, since it provides comparable survival with preservation of the breast.

In several series, no correlation has been found between the size of the primary tumor and the incidence of local recurrence (2, 37, 41, 45), whereas other authors, in agreement with our report, noted an overall higher percentage of failures in patients with T_2 compared with T_1 tumors (46-48). This may be related to the treatment techniques used (completeness ot tumor excision, irradiation boost) or tumor characteristics, such as extensive intraductal component, as suggested by Eberlein et al (12). Fisher et al (49), in a recent analysis of about 2000 patients,

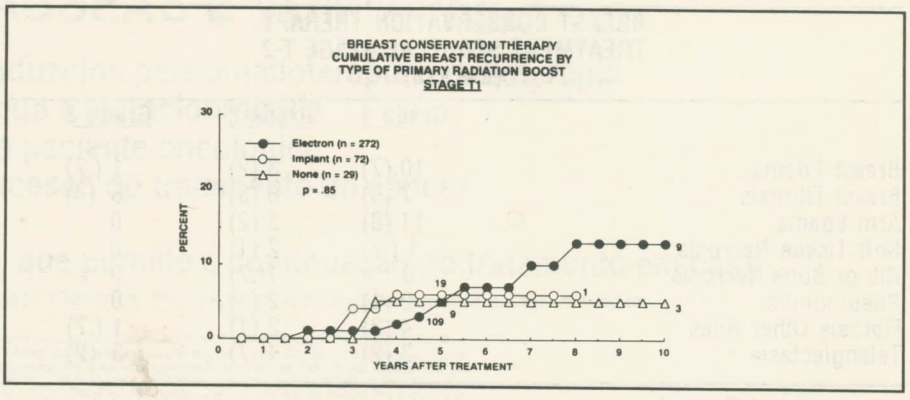


Figure 6 - Breast conservation therapy: Cumulative breast recurrence rate correlated with type of primary radiation boost. (A) T1.

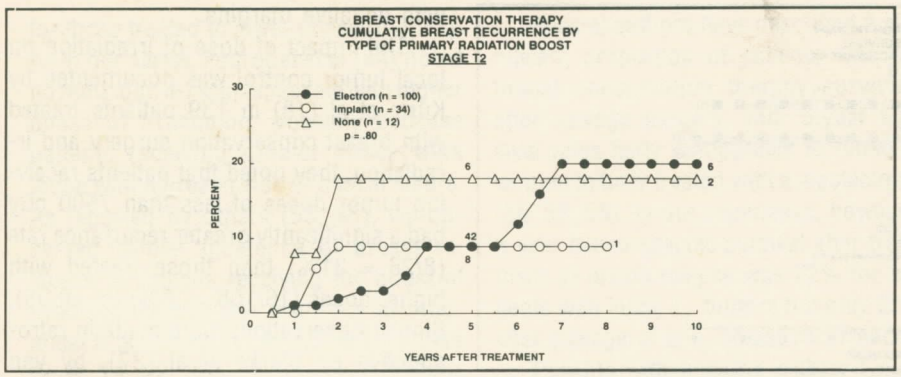


Figure 6(B) T2. (Reproduced with permission from Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Busch C: Organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).

noted that maximum pathological tumor size and type of treatment (lumpectomy alone or combined with irradiation) were the only two significant predictors of time to ipsilateral breast tumor recurrence, in a field of 10 patient- or tumor-related factors analysed; there was no significant correlation with disease-free survival at 9 years for the various treatment groups.

The presence of extensive intraductal component has been correlated with a greater incidence of breast recurrences (50, 51), particularly by the Harvard University group (32). Boyages et al (10) in 783 women described a 26% incidence of breast recurrence (43/166) when extensive intraductal component of the tumor was found compared with 7% (29/418) in patients without EIC. Furthermore, young age (35 years of age or less) was associated with a greater probability of developing a breast recurrence (15/61 = 25%) compared with older age (76/122 = 11%) (p = 0.001). Kurtz et al (15) noted that patients younger than 40 years had a higher frequency of high-grade tumors, greater incidence of mononuclear cell reactions, and a larger proportion of specimens with extensive intraductal component, all of which are recognized as risk factors for increased local tumor recurrence. In contrast, similar to our experience, Clarke et al (37), Fisher et al (13), and Van Limbergen et al (38) found no significant impact on local tumor control with extensive intraductal component. This may be related to the pathological definition used to describe extensive intraductal component, adequacy of tumor excision, and doses of irradiation given.

