Cancer and Metastasis Reviews 4, 153–172 (1985).

Patterns of metastasis and natural courses of breast carcinoma*

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Keywords: metastasis, breast carcinoma

Summary

Breast carcinoma is known to metastatize to all organs. In order to understand the patterns of spread and natural courses, this review summarizes detailed studies of patients with various stages of the disease. After treatment of early breast carcinoma (stage I, II, and some III), the recurrent lesion can be classified as local, regional, distant, or combinations thereof. The sites of dissemination of patients presenting with stage IV disease and of those who had autopsy after diagnosis of breast cancer are presented for comparison. Clinicopathological factors that influence the relative incidence, specific site, subsequent event, and prognosis of recurrent and metastatic breast cancers are discussed.

Introduction

Breast carcinoma is the number one lethal cancer of females in the United States. An estimated 116,000 new cases will be diagnosed in 1984, and 37,600 will die of it(1). The incidence of cancer of the breast is increasing at the rate of 1.8% per year (2). Despite various therapeutic advances and multiple efforts to promote mass screening and early diagnosis, the death rate of patients with carcinoma of the breast has remained unchanged for over 40 years (3).

According to the Cancer Patient Survival Report Number 5 (4), which included 57,425 female patients with breast carcinoma seen from 1950 to 1973, about 49% of the white patients had localized disease, 41% regional, and 8% distant. For black patients, the corresponding figures were 32%, 50%, and 17%, respectively. For white patients diagnosed during 1965 to 1969, the 5-year age-adjusted survival rates for the three stages were 85%, 56%, and 9%, respectively (all figures slightly lower for blacks). The overall 5-year survival rates for all stages was 65%. Thus, of the 116,000 new breast carcinoma cases diagnosed in 1984, about 41,000 patients will develop metastasis and die within five years after diagnosis.

Breast cancer is known to metastasize to all organs of the body, and its manifestations are protean. It is almost impossible to predict which organ system will be invaded. Although occult and/or micrometastases often were present when surgical resection of localized carcinoma was performed, not all breast cancers are biologically predeter-

* The assertions or opinions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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mined to be fatal. Some patients with early breast cancer can be cured with loco-regional treatment alone. For the patients who have metastatic disease initially or who developed recurrent disease, it is important to study their sites and extent of involvement so that appropriate treatment can be planned and their natural course improved.

I. Statistical outcome of patients with breast cancer:

Patients with malignancy who were treated and free of recurrence after long-term follow-up should be considered as cured of their disease. In 1968, Brinkley and Haybittle (5) showed that the life expectancy of 704 patients with stage I-II breast cancer became similar to that of the normal population 16 to 18 years after mastectomy and post-operative radiotherapy. With follow-up of more than 22 years and studying the same patient population, Baum (6) later showed that parallelism between the expected and the observed survival curves occurred after 21 years, and 30% of those with early breast cancer were cured.

Hakulinen and Teppo (7) studied 13,707 cases of breast cancer of all stages recorded in the Finnish Cancer Registry from 1953 to 1970. In all age groups, breast cancer patients had an excess mortality over control population during follow-up of up to 18 years. Older patients were less likely to die of breast cancer than younger patients. The ratio of observed number of deaths due to breast cancer over the expected number was about 63 to 124. The ratio was especially high during the first four years after diagnosis for those with non-localized cancer (ratio = 458).

In the Syracuse Cancer Registry, 3,558 women with breast cancer were recorded from 1955 to 1975. (There was only a 6% increase in stage I registrants over these 19 years). Using this data, Mueller et al. (8) found that 80% of the women were dead 20 years after diagnosis, and 88% of the deaths were due to breast cancer. Although cancer of the breast expressed its lethality more rapidly in the oldest age group than in the youngest, the proportion of patients dying of carcinoma of the breast decreased as the age increased: 97% in the group who had cancer at age 21 to 50 years, 90% in the group age 51 to 70 years, and 78% in the group age 71 to 100 years.

Melnik et al. (9) studied 10,702 breast cancer patients diagnosed in Israel over 16 years (1960–1975). Although they found *no difference in survival between older and younger women* (50% died at the time of their study; cause of death was known in 82% of the patients), *death from breast cancer fell with advancing age and death from other causes increased.* Of the entire group, 89% died of breast cancer. Among women diagnosed under the age of 50, 91% died of breast cancer; 86% of those 50 to 69 years old and 77% of women 70 and older died of breast cancer.

The actual causes of death in patients with solid cancer have seldom been determined and quantitated in the past. Klastersky et al. (10) studied the overwhelming terminal events in 157 cancer patients who had autopsies during 1970–1971. Analyzing 22 patients with breast carcinoma, they said 24% died of infection, 6% of hemorrhage, 54% of cancer itself, and 16% of other causes. Cho and Choi (11) studied the causes of death of 144 patients with mammary carcinoma (autopsied during 1966–1975). Comparing the first and second 5-year periods, deaths caused by a malignant process decreases from 71% to 47%, while deaths due to infection increased from 11% to 24% (probably related to the more aggressive methods of chemotherapy employed in recent years). Most of the infectious processes occurred in the lung (22 of 25), such as bronchopneumonia or interstitial pneumonia.

Hagemeister et al. (12) did a detailed analysis of causes of death among 161 patients with breast cancer (autopsied during 1973–1977). Overall, 26% died of pulmonary insufficiency, 24% infection, 15% cardiac problems, 14% hepatic failure, 9% each of Central nervous system (CNS) failure and hemorrhage, and 2% hypercalcemia. *Metastases were considered as the primary cause of death in 45% of the cases.* These included pulmonary lymphangitic spread (13%), massive lung nodules (4%), metastasis in the liver (14%), brain or meninges (8%), and pericardium (4%). *In another 11%*

of the cases, tumor contributed significantly to the terminal events, such as upper airway obstructions, hypercalcemia, and hemorrhage. Among 31 patients who had leukopenia (WBC <1,000/cc) prior to death, only 16 had infection as the main cause of death. Thirty-two patients had thrombocytopenia (platelets <20,000/cc) terminally, but only six died of bleeding. Tumor replacement of the marrow and thrombocytopenia were not the cause of death in any of their patients. They felt deaths due to chemotherapy were rare and the rise in the infection rate did not correlate with the advent of chemotherapy.

