Have Changing Treatment Patterns Affected Outcome for Operable Breast Cancer?

Ten-year Follow-up in 1288 Patients, 1965 to 1978

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From 1965 to 1978, 1288 patients with primary operable breast cancer were treated by the senior author, using extended radical (ERM), radical (RM), and modified radical (MRM) mastectomy operations exclusively. Results were analyzed for trends in overall and disease-free survival, and patterns of local and distant relapse, the years 1965 to 1970 *versus* 1971 to 1974 *versus* 1975 to 1978. Significant changes ($p < 0.00001$) from 1965 to 1978 included progressively earlier stage of disease, less frequent use of RM and ERM, a decline in the use of postoperative radiotherapy, and the introduction in 1975 of multidrug adjuvant chemotherapy. Ten-year disease-free survival rates improved significantly for all patients (by 11%, $p = 0.00004$) and for node-negative (by 12%, $p = 0.0024$), node-positive (by 8%, $p = 0.012$), clinical stage II (by 15%, $p = 0.0022$), and pathologic stage II (by 12%, $p = 0.016$) disease. Ten-year local recurrence for all patients was 3% (local only) and 2% (local with distant metastasis), and survival from date of recurrence for all patients failing treatment increased two times ($p < 0.0001$) for patients treated most recently. As the primary surgical treatment of breast cancer continues to become more moderate, the promise of systemic adjuvant therapies can be realized only with continued emphasis on earlier diagnosis and maximal local control of disease.

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IN THE LAST TWO decades we have witnessed remarkable changes in the management of primary operable breast carcinoma. The Halstead radical mastectomy, a standard since the 1890s, has yielded to modified radical mastectomy and breast-conserving approaches combining surgery and radiotherapy, encouraged by the results of randomized trials with follow-up now exceeding 10 years.[1,2] Postmastectomy radiotherapy has been used with decreasing frequency, particularly for stages I and II disease, and systemic adjuvant therapy (cytotoxic and hormonal) has come into widespread use. Despite these factors nationwide survival statistics for operable breast cancer have not improved significantly in recent decades[3] and no long-term studies have demonstrated survival rates for breast conservation exceeding those of comparable patients treated by radical surgery. This study reports the results of a large single-surgeon experience with 1288 patients treated from 1965 to 1978 and followed 10 years, with particular attention to trends in pattern of primary treatment, local/distant failure, and long-term survival. Because the primary treatment of breast cancer has become increasingly heterogeneous in the 1980s, these patients (treated exclusively by radical surgery) comprise a unique historical reference for future studies.

Patients and Methods

Between 1965 and 1978, 1395 patients with primary operable breast carcinoma were treated by the senior author (J.A. Urban) on the Breast Service, Department of Surgery, at Memorial Sloan-Kettering Cancer Center. Excluding 107 patients with noninvasive tumors (intraductal or lobular carcinoma *in situ*), 1288 patients with invasive carcinomas form the basis of this study and were grouped into three cohorts: 1965 to 1970 (493 patients), 1971 to 1974 (347 patients), and 1975 to 1978 (448 patients). The 1965 to 1970 patients formed the basis of a previous report,[4] but for this study all data were updated and reanalyzed with particular attention to patterns of local recurrence.

All patients were judged to have operable disease and the only criteria of inoperability were supraclavicular dis-

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Accepted for publication June 21, 1990.

ease, arm edema, inflammatory carcinoma, distant metastases, or medical contraindications to general anesthesia. Excluded were patients with a previous breast (or other) cancer, but patients with bilateral (synchronous or subsequent) breast cancers were included.

All were treated by radical surgery, using radical mastectomy (RM), extended radical mastectomy (ERM), and modified radical mastectomy (MRM) selectively. Modified radical mastectomy was used for patients with the smallest tumors and clinically negative axillae. Extended radical mastectomy was used for patients with larger, medially located tumors and RM for the remaining patients. Operative technique was as previously described.[5] All patients had full axillary dissections and no special nodal 'clearing' methods were used in pathologic examination. Contralateral breast biopsy was performed in most cases.

All patients were staged clinically and pathologically using the 1983 American Joint Committee on Cancer classification (stage I, T1N0; stage II, T2N0, T1-2N1; stage III, T3N0-1).[6] Follow-up for most patients was maintained by regular in-office examination, and for the remaining patients from hospital records, by telephone, and by questionnaire; median follow-up was 10.3 years and was complete at 5 years in 97% and at 10 years in 93% of all patients.

TABLE 1. *Patient and Tumor Characteristics*

Data	1965–1970	1971–1974	1975–1978
No. patients	493	347	448
Age: Mean (years)	54.5	55.8	56
Range	22–85	26–85	25–87
% <50	37	29	30
Tumor location			
UOQ%	41	44	47
LOQ%	22	14	11
UIQ%	21	22	22
LIQ%	7	10	9
C%	9	7	9
Tumor size (cm)			
Clinical			
Mean	NA	2.7	2.3
Median	NA	2.0	2.0
Range	NA	0.5–9.0	0.3–8.0
Pathologic			
Mean	2.5	2.4	2.2
Median	2.0	2.0	2.0
Range	0.2–9.8	0.3–9.0	0.3–9.0
Tumor type			
Inv. duct%	92	95	94
Inv. lobular%	8	5	6
Favorable % (incl. medullary, colloid, tubular, papillary)	3	4	3
Axillary nodes			
Clinical			
Neg. (N0, N1a)%	75	84	83
Pos. (N1b)%	25	16	17
Pathologic			
nodes removed (mean #)			
Ax, level I	NA	11	13
Ax. level II	NA	6	5
Ax. level III	NA	6	5
Total	NA	23	23
Highest level positive			
Neg. %	56	61	59
I%	22	22	24
II%	11	8	9
III%	11	9	8
No. nodes positive			
0%	56	61	59
1–3%	44 (1–3% and >3%)	28	25
>3%		11	16
Micromets			
Only %	NA	8	9

UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; C, central; NA, not applicable.