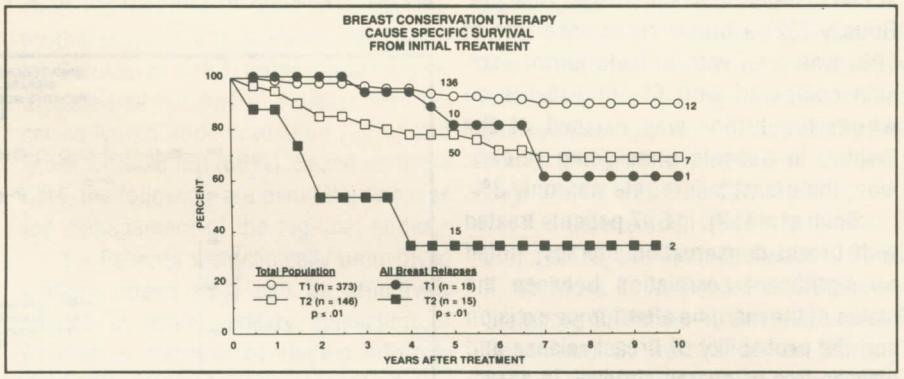


Figure 7 - Breast conservation therapy: Cause-specific survival from initial treatment. (Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C: organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).

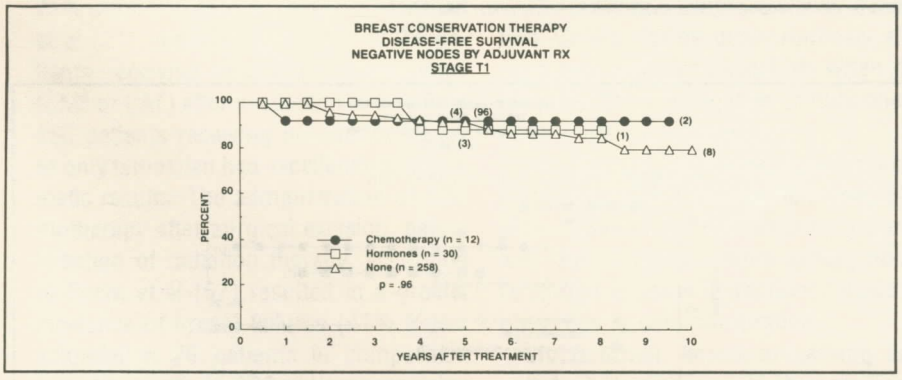


Figure 8 (A)- Breast conservation therapy: Disease-free survival rate correlated with adjuvant therapy in T1 patients. (A) Patients with negative nodes.

The value of re-excision of margins in some of these patients was document by Montague (45), who reported an overall 8.2% breast recurrence rate in 135 patients when the initial excision had been done before referral to M.D. Anderson Cancer Center and only 2% in 210 pa-

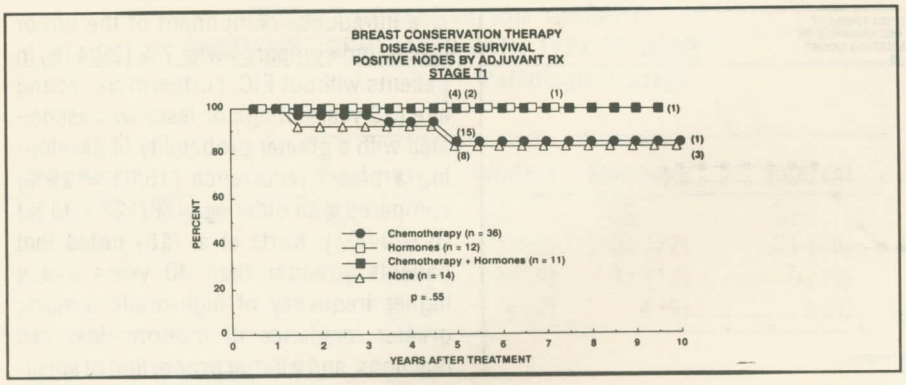


Figure 8(B) Patients with positive nodes. (Perez) CA, Garcia DM., Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C: organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).

tients when the tylectomy was performed at that institution. At the Institut Gustave-Roussy (37) a breast recurrence rate of 10% was seen with outside tumor excision compared with 5% in patients on whom the tumor was excised at the institut; in patients undergoing re-excision, the breast failure rate was only 3%.