II. Development of relapse after therapy of early lesions:

Since metastatic involvement at autopsy represents a summation of all initial and subsequent spread of breast cancer, in order to plan therapeutic intervention and supportive care, we need to have a better understanding of the early events and sequences of dissemination after the initial therapy of early lesions.

a. Patterns of relapse after initial therapy:

Romsdahl et al. (13) studied the time of appearance and outcome of recurrent or metastatic breast cancer after initial treatment (surgery and/or radiotherapy). Among 177 patients, 29% developed recurrence during the first year, 30% the second year, 13% the third year, 20% the fourth to eleventh year, and about 5% after 12 years. Among 253 sites described as the first site of recurrence, 19% were located in the operative region, 8% in the supraclavicular node, 44% in the bone, 12% in the lung, 6% in the pleura, and 2% in the liver (Table 1). Of the 177 patients, 62% were alive one year after relapse, 36% two years later, and 14% after four years. Stage for stage, patients older than 50 years (post-menopausal) developed recurrent disease at a much higher rate within the first five years after mastectomy than premenopausal patients. During the fifth to tenth years, the yearly relapse rate of postmenopausal patients decreased significantly, while in premenopausal patients, cancer recurred at a steady rate similar to the first five years (18).

DiPietro et al. (17) studied 800 patients who had recurrent breast cancer after radical mastectomy (1955–1965). In two-thirds of the patients, recurrence was detected within 3 years after surgery, in another 18% over 5 years, and in 3%, over ten years. Dividing the dominant site of the first relapse into three groups (soft tissue, bone, or viscera), they found that about 20% of the patients had metastases involving two or three groups. A total of 1,232 sites were involved initially. Soft tissue involvement (48%) was more frequent than osseous (38%) or visceral (33%) involvement, mainly due to local recurrence around the scar and regional nodal metastases. Among the 48% with soft tissue relapse, 40% had disease only in soft tissues, while in the other 8%, there were additional osseous and/or visceral metastases. Among 436 sites of bony metastases, the most common sites were the lumbar spine (38%), pelvis (23%), ribs (9%), skull and femur (6% each). Among 320 sites of visceral metastases, common sites were the lung (47%), pleura (23%), liver (20%), and ovary (7%). Concomitant bone and visceral recurrence occured in 11% of the cases.

Smalley (20) evaluated the patterns of first recurrence after therapy of primary breast cancer for the Southeastern Cancer Study Group. Five well-defined recurrent patterns were identified: bone only (19% of all), local skin and node (30%), ipsilateral pleural effusion (15%), pulmonary (13%), and widespread pattern (23%, including 3% with liver metastasis only) (21). The median disease-free intervals from mastectomy to recurrence were 12–14 months for those with relapse of the bone, skin, and nodes, and 30 months for those with pleural or pulmonary metastasis. Excluding patients with widespread involvement of many organs, the majority of the patients in each pattern had metastatic involvement of one or more additional sites. Notably, among patients with predominant recurrence of chest wall and lymph nodes, 43% also had bony metastases. Among those with pleural effusions, 75% had concomitant skin recurrences.

Table 1 summarizes the initial sites of relapse

(local, regional, and distant) among patients who had radical mastectomy for early breast carcinoma. At a mean follow-up of 14 months, Bonadonna et al. (16) reported that 24% of their patients had relapse. Of those whose who had relapse, 17% had only local or regional relapse and 81% had distant metastasis. Fisher et al. (15) reported about 20% of their patients had relapse at 18 months after radical mastectomy (21% for patients who had postoperative radiotherapy and 19% for those who did not; the two groups were randomly assigned). For patients who had no postoperative radiotherapy, the local relapse accounted for 29% of the failures, regional 18%, and distant 53%. With the addition of postoperative radiotherapy to chest wall and regional nodal areas, the local recurrence rate was decreased to 21%, regional to 3%, and distant metastasis proportionally increased to 76%. At 60 months after mastectomy, about 50% of the patients had recurrences and the relative frequency of distant relapse was 5–10% more than at 18 months. It is interesting to note that while the incidence of distant metastases increased progressively over time, nearly 80% of the local-regional recurrence appeared within 3 years after mastectomy.

Table 2 showed that *the rate of overall relapse is muCh higher for patients who had axillary metastasis at the time of mastectomy than for those who did not have nodal metastasis initially* (48% at 4 years, 93% at 10 years versus 18% and 24%, respectively). Despite the fact that the majority of patients did not have postoperative radiotherapy, among patients who did develop recurrence, those who had local or regional relapse are in the minority: 17–19% for those without involvement of axillary nodes and 15–28% for those with axillary nodal

Table 1. Site of first evidence of treatment failure after radical mastectomy for early breast cancer.