TABLE 2A. *Patterns of Treatment by Years Treated*

Treatment	1965–1970	1971–1974	1975–1978
Operation			
RM # (%)	351 (71)	227 (65)	193 (43)
ERM # (%)	102 (21)	48 (14)	45 (10)
MRM # (%)	40 (8)	72 (21)	210 (47)
Contralat BX			
Pos. %	7.3	10.4	10.7
Neg. %	75	76.3	80
Not done %	17.7	13.3	9.3
Postop RT			
Yes %	42	33	27
No %	58	67	73
Chemotherapy			
Yes %*	0	0	19
No %	100	100	81

Statistical Methods

All statistical analyses were done using BMDP programs (BMDP Statistical Software, Los Angeles, CA, 1988 re-

TABLE 2B. *Operation Type by Stage of Disease*

Operation	I	II	III	Total
		Clinical Stage # (%)		
RM	342 (51)	373 (70)	46 (65)	761 (60)
ERM	78 (11)	102 (19)	15 (20)	195 (15)
MRM	253 (38)	57 (11)	22 (15)	322 (25)
Total	673 (100)	532 (100)	83 (100)	1288 (100)
		Pathologic Stage # (%)		
RM	242 (49)	474 (67)	45 (70)	761 (60)
ERM	55 (11)	125 (18)	15 (21)	195 (15)
MRM	207 (40)	117 (15)	8 (9)	322 (25)
Total	504 (100)	716 (100)	68 (100)	1288 (100)

RM, radical mastectomy; ERM, extended radical mastectomy; MRM, modified radical mastectomy.

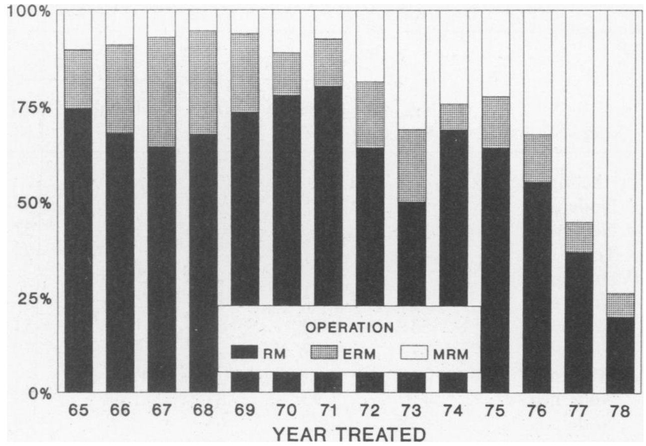


FIG. 1. Distribution of operation type by year of treatment, 1965–1978 ($p < 0.00001$).

lease) on an IBM PS/2 Model 70 E61 computer (IBM, Armouk, NY). Overall and disease-free survival rates were determined using the life table method (BMDP 1L). Patients dying of other causes and known to be cancer free were censored, while patients dying of unknown causes were considered dead of disease. The significance of survival differences was tested by the log rank method (BMDP 1L), univariate comparison of group means by Student's t test (BMDP 3D), and association between categorical variables by the Pearson chi square test (BMDP 4F). Multivariate analysis employed the Cox proportional hazards model, using stepwise regression by the maximized partial likelihood ratio method (BMDP 2L).[7]

Results

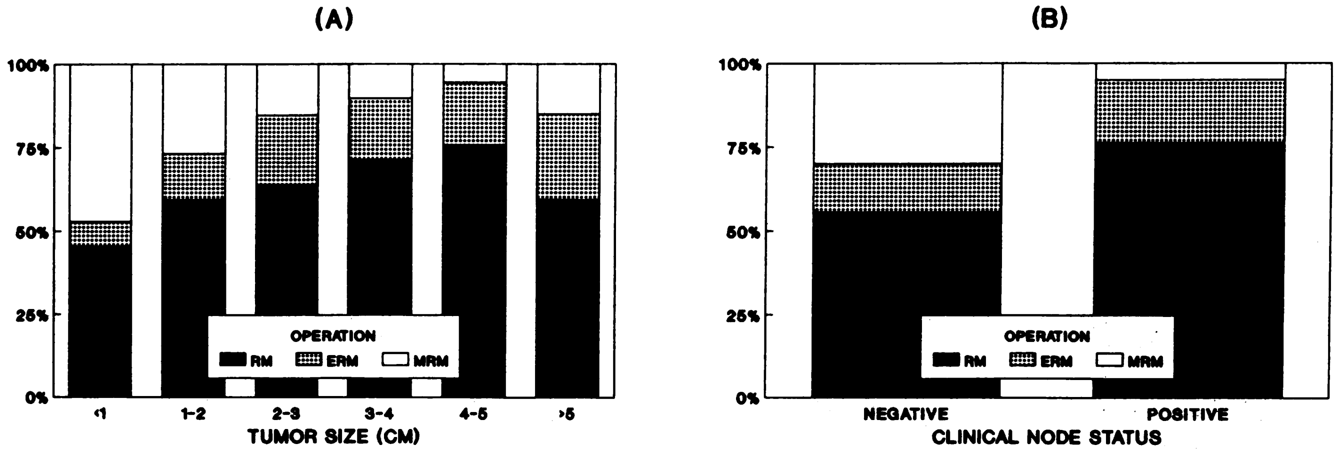
Table 1 compares a variety of patient and tumor characteristics among the three time cohorts. Although median tumor size was constant), there was a significant trend toward smaller mean size ($p = 0.0001$).