Solin et al (52), in 697 patients treated with breast conservation therapy, noted no significant correlation between the status of the margins after tumor excision and the probability of breast relapse and disease-free or overall survival, in agreement with our findings. However, a different total dose of irradiation was administered to the various groups: 5700 to 6000 cGy to patients with negative margins, 6400 to 6500 to patients with positive or close margins, or 6240 to patients with unkown margins.

In contrast the incidence of breast relapses in patients with negative margins was reported to be 9% (10-year actuarial) by Zafrany et al (17), 8% by Kurtz median follow-up 5.9 years), 10% (8-years actuarial) by Fisher et al (2), and 13% by Fowble et al (39) (8-year actuarial); these results were observed with or without boost. Ryoo et al (4) noted a 30% incidence of breast relapses in patients with microscopically positive margins who did not receive a boost after breast irradiation in comparison to 4% with negative margins.

The impact of dose of irradiation on local tumor control was documented by Kurtz et al (18) in 139 patients treated with breast conservation surgery and irradiation; they noted that patients receiving tumor doses of less than 7500 cGy had a significantly greater recurrence rate (8/26 = 31%) than those treated with higher doses (16/108 = 15%) (p. <0.05). Similar observations were made in retrospective by Clarke et al (37), by van Limbergen et al (48), who noted tumor control greater than 90% with doses higher than 1800 ret, and by Recht et al (19), who reported that patients receiving 6000 cGy or more had a 6% breast recurrence rate at 6 years compared with 12%

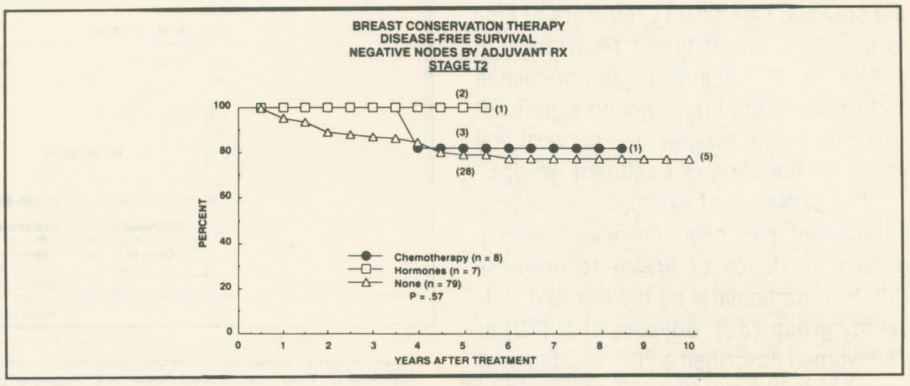
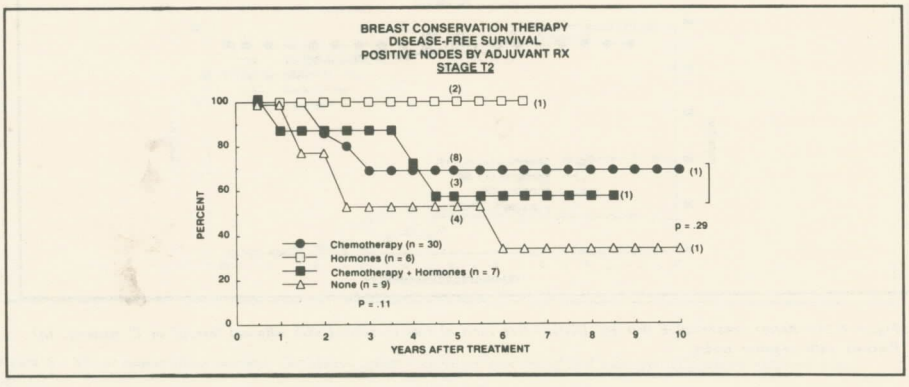


Figure 9 - Breast conservation therapy: Disease-free survival rate correlated with adjuvant therapy in T2 patients. (A) Patients with negative nodes. (B) Patients with positive nodes. (Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C: Organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol, in press) (24).



for those treated to lower doses (p = .37). As in our series, Fourquet et al (54) noted no reduction in recurrence rate with higher doses of irradiation, possibly because patients receiving greater doses were those with a greater risk of a local failure. As reported by others (55, 56), we observed similar incidence of breast relapses in patients receiving the boost of irradiation with either electrons or interstitial brachytherapy. As noted by others (2, 9, 14, 22, 39), we observed that the addition of adjuvant systemic chemotherapy reduces the risk of breast recurrences (1% to 6% adjuvant chemotherapy compared with 4% to 17% withaout chemotherapy.