Reference	Ramsdahl (1970)[13]	Donegan (1979)[14]	Fisher et al. (1970)[15]				Bonadonna et al. (1976)[16]	(1980)[17]
Period	?	1940–1958	1961–1968				1973–75	1983–78
Post-op RT	±	No	Yes	No	Yes	No	No	No
Time post-op.	?	?	18M	18M	60M	60M	Mean 14M	?
Pt. No.	?	?	406	548	180	235	179 (N+)	(N+)
# relapsed	177	261	86 (21%)	106 (19%)	89 (49%)	117 (50%)	43 (24%)	90
Local only	19%	6%	21%	29%	16%	22%	9%	23%
Regional only	12%	28%	3%	18%	1%	11%	8%	
Axilla	–	–	2%	3%	1%	–	5%	±
Supraclavicular	8%	25%	1%	13%	–	11%	3%	±
Parasternum	–	1%	–	2%	–	–	–	±
Opposite breast	4%	2%	–	–	–	–	–	4%
Distant	69%	72%	76%	53%	81%	65%	81%*	77%**
Bone	44%	26%	31%	22%	36%	28%	51%	31%
Lung or pleura	18%	27%	23%	18%	29%	27%	16%	17%
Hemic/ lymphatic	–	11%	4%	6%	2%	3%	1	–
Digestive[a]	2%	5%	10%	5%	8%	4%	12%	2%
Genital	5%	–	1%	–	1%	–	–	–
CNS		2%	1%	2%	1%	1%	–	1%
Miscellaneous		11%	5%	1%	3%	2%	3%	3%
	100%	110%[b]	100%	100%	98%[c]	98%[c]	98%[c]	100%

[a] Mainly liver

[b] About 10% of patients had more than one site involved.

[c] 2% information incomplete.

* Including 21% who had soft tissue and distant lesions, and 37% who had multiple distant lesions.

** Including 18% who had involvement of multiple distant organs.

metastases. The great majority of patients who developed relapse after mastectomy had distant and visceral metastases (74–85%).

Table 3 summarized the cumulative failure rates of soft tissue, bone, or viscera at 2, 3, and 5 years after radical mastectomy among patients who did not have any postoperative radiotherapy. Among patients who had no axillary metastasis initially, 15% had relapse at 3 years postoperatively, and 21% at 5 years. Among patients who had positive asxillary nodes, 52% had relapse at 3 years, and 64% at 5 years. Again the *eventual distribution of site of relapse among those who had relapses were similar after two or five years, whether the axillary lymph nodes were involved or not:* about 21–28% had loco-regional recurrence, 17–28% had bony metastasis, and 44–56% had visceral metastasis.

One study found that relapse and survival rates were directly proportional to the size of primary tumor in patients who had axillary metastasis at the time of mastectomy, but not in those who did not have axillary spread (21). Other studies showed that the size of primary tumor and histological subtypes had prognostic significance, especially in patients who had no axillary metastasis (26, 27).

Fisher et al. (28, 29) have shown that the absolute number of axillary nodes with metastasis, regardless of the number of nodes removed, is the single factor most predictive of 10- and 20-year survival. They divided their patients into three subgroups, and the 5-year relapse-free survival rates were 82% for those with no axillary node metastasis, 50% for those with 1–3 (+) nodes, and 21% for those with 4 or more (+) nodes. A recent report by Fisher et al. (30) showed that although the annual relapse rate of patients with 4 or more (+) node was much higher than those with three or fewer (+) node, by the fifth year after mastectomy, the rate was similar to that of those with fewer (+) nodes or none. They also warned that there is a risk

Table 2. Sites of first recurrence after radical mastectomy* versus presence or absence of axillary metastatis

Reference	Lee (1982)[22]				Haagensen (1971)[23]			
Period	1971–1980**				1935–1957***			
Time post-op.	median 4 Y				at 10 Y			
Pt. No.	182 (N−)	226 (N+)	408 (N±)		316 (N−)	240 (N+)	556 (N±)	
# relapsed	36 (18%)	109 (48%)	145 (35%)		75 (24%)	223 (93%)	298 (54%)	
Local only	8%	8%	8%		4%	13%	11%	
Regional only	9%	7%	8%		15%	15%	15%	
Axilla	6%	6%	6%		0%	–	–	
Supraclavicular					5%	6%	6%	
Other breast					–	3%	2%	
Parasternum	3%	1%	2%		9%	6%	7%	
Distant	83%	85%	84%		81%	72%	74%	
Bone	22%	38%	29%		21%	27%	26%	
Lung/pleura	38%	26%	29%		33%	21%	24%	
Hemic/lymphatic	6%	5%	7%		–	3%	2%	
Liver	6%	5%	7%		7%	7%	7%	
CNS	5%	2%	3%		7%	5%	5%	
Miscellaneous	6%	9%	8%		13%	9%	10%	
	100%	100%	99%		100%	100%	100%	

* Early operable cases including clinical stage I–II or Columbia clinical stage A and B.

** In this series 32% of patients with axillary nodal metastasis and 5% of those patients without metastasis in axilla had post-operative radiotherapy to chest wall and regional lymphatic nodal areas.

*** In this series, 40 among the 556 patients (7%) had proplylactic post-operative irridiation; 35 of the 40 had extensive axillary metastasis (Mean = 11 nodes positive).

in combining all patients with four or more (+) nodes into a single group, since there is a 25% greater disease-free survival in those with 4–6 than in those with 13 or more positive nodes.

Among patients with four or more positive axillary nodes, Lee and Chen (31) found a distinct separation of 5-year disease-free survival curves of those with 4–9 (+) nodes and those with ten or more (+) nodes. Clinically, there is a good correlation and interrelationship of histological subtypes of breast carcinoma, sizes of primary tumor at diagnosis, extent of axillary lymph node involvement at mastectomy, and subsequent rates and patterns of relapse (32). Colloid carcinoma smaller than 4 cm and the less common pathological subtypes (comedo, tubular, papillary carcinomas) rarely metastasize. Considering only the infiltrating ductal and lobular carcinomas, as the cancers become bigger, the percentage of cases with positive axillary nodes increase in linear proportion (33), and there is a progressively worsening prognosis with larger size of primary tumor and number of positive axillary nodes.

b. Factors influencing site of postmastectomy recurrence:

It is well known that the routine use of *postmastectomy radiotherapy does decrease local and regional recurrence but not distant metastases* (Table 1), nor does radiotherapy improve survival rate (15, 22, 34).