Fewer patients in more recent years had clinically positive axillae ($p = 0.003$), although the pathologic extent of axillary node involvement by highest level of metastasis did not change significantly from 1965 to 1978 ($p = 0.35$). Before 1971 axillary involvement was only described by anatomic level and not by number of nodes involved; from 1971 and after, exact numbers of nodes removed and involved were noted for most patients and did not change significantly from 1971 to 1978 ($p = 0.35$).

All patients were treated by radical surgery (Table 2A), with a significant trend during the period studied toward fewer RM and ERM, and more MRM (Fig. 1, $p < 0.0001$). Extent of surgery was based both on tumor size and on clinical axillary node status (Fig. 2, $p < 0.00001$). Operation type was significantly correlated with clinical and pathologic stage of disease (Table 2B, $p < 0.00005$).

Postoperative radiotherapy was used less often in recent years ($p < 0.0001$). Multidrug adjuvant chemotherapy was used only since 1975; in this study patients given chemotherapy for less than 6 months or who were given single-dose or single-drug regimens were considered not to have been treated. About one third of patients with one to three nodes positive and two thirds with more than three nodes positive received chemotherapy since 1975 (Table 3). Four node-negative patients thought to be at high risk based on tumor size and/or extensive lymphatic permeation also received chemotherapy.

All patients were staged both clinically and pathologically (Table 4). More patients in recent years had stage I disease, both clinical ($p = 0.001$) and pathologic ($p = 0.005$). This downstaging appears to be a result of progressively smaller tumor sizes and fewer patients with



FIGS. 2A and B. Selection of operation type by (A) tumor size ($p < 0.00001$) and (B) clinical node status ($p < 0.00001$).

TABLE 3. *Patterns of Chemotherapy Use, 1975–1978*

	% Receiving Chemotherapy		
Nodal Status	Premenopause	Postmenopause	Total
Node negative	2.6	1.1	1.5
1–3 Nodes	33	28	30
>3 Nodes	64	64	64
Total	20	18	19

clinically positive axillae, although as noted above, pathologic extent (by level or number) of axillary nodal disease did not change significantly during this period.

Tables 5 and 6 list 5 and 10-year overall and disease-free survival rates for the entire patient group, by nodal and menopausal status, clinical and pathologic stage, and pathologic TNM status. Of note are the 10-year disease-free survival rates for node-positive disease: 55% for all node-positive, 48% for pathologic stage III, and 34% for patients with level III axillary node involvement.

In Tables 7 to 10, survival by stage, menopausal and nodal status is listed, comparing the results within each subgrouping by chronologic cohorts. Table 7 demonstrates survival improvement in the period studied for all patients, node negatives, and node positives, all with significant probability values.

Survival by menopausal status and number of axillary metastases (Table 10) is reported only for 1971 to 1974 and 1975 to 1978; exact numbers of nodes were not reported before 1971. The most striking, and only significant, improvement is seen in the premenopausal, one to three node-positive group, although small numbers of patients are involved, and only one third of the 1975 to 1978 group received adjuvant chemotherapy (Table 3). No significant improvement was noted in any other grouping by menopausal status and number of axillary metastases.

Tables 11 and 12 list patterns of 10-year local recurrence, for all patients whose first site of treatment failure was a local recurrence (parasternal, skin flap, chest wall, or axillary) without evidence of distant metastases. Supraclavicular node relapse was not considered a local failure. An additional 2% of the entire group had local recurrence coincident with (or subsequent to) the development of distant metastases. By clinical and pathologic stage (Table 12), local recurrence increased with increasing stage. Because of the small numbers of patients developing local recurrence, there were no significant differences in

TABLE 4. *Stage of Disease*

Stage	1965–1970	1971–1974	1975–1978
AJC Clinical			
I # (%)	225 (46)	178 (51)	270 (60)
II # (%)	245 (49)	139 (40)	148 (33)
III # (%)	23 (5)	30 (9)	30 (7)
AJC Pathologic			
I # (%)	165 (34)	138 (40)	201 (44)
II # (%)	305 (62)	188 (54)	223 (50)
III # (%)	23 (4)	21 (6)	24 (6)

TABLE 5. *Survival Totals by Nodal Status, 1965–1978*

		5 Years		10 Years	
Nodal Status	No. Patients	Overall %	NED %	Overall %	NED %
Premenopause					
Node neg.	230	95	88	90	85
Node pos.	186	76	63	65	57
Total	416	87	77	79	72
Postmenopause					
Node neg.	521	92	87	88	80
Node pos.	351	79	65	63	54
Total	872	87	78	78	70
All Patients					
Node neg.	750	93	87	89	82
Node pos.	538	78	65	64	55
L I +	299	85	74	71	64
L II +	117	81	64	67	55
L III +	122	60	43	43	34
Total	1288	87	78	79	71

NED, no evidence of disease.