Cosmesis was judged to be excellent/good in 82% of the patients, results similar to those noted by other (7, 9, 39, 55). As described by Kuske et al (8), surgical technique, type of incision, and volume of breast removed had a significant influence on cosmetic results. With regard to boost technique, we found no significant difference in comesis between the patients receiving the additional dose with electrons or interstitial implants.

Concomitant administration of irradiation and adjuvant chemotherapy affects cosmesis negatively, Rose et al (9) described 40% excellent cosmetic results with adjuvant chemotherapy versus 71% without it. As in our patients, Hallahan et al (21) observed that 90% of 34 patients receiving adjuvant chemotherapy (CMF or CAF) after irradiation and 93% of 166 patients receiving no chemotherapy or only tamoxifen had excellent/good cosmetic results. The administration of chemotherapy after surgical excision, before initiation of radiation therapy, according to Recht et al (57) resulted in a greater incidence of breast failures (41% 5-year actuarial in 26 patients in comparison with 4% to 8% in 269 patients receiving irradiation before or concurrently with chemotherapy).

Several authors have described a significant proportion of patients who fail breast conservation therapy surviving after salvage surgery, with 5-year survival rates fairly comparable to those of women initially treated with a mastectomy (50, 58, 59). In our experience, however, 5-year cause-specific survival after treatment of breast relapse was 72% for patients with initial T_1 tumors but only 25% after salvage of a T_2 breast recurrence.

Patients with negative axillary lymph nodes do not gain any therapeutic advantage from lymphatic irradaiation. The role of regional lymph node irradiation in patients with positive node treated with conservation therapy remains controvertial (most receive adjuvant chemotherapy) (60, 61). In randomized studies Sarrazin et al (33) noted similar 5-year disease-free survival in patients who received lymph node irradiation (62%) and those who did not (66%). Based on these data, the following are general guidelines for management of the regional nodes:

1 - Patients with clinically uninvolved axillary nodes (N0) can be effectively treated by either axillary dissection or irradiation. Because of staging information, axillary dissection is preferred.

2 - Patients with palpable or suspicious axillary nodes (1) should undergo therapeutic axillary dissection.

3 - Axillary or supraclavicular irradiation should not be given routinely after adequate axillary dissection when the lymph nodes are negative or only one to three nodes are positive.

4 - At the present time, data are insufficient to justify a firm opinion regarding regional lymphatic irratiation for patients with four or more positive axillary nodes (although at some institutions, including ours, this is common pratice.

In contrast, breast-preserving surgery and irradiation yield therapeutic results comparable to more radical surgical procedures in a large number of women with breast cancer. Careful study of prognostic factors and patient selection, as well as further refinements in treatment techniques, will enhance the application of this approach with better cosmesis and quality of life.

+ VAX 8600 Computer, Digital Equipment Corp.
* BMDP Statistical Software, University of California Press, Berkeley, California.

REFERENCES

1 - Blichert-Toft M: A Danish randomized trial comparing breast preservation with mastectomy in mammary carcinoma. Proceedings of the NIH Consensus Development Conference Early Stage Breast Cancer, June 1990, pp 28-31.

2 - Fisher B, Redmond C, Poisson R, et al: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the tratment of breast cancer. N Engl J Med. 320:822-828, 1989.

3 - Glatstein E, Straus K, Lichter A, Lippman M, Danforth D, Swain S, Cowan K, de Moss E, McDonald H, d'Angelo T, Steinberg S, Merino M, Bader J, Findlay P, Rosenberg S: Results of the NCI early breast cancer trial. Proceedings of the NIH Consensus Development Conference Early Stage Breast Cancer, June 1990, pp 32-33.

4 - Ryoo ME, Kagan AR, Wollin M, Tome MA, Tedeschi AA, Rao AR, Hintz BL, Kuruvilla AM, Nussbaum H, Streeter OE, Jabola BR, Miller MJ: Prognostic factors for recurrence and cosmesis in 393 patients after radiation therapy for early mammary carcinoma. Radiology 172:555-559, 1989.