In one randomized clinical trial (1964–1972), three types of adjuvant radiotherapy were compared: preoperative, postoperative radiotherapy, and none (35). Among the surgery only group, 45% of the patients had relapse. The relapse rates of local only or regional nodal only was very low (<2%). Distant metastases only accounted for 24%; local and distant, 5%; regional and distant, 11%; loco-regional and distant, 3%. Adjuvant radiotherapy mainly decreased the number of recurrences in the chest wall, axilla, or supraclavicular region (36). Brincker et al. (37) showed that the addition of adjuvant systemic chemotherapy significantly improved the relapse-free survival over those who had postoperative radiotherapy alone.

Table 3. Cumulative percentages of recurrence after radical mastectomy without any postoperative radiotherapy.

Reference	PTBCSG (1978)[24]		Valagussa et al. (1978)[25]					
Period	–1973		1964–1968					
Pt. number	381 (N±)		335 (N–)				381 (N+)	
Time post-op	24M		36M		60M		36M	60M
# relapsed	78 (20%)		50 (15%)		70 (21%)		197 (52%)	242 (64%)
Loco-regional		28%		25%		21%	28%	26%
Bone		28%		19%		25%	17%	18%
only	22%							
Bone + Local	6%							
Visceral		43%		55%		53%	54%	57%
Lung	10%		17%		12%		13%	14%
CNS	1%							
Liver	4%							
Others	10%		18%		20%		8%	12%
Combinations	4%		–	–	–	–		
Viscera + Local	9%		5%		6%		13%	12%
Viscera + Bone	4%		>15%		>15%		>20%	>19%
Viscera, local, bone	1%							
		99%		99%		99%	99%	101%

Data in Tables 2 and 3 showed that axillary metastasis did signify a greater chance of having relapse. But *among patients who developed relapse, the relative distribution of loco-regional versus distant recurrence was similar whether the axillary node was involved initially or not.* However, there are reports in the literature showing that the specific site(s) of relapse can be different between patients who had nodal metastasis initially and those who did not. Donegan (38) noted patients with axillary metastases at mastectomy most often had initial dissemination to lymph nodes, while those with a free axilla were more likely to have metastases in bone, lung, or pleura. Patients without axillary metastasis also had a significantly higher frequency of brain and breast metastases. Denoix (39) showed that patients without axillary metastasis are more likely to have secondary deposits in bone (29% vs 6%) or disseminated metastasis (16% vs 3%), while those with axillary metastasis are more likely to have loco-regional recurrences (23% vs 4%). In his series, the chance of having secondary deposit in lungs was similar for those with or without axillary spread (about 14%). Haagensen (23) noted metastasis in opposite axillary nodes and the other breast only in patients who had ipsilateral axillary metastasis initially.

Data presented in Table 2 showed that *patients without metastasis in axillary nodes at mastectomy had a higher proportion of having initial recurrence in the lung, pleura, or brain* than those who did have axillary nodal metastasis (33–38% and 5–7% vs 21–26% and 2–5%, respectively). *However, the chance of having bone as the site of first recurrence was actually higher in patients who had nodal metastasis* (27–38% vs 21–22%).

The detection and quantitation of specific estrogen-binding protein (estrogen receptor, ER), first reported in 1970, have changed our approach of using endocrine therapy in breast malignancy. In 1977, Knight et al. (40) showed that lack of ER in the primary breast tumor is correlated with an increased recurrence rate. With a mean follow-up of 16 months, patients with ER(−) tumors had a recurrence rate of 32% as contrasted with 10% for those with ER(+) lesions. Lee and Markland (41) noted a similar difference, especially marked for those with documented metastasis in axillary nodes (at a median follow-up of 12 months after mastectomy, 60% ER− tumors had relapsed versus 9% ER+). Also, patients with ER+ tumors are more likely to have a longer disease-free interval after therapy of primary cancer (41, 42).

However, it needs to be pointed out that there are many reports in the literature involving over one thousand patients showing that the presence or absence of ER did not influence prognosis (43, 44). A few reports showed that the presence of progesterone receptors (PR) was more significant than ER for predicting the disease-free survival (45). There is a 20% variability rate of steroid receptors in multiple biopsies of breast cancer (46). Among multiple specimens taken within one month without any therapy, the chance of reversal of the ER subgroup is similar for ER(+) or (−) tumors. Amongh asynchronous studies, it is more likely to have ER(+) become (−) than vice versa (31% vs 12%). Thus, concordant results of ER and PR of primary and later metastatic tumor were found only in half of the cases (47).

In 1976, Singhakowinta et al. (48) reported that *patients with ER(+) in tumors had more bony metastasis, while visceral metastasis occurred more often with ER(−) tumors.* The latter patients had a more malignant course with significantly shorter survival. Studying 80 mastectomy patients, Lee and Markland (41) found that the recurring lesions of patients who had high ER levels (90+ fmoles/mg) were much more likely to be of soft tissue only. Among all patients with recurrent or disseminated disease, those with ER(+) lesions were more likely to have bony metastasis than those with ER(−) lesions (42% vs 20%) (49). Samaan et al. (50) also found ER(+) tumors had a higher incidence of involvement of skin, bone, and lymph node, while ER(−) tumors more commonly metastasized to the viscera and brain.

Stewart et al. (51) noted no significant differences in initial sites of relapse between patients with ER(+) or ER(−) tumors. However, patients with ER(−) tumors more frequently develop hepatic involvement (38% vs 21%) or brain metastasis; the latter was most marked for those with Stage I disease at presentation (20% vs 2%). Osseous invol-

vement is more frequent among patients with ER(+) tumors, and this difference is most marked for those with Stages I and II disease at presentation (67% vs 44%). Soft tissue, lung, and pleural involvement did not vary with receptor status.

Qazi (52) reported on 100 patients with recurrent breast cancer who had ER assayed on their primary tumor. In both premenopausal and postmenopausal patients, those who had ER(−) tumors showed a significant predilection for viscera as the first site of relapse (46%–69% vs zero of ER+'s, $p = 0.005$). While in patients with ER(+) tumors, bone was the most common site of first metastases, especially in postmenopausal patients (67% vs 0% of ER−'s, $p = 0.005$). Differences of loco-regional recurrence and metastasis at other sites were not statistically significant.