TABLE 6. *Survival Totals by Stage and TNM Status, 1965–1978*

		5 Years		10 Years	
Stage	No. Patients	Overall %	NED %	Overall %	NED %
		Clinical			
I	673	94	87	88	81
II	532	80	69	68	60
III	83	72	61	69	55
		Pathologic			
I	504	96	91	93	87
II	716	82	70	69	61
III	68	67	54	61	48
		TNM (Pathologic)			
T1N0	504	96	91	93	87
T2N0	237	86	78	79	73
T3N0	23	100	94	100	83
T1N1	215	86	74	76	67
T2N1	264	74	58	54	45
T3N1	45	61	52	53	48
Total	1288	87	78	79	71

NED, no evidence of disease.

TABLE 7. *Survival by Nodal Status*

Nodal Status	No. Patients	5 Years Overall %	5 Years NED %	10 Years Overall %	10 Years NED %
Node Negative					
1965–1970	274	88	82	82	75
1971–1974	213	95	90	89	84
1975–1978	263	97	91	96	87
					(p = 0.0024)
Node Positive					
1965–1970	219	71	62	58	51
1971–1974	134	74	61	58	56
1975–1978	185	92	70	77	59
					(p = 0.012)
Total Patients					
1965–1970	493	81	73	72	65
1971–1974	347	87	79	77	73
1975–1978	448	95	82	89	76
					(p = 0.0004)

NED, no evidence of disease.

TABLE 8. *Survival by Year Treated*

Stage/Years	No. Patients	5 Years Overall %	5 Years NED %	10 Years Overall %	10 Years NED %
Clinical Stage					
Stage I					
1965–1970	225	91	86	86	79
1971–1974	178	94	88	88	83
1975–1978	270	97	88	91	82
					(p = 0.72)
Stage II					
1965–1970	245	72	63	58	52
1971–1974	139	82	72	70	67
1975–1978	148	93	76	85	67
					(p = 0.0022)
Stage III					
1965–1970	23	64	56	64	50
1971–1974	30	63	53	52	45
1975–1978	30	85	67	80	62
					(p = 0.39)
Pathologic Stage					
Stage I					
1965–1970	165	93	88	88	83
1971–1974	138	98	93	94	89
1975–1978	201	98	93	97	89
					(p = 0.22)
Stage II					
1965–1970	305	75	66	62	55
1971–1974	188	82	71	68	65
1975–1978	223	93	75	81	67
					(p = 0.016)
Stage III					
1965–1970	23	64	56	64	50
1971–1974	21	56	47	45	41
1975–1978	24	80	59	73	53
					(p = 0.69)

NED, no evidence of disease.

TABLE 9. *Survival by Menopausal and Nodal Status*

Years	No. Patients	5 Years Overall %	5 Years NED %	10 Years Overall %	10 Years NED %
Premenopausal					
Node Negative					
1965–1970	99	91	86	86	82
1971–1974	51	96	90	87	87
1975–1978	80	98	90	98	85
					(p = 0.76)
Node Positive					
1965–1970	85	68	60	59	51
1971–1974	49	75	59	58	54
1975–1978	52	93	73	82	69
					(p = 0.13)
Total					
1965–1970	184	80	74	74	68
1971–1974	100	86	75	73	71
1975–1978	132	97	83	93	79
					(p = 0.07)
Postmenopausal					
Node Negative					
1965–1970	175	87	80	79	71
1971–1974	162	94	89	90	83
1975–1978	184	96	91	94	89
					(p = 0.0006)
Node Positive					
1965–1970	134	73	63	57	50
1971–1974	85	73	62	58	57
1975–1978	132	91	69	75	55
					(p = 0.52)
Total					
1965–1970	309	81	73	70	62
1971–1974	248	87	80	79	74
1975–1978	316	94	82	87	75
					(p = 0.0018)

NED, no evidence of disease.

local recurrence rates by year of treatment in either the entire patient group (p = 0.13) or in any subgrouping by stage or extent of axillary involvement.

Table 13 reports 5-year survival from date of first treatment failure for all patients who experienced recurrence, by site of first recurrence, local-only *versus* local-with-distant, and distant-only. These survival rates improve strikingly for the most recent patient group (1975 to 1978), and by a significant margin in the larger group with distant disease. Expressed as months of median survival (± SEM),

TABLE 10. *Survival by Menopausal Status and Number of Nodes Positive*

		5 Years		10 Years	
Years	No. Patients	Overall %	NED %	Overall %	NED %
Premenopausal					
		1-3 Nodes+			
1971-1974	40	73	57	53	51
1975-1978	32	97	87	87	83
					(p = 0.01)
Total	72	83	70	67	65
		>3 Nodes+			
1971-1974	9	75	50	63	50
1975-1978	20	88	56	74	50
					(p = 0.61)
Total	29	84	54	70	50
Postmenopausal					
		1-3 Nodes+			
1971-1974	58	78	73	65	65
1975-1978	81	91	76	80	66
					(p = 0.96)
Total	139	86	75	73	66
		>3 Nodes+			
1971-1974	27	61	37	37	33
1975-1978	52	91	58	68	38
					(p = 0.18)
Total	79	79	50	56	36
		Total Patients			
		1-3 Nodes +			
1971-1978	211	85	73	71	66
		>3 Nodes +			
1971-1978	108	81	52	60	40

NED, no evidence of disease.

a similar improvement was seen for all patients failing treatment: 22 (± 3) for patients from 1965 to 1974 *versus* 55 (± 15) for patients from 1975 to 1978. Of note in these survival-from-date-of-recurrence statistics is the rapid occurrence of censoring in all groups of patients (most have distant metastases), which may distort the accuracy of statistical comparisons between groups, *i.e.*, if all censoring in the 1975 to 1978 cohort occurred as a result of death from disease, then, in fact, the observed survival advantage may only be an artifact.