5 - Van Dongen JA: Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer: EORTC trial 10801. Proceedings of the NIH Consensus Development Conference Early Stage Breast Cancer, June 1990, pp. 25-27.

6 - Veronesi U, Banfi A, DelVecchio M, Saccozzi R, Clement C, Greco M, Luini A, Maruloini E, Muscolina G, Rilke F, Sacchini V, Salvatori B, Zecchini A, Zucali R: Comparison of Halsted mastectomy with quadrantectomy, axillary dissection and radiotherapy in early breast cancer: Long-term results. Eur J Cancer Clin Oncol. 22:1085-1089, 1986.

7 - Beadle GF, Harris JR, Silver B, Botnick L, Hellman S: Cosmetic results following primary radiation therapy for early breast cancer. Cancer. 54:2911-2918, 1984

8 - Kuske RR, Garcia DM, Perez CA, Philpott GW, Lyss AP, Movsas T, Fineberg B: Cosmesis after breast conservation therapy: Surgical radiotherapeutic, chemotherapeutic, host, and tumor factors influencing results. Int J Radiat Oncol Biol Phis. (submitted for publication).

9 - Rose MA Olivotto I, Cady B, et al: Conservative surgery and radiation therapy for early breast cancer: Long-term cosmetic results. Ann urg. 124:153-157, 1989.

10 - Boyages J, Recht A, Connolly SJ, Gelman R, Kooy H, Love S, Osteen RT, Cady B, Silver B, Harris JR: Early breast cancer: Predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. Radiother Oncol. 19:29-41, 1990.

11 - Danoff B, Goodman RL: Identification of subset of patients with early breast cancer in whom conservative surgery and radiation is contraindicated. Int J Radiat Oncol Biol Phys. 11:104, 1985.

12 - Eberlein TJ, Connolly JL, Schitt SJ, Recht A, Osteen RT, Harris JR: Predictors of local recurrence following conservative breast surgery and radiation therapy: The influence of tumor size. Arch Surg. 125:771-777, 1990.

13 - Fisher ER, Sass R, Fisher B, Gregory R, Brown R, Wickerham L, NSABP Investigators: Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 6). II. Relation of local breast recurrence to multicentricitty. Cancer 57:1717-1724, 1986.

14 - Haffty BG, Fischer D, Rose M, Beinfield M, Mckhann C: Prognostic factors for local recurrence in the conservatively treated breast cancer patient: A cautious interpretation of the data. J Clin Oncol. 9:997-1003, 1991.

15 - Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, Bressac C, Roth J, Spitalier J-M: Risk factors for breast recurrence in premenopausal and postmenopausal patients with ductal cancers treated by conservation therapy. Cancer. 65:1867-1878, 1990.

16 - Schitt SJ, Connoly JL, Recht A, Silver B, Harris JR: Breast relapse following primary radiation therapy for early breast cancer. II. Detection of pathologic features and prognostic significance. Int J Radiat Oncol Biol Phys. 11:1277-1284, 1985.

17 - Zafrani B, Vielh P, Fourquet A, Mosseri V, Durand JC, Salmon RJ, Vilcoq JR: Conservative treatment of early breast cancer: Prognostic value of ductal in situ component and other pathologic variables on local control and survival. Eur J Cancer Clin Concol. 25:1645-1650, 1989.

18 - Kurtz JM, Amalric R, Brandone H, Qyme Y, Spitalier J-M: How important is adequate radiotherapy for the long-term results of breast-conserving treatment? Radiother Oncol. 20:84-90, 1991.

19 - Recht A, Silver B, Schnitt S, Connelly J, Hellman S, Harris JR: Breast relapse following primary radiation therapy for early breast cancer. I - Classification, frequency and salvage. Int J Radiat Oncol Biol Phys 11:1271-1276, 1985.

20 - Haffty BG, Goldberg NB, Fisher D,, Mckhann C, Beinfield M, Weissberg JB, Carter D, Geral W: Conservative surgery and radiation therapy in breast carcinoma: Local recurrence and prognostic implications. int J Radiat Oncol Biol Phys. 17:727-732, 1989.

21 - Hallahan De, Michel Ag, Halpern HJ, Awan AM, Desser R, Bitran J, Recant W, Wyman B, Spelbring DR, Weichselbaum RR: Breast conservating surgery and definitive irradiation for early stage breast cancer. Int J Radiat Oncol Biol Phys. 17:1211-1216, 1989.