Patients who had bone or soft tissue as the initial site of relapse and those who had longer disease-free intervals responded to hormonal manipulation better (53). Such patients also have longer survivals after relapse. Thus, *patients with ER(+) breast cancer had better overall survival rates* because of: (1) lower relapse rate and longer disease-free interval after initial therapy of localized disease; (2) higher chance of having relapse in bone and/or soft tissue, which is associated with a better prognosis than metastasis of other sites; (3) higher possibility of recurrent or metastatic lesions to respond to ablative or additive hormonal therapy; and (4) better survival rate after relapse for those who responded to the hormonal manipulation.

c. Postmastectomy loco-regional recurrence:

Donegan et al. (54) studied factors influencing local recurrence within the boundaries of radical mastectomy in 704 patients who had no postoperative radiotherapy (1940–1958). The annual recurrence rate is highest during the first two years (6% each). At the end of five years, 18% of the patients had recurrence, by the tenth year, 20%. The predominant site of local recurrence is in the central scar and below the skin graft, relapse in the axilla accounted for only 15% of the total loco-regional recurrence.

Donegan et al. (54) found no correlation between the size of the primary tumor, nor the frequency of use of skin grafts with the rate of local recurrence. When the margin of normal skin measured from the lateral palpable edges of the neoplasm was larger than 3.5 cm, the local recurrence rate was a minimum. *When the skin margin was smaller than 3.5 cm, there was a significant increase in the likelihood of developing local recurrence.* As the number of axillary lymph nodes containing metastasis increased, the rate for local recurrence also increased; however, even with an extremely large number of positive lymph nodes, local recurrence rate did not exceed 40–45%.

Haagensen (23) also noted a very low relapse rate in the axilla: only one among 556 patients who had a 10-year follow-up after radical mastectomy for early breast cancer (1935–1957). But a more recent report from the multi-institutional Primary Therapy of Breast Cancer Study Group (PTBCSG) showed that 20% of the patients had relapse two years after radical mastectomy for operable breast cancer (24). Among those who had relapse, 28% had loco-regional recurrence (Table 3). Their figures showed that nodal recurrent disease is most common (15%), followed by lesions of the skin (5%), soft tissue (3%), and combinations (5%).

It is well known that radiotherapy can control over 90% of the local recurrent disease; 67% complete control and 24% partial control (55). Bedwinek et al. (56) showed that the incidence of failure to control loco-regional recurrence was essentially the same whether the recurrence was treated with radiotherapy alone, surgery alone, or both. If the radiotherapy dose was at least 4500 rad and if the field was large enough to encompass the entire site containing the recurrence, the incidence of failure for the patients' remaining life could be decreased from 79% to 27% (57). They pointed out that the whole chest wall and supraclavicular area should be treated prophylactically when radiating any loco-regional relapse, because 30–50% will develop subsequent recurrence in these two areas (56).

Valagussa et al. (58) showed that, in spite of prompt irradiation given to loco-regional recurrences, 79% of women with and 60% without

nodal involvement had further progression within 2 years. In the majority of cases, disease progression was documented in distant sites. Spratt (59) showed that *local recurrence on the chest wall after radical mastectomy was most likely a manifestation of systemic disease* because the 5-year survival rate after the appearance of local relapse was only 4%, and none survived 10 years.

Bruce et al. (60) studied 423 patients who had undergone simple mastectomy and radiotherapy for potentially curable cancer (1946–1957, stage I-II), 399 (79%) had recurrent disease. They also found that local recurrence alone is rare (4%), while distant metastases are common (49%, more than half appeared in bone). About 26% of the patients had both types of recurrence; the local and the distant lesions appeared synchronously.

Gilliland et al. (61) showed that the prognosis of isolated chest wall recurrence varied according to the pathological stages of the original lesion. Among 170 patients with local recurrence (1944–1977), 60 had local recurrence as the first sign of therapeutic failure after mastectomy and post-operative radiotherapy. Local recurrence after stage I disease (primary 5 cm or less and axilla negative) appeared usually after a mean of 6.2 years, and another 4.2 years elapsed before distant metastasis became evident; while local recurrence after stage III lesions (locally advanced primary, positive axilla nodes +2 cm, etc.) appeared on the average 2.1 years, and distant metastasis developed in about 1.2 years.

Badwinek et al. (62) studied the prognosis of 98 patients who had truly isolated loco-regional recurrence and who had only loco-regional therapy (1968–1977). The overall survival and disease-free survival rates 5 years later were 36% and 13%, respectively. The initial clinical stage, the number of histologically positive nodes at mastectomy, menopausal status, and the location of the recurrence (chest wall vs nodal) all had no significant effect on survival result. On the other hand, *a single recurrence, the size of the largest recurrence being less than 1 cm, and a disease-free interval of 24 months or longer predicted a better prognosis.* Eighty-one percent of the patients ultimately developed distant metastases. The incidence of distant metastases was the same for patients with good or bad prognostic factors. However, the time to the appearance of distant metastases was significantly longer in the former group of patients than in the latter.

d. Sequence of relapses and prognosis:

Among 108 consecutive patients who died of disseminated breast cancer after mastectomy and studied before the wide use of radioisotopic scans and computed tomography, Donegan (38) said the initial metastasis was to multiple sites in 22%. Another 22% of the patients had local recurrence first, of these, 21% had spread next to lymph nodes. Among a third 22% who had disease appearing in lymph nodes first, the disease spread to bone in 24% of the cases. Among the 21% who had initial spread to bone, 45% had no other dissemination later. Counting all the above three groups of patients who had single recurrence in chest wall, node, or bone, over 20% had lung or pleura as the second site of recurrence. Five patients had isolated pulmonary or pleural recurrence; the most frequent site of next spread was bone. Eventually before death, about 44% of the 108 patients had relapse in lymph nodes or chest wall, 40% each in bone or lung (including 19% of pleura), 27% in abdomen (mainlyliver), and 10% in central nervous system. Among the four most common sites of metastasis (nodes, chest wall, bone, or lung/pleura), the frequency of any pair having concurrent metastasis is very similar (about 18%), except bone and local recurrences coexisted significantly less often (in 12% only).