In an effort to determine whether disease-free survival rates improved by year of treatment independently of other known prognostic variables, multivariate analysis for all patients treated from 1965 to 1978 was done (Table 14). The list of covariates was limited deliberately to those known to be most predictive of survival (pathologic/clinical node status, and tumor size). In both univariate and multivariate calculations, year of treatment exerts a small but significant effect. This may reflect the benefit of treatment modalities (such as systemic adjuvant chemotherapy) added in more recent years, although when the analysis was repeated for the 1965 to 1970 and 1971 to 1978 groups separately (using number of positive axillary nodes rather than highest level), year of treatment was unrelated to survival, indicating the relatively borderline significance of this finding.

TABLE 11. *Local Recurrence by Nodal Status*

Nodal Status	No. Patients	Local Recurrence %
Node Negative		
1965-1970	274	1.5
1971-1974	213	3.8
1975-1978	263	0.8
Total	750	1.9
Node Positive		
1965-1970	219	5.0
1971-1974	134	5.3
1975-1978	185	3.2
Total	538	4.5
All Patients		
1965-1970	493	3.0
1971-1974	347	4.3
1975-1978	448	1.8
Total	1288	3.0

Discussion

This study was undertaken to examine the 'bottom line' in a large group of patients treated for operable breast

TABLE 12. *Local Recurrence by Stage*

	Clinical		Pathologic	
Stage/Years	No. Patients	Local %	No. Patients	Local %
Stage I				
1965-1970	225	3.1	165	1.8
1971-1974	178	2.2	138	2.9
1975-1978	270	1.5	201	1.0
Total	673	2.2	504	1.8
Stage II				
1965-1970	245	2.4	305	3.3
1971-1974	139	5.8	188	4.8
1975-1978	148	1.3	223	1.8
Total	532	3.0	716	3.2
Stage III				
1965-1970	23	8.7	23	8.7
1971-1974	30	16.7	21	10.0
1975-1978	30	6.7	24	8.3
Total	83	9.9	68	9.2

TABLE 13. *Survival from Date of Recurrence by Site of First Recurrence*

Years	No. Patients	5-year Survival %	
	Local only		
1965–1970	15	44	
1971–1974	15	35	
1975–1978	8	86	($p = 0.37$)
Total	38	46	
	Local/distant or distant only		
1965–1970	153	12	
1971–1974	82	11	
1975–1978	83	47	($p < 0.0001$)
Total	318	19	
	All patients failing treatment		
1965–1970	168	15	
1971–1974	97	15	
1975–1978	91	47	($p = 0.0001$)
Total	356	21	

cancer with radical surgery during a 13-year period by one surgeon at one institution. Did changes in patient population, tumor factors, and pattern of local/systemic therapy affect 10-year survival rates and local control?

Progressively earlier stage of disease was a consistent finding throughout the study, and perhaps the greatest influence on the improved survivals noted. Mean tumor size decreased steadily and is part of a trend at Memorial Hospital: mean tumor size was 3 cm in 1194 patients (from 1940 to 1943),[8] 3 cm in the first 70 patients having extended radical mastectomy (in the early 1950s),[9] 2.5 cm (from 1965 to 1970), and 2.2 cm (from 1975 to 1978). Median was constant at 2 cm (from 1965 to 1978), indicating fewer patients with large tumors in recent years. Pathologic axillary node involvement decreased comparably: 62.6% positive (1940 to 1945),[10] 55.7% (1950 to 1955),[9] 44% (1955 to 1964),[11] 44% (1965 to 1970), and 41% (1975 to 1978). These data indicate a leveling off both in tumor size (which did nevertheless decline significantly from 1965 to 1978) and in frequency of axillary involvement (which did not). We hope that the more widespread and frequent mammographic screening of the 1980s will result in still earlier stage at diagnosis.