22 - Rutqvist LE, Cedermark B, Glas U, Johansson H, Rotstein S, Skoog L, Somell A, Theve T, Askergren J, Friberg S, Bergstrom J, Blomstedt B, Rat L, Silfversward C, Einhorn J: Radiotherapy, chemotherapy, and taxoxifen as adjuncts to surgery in early breast cancer: A summary of three ramdomized trials. int J Radiat Oncol Biol Phys. 15:629, 1989.

23 - Beahrs OH, Henson DE, Hutter RVP, Myers MM (eds): Manual for staging of cancer, 3rd ed. Philadelphia, JB Lippincott, 1988.

24 - Perez CA, Garcia DM, Kuske RR, Halverson KJ, Coke C, McBurney L, Myerson R, Philpott G, Levy J, Simpson JR, Tucker G, Vest M, Lockett MA, Rush C: Organ preservation therapy in stage T1 and T2 carcinoma of the breast. Front Radiat Ther Oncol. (in press).

25 - Dixon WJ: BMDP Statistical Software. Los Angeles, University of California Press, 1982.

26 - Dixon WJ: News for 1987 release of BMDP statistical software. Los Angeles, University of California press, 1986.

27 - Cutler SJ, Ederer F: Maximum utilization of the life table method in analyzing survival. J Chron Dis. 8:699-713, 1958.

28 - Miller R: Survival Analysis. New York, John Willey, 1981.

29 - Tarone R, Ware J: On distribution free tests for equality of survival distributions. Biometrika. 64:156-160, 1977.

30 - Tarone R: Tests for trend in life table analysis. Biometrika.

31 - Perez CA, Garcia DM. Kuske RR, levitt SH: Breast: Stage T_1 and T2 tumors; In Perez CA, Brady LW (eds): Principles

and practice of radiation oncology, 2nd ed. Philadelphia, JB Lippincott, 1992.

32 - Harris JR, Connolly JL, Schnitt SJ, Cady B, Love S, Osteen RT, Patterson WB, Shirley R, Hellman S, Cohen RB, Silen W: The use of pathologic features in selecting the extent of surgical resection necessary for breast cancer patients treated by primary radiation therapy. Ann Surg. 210:164-169, 1985.

33 - Sarrazin D, Le MG, Arriagada R, Contesso G, Fontaine F, Spielmann M, Rochard F, le Chevalier TH, Lacour J: Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol 14:177, 1989.

34 - Calle R, Pilleron J, Schlienger P, Vilcoq JR: Conservative management of operable breast cancer: Ten years' experience at the Foundation Curie. Cancer. 42:2045-2053, 1978.

35 - Cedermark B, Askergren J, Alveryd A, et al: Breast-conserving treatment for breast cancer in Stockholm, Sweden, 1977 to 19881. Cancer. 53:1253-1255, 1984.

36 - Clark RM, Wilkinson RH, Mahoney LJ, Reid JG, MacDonald WD: Breast cancer: A 21 year experience with conservative surgery and radiation. Int J Radiat Oncol Biol Phys. 8:967-975, 1982.

37 - Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fountaine F, Travagly J-P, May-Levin F, Contesso G, Arriagada R: Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: Experience of the Institut Gustave-Roussy. int J Radiat Oncol Biol Phys. 11:137-145, 1985.

38 - Dubois JB, Gary-Bobo J, F Pourquier H, Pujol H: Tumorectomy and radiotherapy in early breast cancer: A report on 392 patients. Int J Radiat Oncol Biol Phys. 15:1275-1282, 1988.

39 - Fowble BL, Solin LJ, Schultz DJ, Goodman RL: Ten year results of conservative surgery and irradiation for stage I and II breast cancer. Int J Radiat Oncol Biol Phys. 21:269-277, 1991.

40 - Sarrazin D, JA Arriagada R, Behamou S, Benhamou E, Lasser P, Fontaine F, Travagly JR, Spielmann M, le Chevalier T, Contesso G: Conservative management of breast cancer. Br J Surg. 77:604-606, 1986.

41 - Bartelink H, Borger JH, van Dogen JA, et al: The impact of tumor size and histology on local control after breast-conserving therapy. Radiother Oncol. 11:297-303, 1988.