Among patients with colon cancers, post-resectional serial tests of carcino-embryonic antigen (CEA) could detect subclinical recurrence or progression of cancer. *There are conflicting results in the literature regarding the value of using CEA test to monitor relapse after mastectomy.* Among patients with known recurrent disease, only 48% had elevated CEA values, and among those known to be free of disease for six months or more after the test, 10% also had elevated CEAs (63). It was noted that patients with chest wall and nodal recurrence only had mildly elevated CEAs, while those

with visceral metastasis had higher values. If 20 ng/ml CEA is used as the cut-off point, no patients with loco-regional relapse had elevated values, while 10–15% of those with bone or lung disease and 30–40% of those with pleura or liver metastasis had abnormal levels (64).

Metastatic and/or recurrent breast cancer become apparent clinically over a wide range of time, but the median time of appearance becomes shorter if the initial clinical stages was more advanced (65). Pearlman and Jochimsen (66) studied 464 patients with recurrent breast cancers admitted during 1961–1970. *The site of first recurrence and rate of tumor progression were the most important prognostic factors,* with the choice of therapy having less influence. The overall median survival was 22–26 months for those with bone or soft-tissue recurrence, 10–12 months for pleura/lung involvement, and 4–6 months for liver/brain metastases. At each site of involvement, patients with long intervals between first and second relapses had substantially better survival than those with short intervals. The distribution of first recurrence among premenopausal and postmenopausal patients was similar: 29–32% had osseous metastasis, 35–37% soft tissue, 15–19% pleural or lung, and 15–18% liver or brain. Although all patients eventually developed multiple sites of disease, the first and second recurrences were separated by more than three months in 90% of instances. Patients whose disease progressed in less than three months had the worst prognosis. Whether liver and bone metastasis might be detected earlier by the wider use of radioisotopic scans remains to be studied.

Langlands et al. (67) found that the duration of survival once recurrence appeared was independent of the original tumor size, clinical stage, or menstrual status, but was directly proportional to the duration of the disease-free interval. However, Papaioannou et al. (68) found that the metastases that were latent for many years did not pursue a slower course after becoming clinically evident. They studied 57 women with breast cancer (1954–1964) whose recurrence developed 5 or more years after initial treatment (42% local, 35% osseous, and 23% visceral). Although the mean interval from treatment to recurrence was 10 years, the survival time after recurrence averaged 1.9 years. This latter figure was very similar to that of 66 patients who developed recurrences between one and 2 years after initial treatment (mean survival 1.4 years).

e. Effect of adjuvant chemotherapy on post-mastectomy recurrence:

Adjuvant chemotherapy of breast cancer involves the early use of cytotoxic drugs after local and regional therapy before occult micrometastases become clinically evident. It received extensive notice throughout the latter half of the 1970s and is now an established therapeutic concept (69).

In the randomized study comparing the effectiveness of adjuvant combination chemotherapy of CMF (Cytoxan, methotrexate, and fluorouracil) versus no treatment for patients who had metastasis in axillary nodes, at a mean follow-up time of 14 months, Bonadonna et al. (16) showed that systemic adjuvant chemotherapy decreased the overall recurrence rate from 24% to 5%. Specifically, *systemic chemotherapy not only decreased the incidence of distant metastasis* (i.e., for bone 12% to 2%, liver 3% to 0.5%, multiple sites 9% to 0.5%) *but also significantly decreased the frequency of relapses in chest wall and ipsilateral supraclavicular node without any postoperative radiotherapy* (9% to 1.5%).

Bonadonna and Valagussa (69) emphasized that there was a clear dose-response effect of chemotherapy, showing that the three drugs were useful only when given in nearly full dose (+85% of the planned dose). Those getting 12 months of adjuvant CMF chemotherapy at this dose had a 5-year relapse-free survival rate of 77%, as compared with 45% of those treated only with mastectomy. The subgroup receiving less than 65% of the planned dose had a 5-year disease-free survival rate of 48%. In a subsequent randomized study, six cycles of CMF was just as effective as 12 cycles of CMF in delaying the relapse and improving survival (70). In both pre- and post-menopausal groups treated with adjuvant chemotherapy, the disease-free interval was not significantly affected by the ER status.

Because of drug toxicity and other side effects, only about one-third of the patients can receive 85% or more of the planned doses of CMF adjuvant chemotherapy (71). The myelosuppressive effect of radiotherapy is known to significantly decrease the maximum chemotherapy dose that can be given (72). Furthermore, radiotherapy may have a prolonged detrimental effect on immunocompetence. Sternswärd (73) reviewed six controlled clinical trials and found survival was decreased from 1–10% in irradiated patients when compared with those treated by mastectomy alone. Nevin et al. (74) showed that postoperative radiotherapy was related with a significant decline in 5- and 10-year survival rates of patients with stage II and III disease with negative nodes. Thus, *currently, systemic combination chemotherapy ± hormonal therapy has replaced postoperative radiotherapy as the postmastectomy adjuvant therapy for early breast carcinoma.*

Fisher et al. (75) showed that the combination of fluorouracil with melphalan as postmastectomy chemotherapy resulted in a greater reduction of treatment failure than that observed with melphalan alone. And these two drugs gave similar results to those using CMF three drugs. Fisher et al. (76) also showed that there was a true reduction in the incidence of treatment failure in every subgroup of patients who received adjuvant chemotherapy. Patients who were disease-free after completing two years of chemotherapy displayed a subsequent relapse rate similar to that observed in untreated patients who survived two years without recurrence. This suggests that adjuvant chemotherapy does achieve a real decrease of relapses rather than just a postponement of treatment failure. Whether differences in early relapse frequency after combination adjuvant chemotherapy will translate into improved long-term survival or not remains to be proven, since there are suggestions that patients who develop relapse after early adjuvant chemotherapy may respond less to systemic treatment later (77).