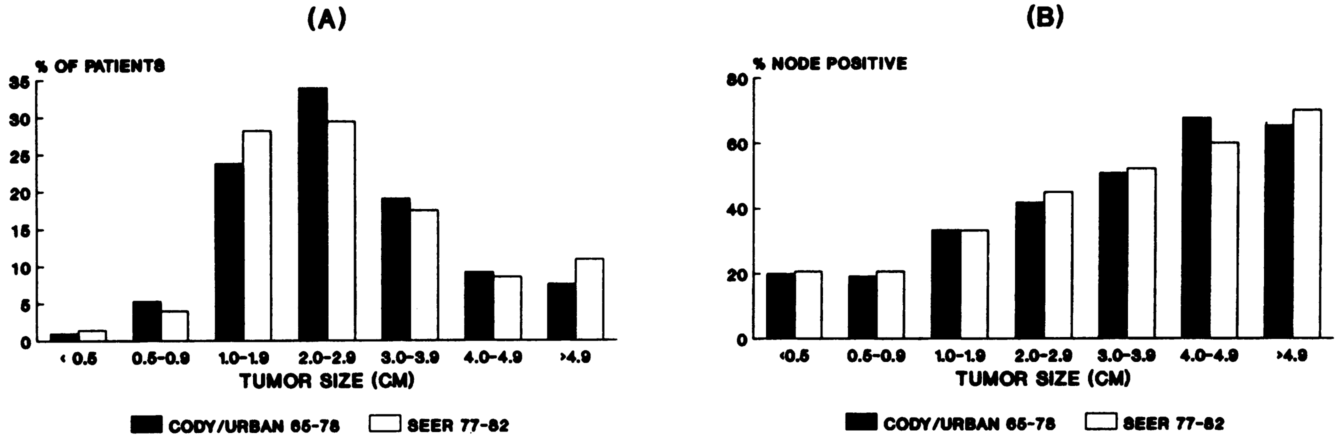
Recent data from the SEER Program of the National Cancer Institute correlate tumor size and axillary node involvement in 24,170 breast cancer patients (treated nationwide from 1977 to 1982), and indicate a linear relationship between the two.[12] The present data confirm this finding and indicate both by size distribution and extent of axillary node involvement (Figs. 3 and 4) that the patients in this study are comparable to those treated for operable breast cancer nationwide (of whom the SEER data represent about 10%). A frequent explanation for the excellent results reported from single-surgeon or single-institution studies has been the selection of an unusually favorable patient population. The patients in this study are, in fact, representative of the average breast cancer patient treated nationally, especially for the vast majority (94% to 96% in this series) with T1 or T2 disease; the T3 (stage III) patients in this study, 4% to 6% of the total, by contrast comprise a more favorable group than the T3 patients, 10.9% of the total, in the SEER data (Fig. 4).

Primary surgical treatment changed dramatically during the period studied. In 1965, 89.7% of patients underwent RM or ERM. By 1978, 73.8% had MRM. The trend away from RM and ERM and toward MRM parallels that noted in the 1982 National Survey taken by the American College of Surgeons (ACS),[13] in which the use of RM decreased from 48% to 3% in the years 1972 to 1981, while MRM increased from 28% to 73% during the same time period. Overall the pattern of surgical treatment nationwide was considerably less radical than in the present series. Nationally only 0.6% to 1.1% of patients had ERM, and 10.6% to 12.4% had lesser procedures than MRM (either total mastectomy alone or partial mastectomy). This trend has undoubtedly continued, particularly in view of the results of randomized studies from Milan (10-year follow-up)[1] and the NSABP B-06 trial (8-year follow-up)[14] indicating the efficacy of local excision, axillary dissection, and radiotherapy for patients with favorable disease (*i.e.*, smaller tumors and clinically negative axillae). While in other prospective randomized studies Veronesi and Valagussa[15] have questioned the benefit of ERM compared with RM, conflicting data from Lacour[16]

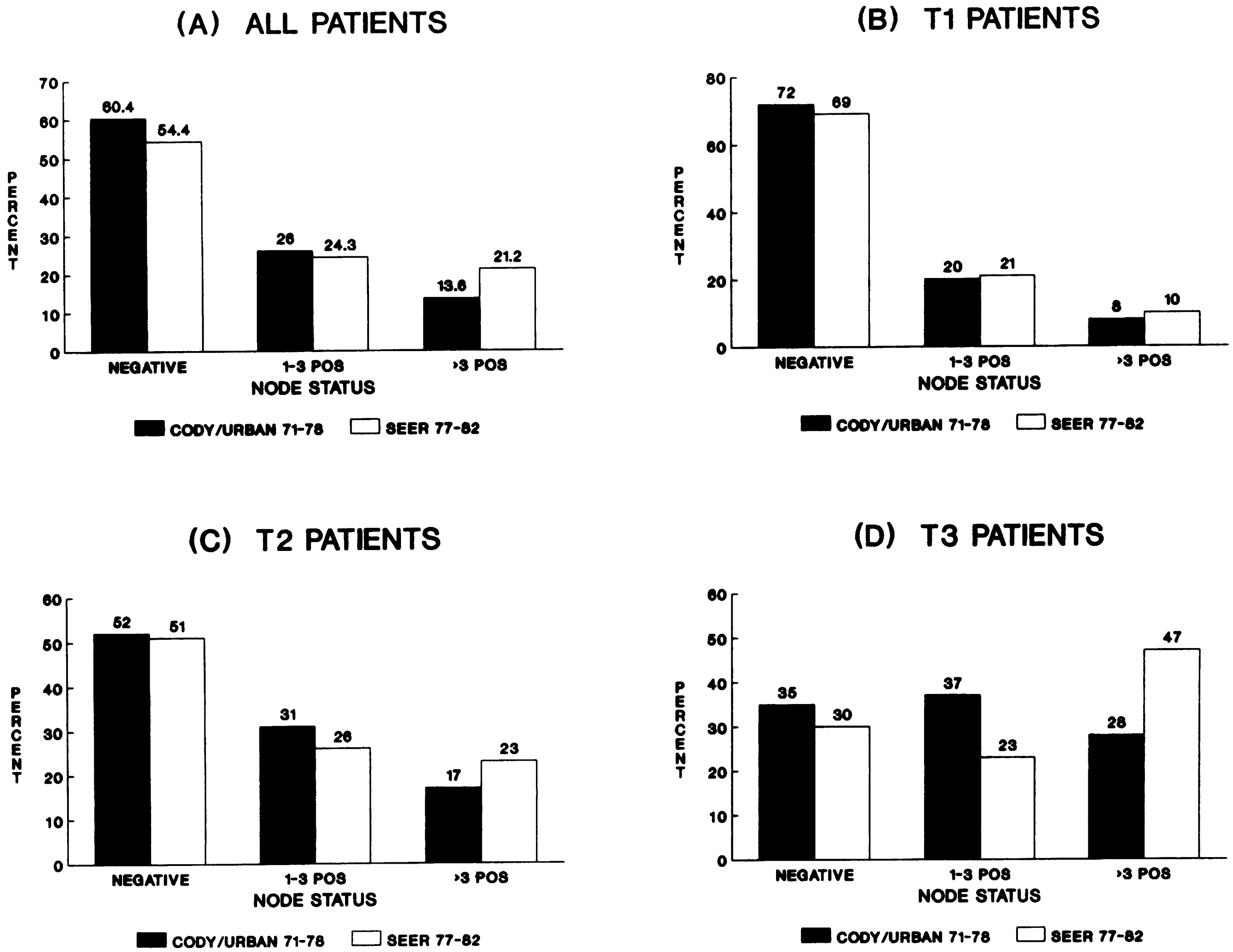
TABLE 14. *Univariate and Multivariate Analysis Determinants of NED Survival*