42 - Fisher B, Redmond C, Dimirov NV, Bowman D, Legault-Poisson S, Wicherham L, Wolmark N, Fisher E, Margolese R, Sutehrland C, Glass A, Foster R, Caplan R: A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. N Engl J Med. 320:473-478, 1989.

43 - Veronesi U, Salvador B, Luini A, Banfi A, Zucali R, Del Vecchio M, Saccazzi R, Beretta E, Boracchi P, Farante G, Galimberti V, Mezzanotte G, Sacchini V, Tana S, Marubini E: Conservative treatment of early breast cancer: Long-term results of 1232 cases treated with quadrantectomy, axillary dissection and radiotherapy. Ann Surg. 211:250-259, 1990.

44 - NIH Consensus Conference: Treatment of early-stage breast cancer. JAMA. 265:391-395, 1991.

45 - Montague ED: Conservation surgery and radiation therapy in the treatment of operable breast cancer. Cancer. 53:700-704, 1984.

46 - Calle R, Volcoq JR, Zafrani B, Vielh P, Fourquet A: Local control and survival of breast cancer treatment by limited surgery followed by irradiation. Int J Radiat Oncol Biol Phys. 12:873-878, 1986.

47 - Delouche G, Bachelot F, Premont M, Kurtz JM: Conservation treatment of early breast cancer: Long-term results and complications. Int J Radiat Oncol Biol Phys. 13:29-34, 1987.

48 - Van Limbergen E, Van den Bogaert W, van der Schueren E, Rijnders A: Tumor excision and radiotherapy as primary treatment of breast cancer: Analysis of patients and treatment parameters and local control. Radiother Oncol. 8:1-9, 1987.

49 - Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, Mamounas EP, Deutsch M, Margolese R: Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet. 338-327-331, 1991.

50 - Kurtz JM, Spitalier JM, Amalric R: Late breast recurrence after lumpectomy and irradiation. Int J Radiat Oncol Biol Phys. 9:1191-1194, 1983.

51 - Schnitt SJ, Connolly JL, Khettry U, Mazoujian G, Brenner M, Silver B, Recht A, Beadle G, Harris JR: Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. Cancer. 59:675-681, 1987.

52 - Solin LJ, Fowble BL, Schultz DJ, Goodman RL: The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. Int J Radiat Oncol Biol Phys. 21:279-287, 1991.

53 - Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, Bressac C, Spitalier J: Why are local recurrences after breast conserving therapy more frequent in young patients? J Clin Oncol. 8:591, 1990.

54 - Fourquet A, Campana F, Zafrani B, Mosseri V, Vielh P, Durand J-C, Vilcoq JR: Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up. Int J Radiat Oncol Biol Phys. 17:719-725, 1989.

55 - Olivotto IA, Rose MA, Osteen RT, Love S, Cady B, Recht A, Harris JR: Late cosmetic outcome after conservative surgery and radiotherapy: Analysis of causes

of cosmetic failure. Int J Radiat Oncol Biol Phys. 17:747-753, 1989.

56 - Ray GR, Fish VJ: Biopsy and definitive radiation therapy in stage I and II adenocarcinoma of the female breast: Analysis of cosmesis and the role of electron beam supplementation. Int J Radiat Oncol Biol Phys. 9:813-818, 1983.

57 - Recht A, Come SE, Gelman RS, Goldstein M, Tishler S, Gore SM, Abner AL, Vicini FA, Silver B, Connoly JL, Schnitt SJ, Coleman CN, Harris JR: Integration of conservative surgery, radiotherapy, and chemotherapy for the treatment of early-stage, node-positive breast cancer: Sequencing, timing, and outcome. J Clin Oncol. 9:1662-1667, 1991.

58 - Fowble B, Goodman RL, Glick JH, Rosato EF: Breast cancer treatment: A comprehensive guide to management. St. Louis, Mosby Year Book, 1991.

59 - Harris JR, Hellman S, Henderson IC, Kinne DW: Breast Diseases, 2nd ed. Philadelphia, JB Lippincott, 1991.

60 - Dewar JA, Sarrazin D, Benhamou E, et al: Management of the axilla in conservatively treated breast cancer: 592 patients treated at Institu Gustave-Roussy. Int J Radiat Oncol Biol Phys. 13:475-481, 1987.

61 - Fowble B, Solin LJ Schultz DJ, Goodman RL: Frequency, sites of relapse, and outcome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys. 17:703-710, 1989.