Among patients with axillary nodal metastasis who received various postoperative adjuvant chemotherapy, premenopausal patients had an increased risk of recurrence if they had unfavorable local signs, large numbers of lymph nodes involved, greater body weight, and younger age (78). For postmenopausal patients, only three factors were associated with an increased risk of recurrence (large tumor size, many positive lymph nodes, and inner or central primary lesions). After six years of follow-up, premenopausal women treated with adjuvant CMF chemotherapy had significantly improved disease-free survival than those treated with mastectomy alone (60% vs 43%) (79). Adjuvant chemotherapy of five drugs (CMF, vincristine, prednisone) was shown to be better than CMF in improving the prognosis of patients with four or more positive axillary nodes, especially in postmenopausal patients (80).

Paterson et al. (81) performed a retrospective study comparing the incidence of the brain as the site of first recurrence in patients who had positive axillary nodes and who received adjuvant chemotherapy during 1973–1979 (CMF, thiotepa, melphalan ± 5-FU). Five of 115 patients (4.3%) had initial brain metastases after adjuvant chemotherapy as compared to zero in the matched control group who had local therapy only. The brain metastasis comprised 12.8% of first distant recurrences in the adjuvant group. *This increased incidence of brain metastasis and meninge* (vida infra IVb) *as site of first recurrence reflected suppression of systemic disease by adjuvant chemotherapy which had less effect in controlling metastases in the brain.*

Among patients with intracerebral metastasis of various solid tumors, favorable prognostic factors included solitary brain metastasis, ambulatory performance status, symptoms of headache, visual disturbance, and estrogen receptor positivity in breast cancer patients (82). Poor prognostic factors included advanced age and evidence of impaired consciousness. Median survival time after diagnosis of intracerebral metastasis was 3.7 months. Among patients with a single intracerebral metastasis and minimal tumor burden, those treated with surgery and radiation had a median survival of 9.7 months versus 3.7 months for those treated with radiation alone. Brain metastasis was the immediate or contributing cause of death in 50% of the patients who had intracerebral spread.

f. Loco-regional relapse after limited surgery and primary radiotherapy:

In Europe, radiation therapy (RT) and limited surgery have been used as the primary treatment of operable breast cancer for over 40 years. It has challenged surgical therapy in this country only in the last 10–15 years.

From 1955–1979, 265 patients with minimal breast cancer (lobular or ductal carcinoma in situ and invasive cancer of 5 mm or smaller), stage I (tumor 1–2 cm without palpable axillary node) and stage II lesions (tumor 2–4 cm ± palpable node) were treated by Montague et al. (83) at Houston, Texas. These patients had 5-and 10-year survival rates similar to the 65 patients treated with radical or modified radical mastectomy. Loco-regional recurrence rates were also similar (0.5%, 4.4%, and 8.4% for radical mastectomy vs 2.5%, 6.8%, and 4.9% for conservative surgery and RT, respectively in the three successive stages of disease). Some authors used RT to treat patients with intraductal carcinoma of the breast, but Findley and Goodmen (84) said two of their 14 patients required mastectomy at 19 and 36 months because of recrudescence of disease.

Amalric et al. (85) of France reported on their experience of 1,440 consecutive patients (1960–1974). When the tumor was 5 cm or smaller with no axillary adenopathy, lumpectomy, or wedge resection was performed first. Patients with larger lesions were treated with radical RT without surgical excision. For the former group, the 10-year crude survival rate is about 63% to 77%; for the latter group, 34%. *The failure rate of control of breast lesion at 10 years varied with the size of the primary tumor:* for lesions less than 2 cm in size, 21–27%, for lesions 2–5 cm in size, 20–40% (higher figures if the primary tumor was not excised before RT). Surprisingly, local-regional recurrence had no adverse effect on 10-year survival. However, 24% of the 1,440 patients, and 35% of the patients alive free of disease at 10 years, had some kind of salvage operation (mainly mastectomy) for presumed local or regional tumor persistence or recurrence.

Osborne et al. (86) reported that the relapse-free survival rates of patients with 0–2 cm or 2–5 cm tumors were not too different, but patients with axillary lymphadenopathy had a significantly worse survival after RT. With a minimal follow-up of 10 and a maximum of 20 years, *loco-regional relapse occurred in 22% of those with no axillary involvement and in 50% of those with axillary lymphadenopathy.* About 50% of the loco-regional relapse occurred 5 years or more after RT; this contrasted with 75–80% relapse within 5 years after mastectomy. Salvage mastectomy produced a 42% relapse-free rate at 5 years if the initial tumor was stage I. These results suggest that *post-RT recurrent carcinoma in the breast is not as ominous as chest wall recurrence after radical mastectomy.*

Segmental mastectomy without radiotherapy has a high recurrence rate as expected (87). Among patients with 1–5 cm breast carcinomas and with a mean follow-up of 2 years, 7% of those who had total mastectomy and axillary dissection had relapse versus 19% of those treated by segmented mastectomy. Nearly all of these differences were due to a higher frequency of local recurrence in the latter group. When the resection margin had microscopic carcinoma, the local recurrence rate was over five times higher (71% vs 13%). Thus, segmental mastectomy alone is an inadequate form of therapy, especially for those with positive margin at excision, larger tumors, less differentiated histology, stage II or higher.