Variable	Chi Square	p
	Univariate	
Highest level positive	137	<0.00005
Clinical node status	51	<0.00005
Tumor size (pathologic)	48	<0.00005
Year treated	9.5	0.002
	Multivariate	
Highest level positive	137	<0.0005
Tumor size (pathologic)	24	<0.0005
Clinical node status	9.3	0.017
Year treated	5.7	0.002

NED, no evidence of disease.



FIGS. 3A and B. Comparison of patients in this study (1965–1978) with the SEER study (1977–1982),[12] by (A) size distribution and (B) percentage node positive by tumor size.



FIGS. 4A–D. Comparison of patients in this study (1971–1978) with the SEER study (1977–1982),[12] by extent of nodal involvement for (A) all, (B) T1, (C) T2, and (D) T3 patients.

and Ferguson[17] demonstrate a role in the subset of patients most likely to have involved internal mammary nodes: Lacour found that for patients with inner quadrant, axillary node-positive lesions, the 15-year NED survival rate was markedly better with ERM than RM (44% *versus* 25%; p = 0.05), and Ferguson found that for inner quadrant tumors, his personal 10-year overall survival rate for ERM surpassed RM significantly (86% *versus* 60%, p = 0.025). In the present study the trend toward less radical surgical treatment has not adversely affected either local recurrence or long-term survival rate. Currently in this practice, patients are treated most frequently with MRM (65% to 70%), breast conservation (25% to 30%), RM (about 5%), and ERM (rarely).

Postoperative radiotherapy was used with decreasing frequency throughout this study, from 42% (from 1965 to 1970) to 27% (from 1975 to 1978), again parallel to trends in the 1982 ACS survey.[13] Radiotherapy was given selectively for various indications: (1) positive axillary nodes, particularly at levels II and III; (2) large, locally extensive or medially placed primary tumors; or (3) biopsy-proved internal mammary node metastases (in patients not having ERM). Most frequently a 'hockey stick' portal was used, treating internal mammary and supraclavicular nodes. Few patients received full chest-wall radiation (usually those with the largest tumors). Because complete axillary dissections were performed, radiation to the axilla was rare. In all cases radiation was used to maximize local control in patients at greatest risk of having residual microscopic local/regional disease. Randomized trials of postmastectomy radiotherapy, as recently reviewed by Harris and Hellman[18] and, in a meta analysis, by Cuzick et al.,[19] clearly demonstrated improved local control but equivocal survival benefit (perhaps in the range of 5%) for treated patients, presumably because the fraction of patients with residual local disease and without occult systemic metastasis after mastectomy is relatively small. Recent thought has increasingly emphasized the eradication of occult residual disease by adjuvant chemotherapy, although this modality is probably less effective than radiotherapy in preventing local recurrence.[18] The decreased frequency of postoperative radiotherapy from 1965 to 1978 in this study resulted in neither an increase in local recurrence nor a decrease in survival. Our current practice is to give postmastectomy radiotherapy after completion of chemotherapy to patients with biopsy-proved internal mammary node disease or more locally advanced cancers (stages III to IV, including inflammatory).

The impact of adjuvant chemotherapy, begun in 1975 following the reports of Bonnadonna et al.,[20] is difficult to determine from these data, primarily because the indications for treatment were still evolving at the time. The most striking survival improvement in the 1975 to 1978 group was within the subset of 32 premenopausal/one to three node-positive patients (7% of the entire group), precisely those patients found in controlled trials to benefit most from chemotherapy; however only one third of these 32 patients actually received chemotherapy after operation (Table 3). Why so few? Possible explanations include (1) a relative scarcity of supportive randomized trial data at the time, (2) short follow-up periods for patients treated in trials, (3) the possibility that chemotherapy was simply delaying recurrence without affecting overall survival, and (4) the perceived need for 12 to 24 months' total treatment. Since 1978 the criteria for adjuvant chemotherapy have become much clearer, with a trend toward treatment of many more premenopausal patients, ER-negative postmenopausal patients, and node-negative patients with additional risk factors.

Most intriguing is the suggestion in Table 13 that patients from 1975 to 1978 failing treatment survived longer from date of recurrence than did patients in earlier years. If this finding of a twofold prolongation of median survival is not artifactual, a clear implication is that multidrug chemotherapy (also begun in the mid-1970s) for recurrent disease may have exerted a significant survival impact. Unfortunately sufficient information about the treatment of all patients with recurrent disease was not available to address this issue in greater depth. Despite the enormous effort and expense devoted to the treatment of recurrent breast cancer, surprisingly few studies address the survival benefit of such treatment; Ross et al.[21] compared survival from date of recurrence in patients treated at the M.D. Anderson Hospital in the 1970s (using chemotherapy) with historical controls (using hormonal measures), and demonstrated only a 9- to 12-month improvement in median survival.

The overall and disease-free survival data in this study clearly demonstrate that the above trends in primary breast cancer treatment have not compromised either 10-year cure or local control of disease. Ten-year disease-free survival improved significantly for all patients, node positives, node negatives, and patients with either clinical or pathologic stage II disease. Multivariate analysis suggests (with the caveats noted above) that, even when controlled for pathologic stage (extent of nodal disease and tumor size), survival rate improved by year of treatment. Local-only recurrence at 10 years was 3% for all 1288 patients (with local-distant recurrence at 2%) and did not increase in recent years, despite fewer radical operations and less frequent radiotherapy.

Every patient in this series was treated with the 'Halsteadian' premise that a meticulous and thorough local treatment, individualized for each patient's disease and with the constant goal of maximizing local control, would yield superior long-term survival rates. This assumption cannot be proved true despite the excellent results observed. Conversely Fisher[22] has hypothesized that because most breast cancers are systemic from the outset, variations in local treatment (and local control) are unlikely to affect survival. The equivalent long-term survival rates among the three node-negative and two node-positive arms of the NSABP B-04 trial[2] are consistent with this premise, although the survival rates throughout (particularly for node-positive patients) are disappointingly low. The Halsteadian and Fisher hypotheses are not mutually exclusive and should be seen as complementary aspects of the same problem. Efforts to improve results further in operable breast cancer must seek to combine the systemic treatment of those patients most likely to have occult metastases, with an equally aggressive pursuit of local control. Whatever small survival increment is gained by systemic adjuvant therapy will otherwise be nullified by inadequate local treatment.

Since 1978 the local and systemic treatment of breast cancer has continued to evolve rapidly. Breast conservation has become well established as a treatment option for patients with early disease. The Milan trial (1973 to 1980)[1] comparing quadrantectomy, full axillary dissection, and radiotherapy with RM (± CMF), limited to patients with T1N0 cancers, showed no overall or disease-free survival differences between the two arms at follow-up now exceeding 10 years. The NSABP B-06 trial (1976 to 1984)[14] comparing total mastectomy, local excision-RT, and local excision alone (all done with axillary dissection) showed no overall or disease-free survival difference between total mastectomy and local excision-RT at 81 months mean follow-up. Of particular note, however, was the 39% local relapse rate in patients treated by local excision without radiotherapy; the 8-year disease-free survival rate in this group was 5% worse ($p = 0.01$) than in patients treated with local excision-RT. A further cautionary note is sounded by the long-term results of the first and second Guy's Hospital trials[23] comparing RM with local excision and 3500 to 3800 R radiotherapy (inadequate by current standards). The first trial (1961 to 1971) showed equivalent survival rates for patients with stage I disease (despite more local recurrences in the local excision group), but a marked advantage both in local recurrence and long-term survival rate for RM in stage II patients. The second trial (1971 to 1975), limited to stage I patients treated only by experienced full-time surgeons in a dedicated breast cancer unit, demonstrated less frequent local recurrence ($p < 0.000009$) and better survival ($p < 0.002$) for RM. When adjusted for tumor size, this advantage was limited to patients with T1 lesions, precisely the group chosen most often at present for breast conservation. Even with full doses (4500 to 7500 R) of radiotherapy to the involved breast, local relapse after breast conservation for early cancers (in data pooled from major centers) has averaged 1% to 2% per year for the first 15 years after treatment.[24] Another prospective randomized trial by Maddox et al.[25] (1975 to 1978) compares RM and MRM in 311 patients with stages I to III breast cancer. Ten-year local relapse was 6% for RM and 11% for MRM ($p = 0.04$). Overall 10-year survival rates did not differ 'significantly' (71% *versus* 64%, $p = 0.14$), but among patients with node-positive T2 and all T3 tumors there was a marked survival advantage for RM (59% *versus* 38%, $p = 0.05$). The above studies suggest a clear relationship between adequacy of local control and long-term disease-free survival, although the threshold beyond which local recurrence begins adversely to impact overall and disease-free survival is unclear. The advantage for radical surgery is clearest in patients with more locally advanced disease and may be undetectibly small with early cancers. The proportion of cancers for which breast conservation is appropriate remains controversial, although as the fraction of T1N0 patients increases through earlier detection, this number should increase correspondingly.

The 1288 patients in this series may be among the last to be treated exclusively by radical surgery: RM, ERM, or MRM. The results are reported in sufficient detail to allow comparison with patients staged clinically or pathologically, or grouped by age and extent of axillary node involvement. Changing treatment patterns from 1965 to 1978 did not compromise outcome and, in fact, overall results improved. We hope current studies of patients treated in this practice since 1978 will continue to demonstrate the same result.

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