III. Distribution of metastasis of stage III or IV disease:

Inflammatory carcinoma of the breast is a virulent variant, and it has been classified as stage IV lesion. Robbins et al. (88) said about 1% of the breast cancers were inflammatory cancers, and an equal number of patients might have recurrent disease diagnosed as such. Barber et al. (89) noted all their 53 patients with inflammatory carcinoma had axillary metastasis. Ultimately metastatic lesions developed in skin of the chest wall (15 patients), opposite breast (14 patients), bone (13 patients), and the lung (8 patients). Only about 10% survived five or more years. Droulias et al. (90) said supravoltage therapy improved local control of in-

flammatory breast cancer, and, when followed by mastectomy, gave the longest local control and mean survival. Since combination chemotherapy can shrink bulky primary breast carcinoma, many authors used chemotherapy initially (91), adding debulking surgery for the responders, and reserving radiotherapy for the nonresponders.

Stage III non-inflammatory carcinoma of the breast includes tumor greater than 5 cm, or any tumor with 'grave signs' of skin edema or ulceration, fixation to pectoral muscle or chest wall, matted or fixed axillary nodes. Among 488 patients who had radical surgery for stage III lesions, Fracchia et al. (92) said the initial sites of recurrence or metastasis were multiple in 23%, 18% involving local site, bone or viscera, 14% each. Postoperative prophylactic radiotherapy or oophorectomy did not effect survival rate. Among the 430 patients who had axillary nodal involvement, the 5-year and 10-year recurrent rates were 68% and 77%, respectively, and survival rates were 41 and 21%. Among the 58 patients without nodal invasion, the 5- and 10-year survival rates were quite good, 82% and 75%, respectively (23% had recurrence at 4–10 years).

Rao et al. (93) also studied 147 patients with non-inflammatory stage III breast cancer (one-third had RT only, two-thirds had surgery plus RT). They noted that the local, regional, or distant failure rate and 5-year disease-free survival were all unaffected by the presence or absence of 'grave signs,' whether treated by RT alone or surgery plus RT. In patients treated with RT alone, the size of the primary tumor influenced the rate of local failure (44% for tumors 0–8 cm and 76% for ≥8 cm) and 5-year disease-free survival (30% vs 4%, respectively). Axillary nodal stage (N) also influenced the prognosis. The regional failure rate increased from 9% for N_0, N_1 tumors to 58% for N_2, N_3 lesions. Patients with advanced nodal disease had very low disease-free survival (4% vs 30%). No such difference was noted when the tumor and nodal disease were treated with a combination of surgery and irradiation. *Even in patients receiving radiotherapy and additional combination chemotherapy, local control for stage III breast cancer was difficult, suggesting that debulking surgery should be added* (94). Although chemotherapy did delay the onset of recurrence in patients with locally advanced breast cancer, it did not affect the ultimate rate of recurrence or the overall survival.

Among 305 patients with inoperable cancer of the breast, Pearlman et al. (95) said 129 (42%) had extensive local disease, 88 (29%) had distant metastasis, and 88 had both. Among those with distant lesions only, 38 had metastasis in bone, 27 pleura or lung, 16 bone and pleura-lung, and 7 mediastinum. Among the 88 patients who had both loco-regional and distant disease, metastasis to pleura or lung was more common than to bone (48 lung-pleural, 25 bone, and 15 liver or brain).

Donegan (38) studied 1,647 patients with documented distant metastasis (stage IV) admitted during 1940–1965 to a cancer hospital (before the common use of radioisotopic scans or computed tomography). In about 18% of the patients, multiple areas of spread were diagnosed simultaneously. Otherwise, lymph nodes were the most common site of first spread (29%), followed by bone (16%), lung or pleura (11%). Skin and opposite breast were involved in 3–4% of the cases, liver as initial site in 2%, brain and gastrointestinal tract each in about 1% (Table 4).

Cutler et al. (96) studied 920 patients from eight institutions with disseminated breast carcinoma diagnosed during 1950–1961. *The most common organs of clinical involvement of patients with stage IV disease were bone* (34% of all patients), *lymph nodes* (27%; 2% ipsilateral nodes, 21% distant nodes, and 4% involving both), *lung* (18%), *skin and/or subcutaneous tissue* (17%), *and pleura* (15%). The operative site, breast, or liver each was involved in 8% of the cases. Excluding 12% of the patients with dire prognosis (those with metastasis in the liver, peritoneum, brain, and spinal cord), 249 of the 614 remaining patients (41%) had a single site of distant metastasis. About 33% had two sites and 26% three or more sites. Among those with single metastasis, again bone was the most common site (57%), next lymph nodes or lung (16% each), followed by pleura (10%).

Among patients with metastatic breast cancer treated with combination chemotherapy, Swenerton et al. (97) showed that pretreatment weight

loss, poor performance status, abnormal biochemical and hematological values had adverse prognostic significance. Patients with bone involvement had longer survival than did patients with metastasis of other organ sites. Specifically, unfavorable factors were weight los of greater than 10%, having radiotherapy to three or more ports, non-Caucasian, alkaline phosphatase greater than 350 μU/ml, LDH greater than 450 μU/ml, hemoglobin less than 11 gm %, two or more sites of metastasis (especially involving lung), and poor performance status (98). Among 25 prognostic factors, George and Hoogstraten (99) found that the three most important factors were disease-free interval, liver involvement, and performance status. After adjustments were made for these three covariates, the remaining covariates such as menopausal status, bone involvement, number of metastatic sites, and duration of metastatic disease were not significantly related to response to chemotherapy.

IV. Distribution of metastasis at autopsy:

a. Common sites of involvement

From 1950 to 1982, there were seven autopsy series of breast carcinoma published in the American literature (Table 5). Each report studied more than 100 patients with breast cancer, and there were a total of 2,147 patients. Although the data came from different institutions and spanned over 35 years (1943–1977), the findings regarding metastatic involvement of specific organs are fairly similar (105).

At autopsy, the five leading sites of metastatic involvement of breast carinoma were the lung, bone, lymph node, liver, and pleura. All five sites were reported by at least two of the seven series as containing metastasis in more than 50% of the cases. The reported median incidence (and ranges) of metastasis in these five sites were lung 71% (57–77%), bone 71% (49–74%), lymph node 67% (50–76%), liver 62% (50–71%), and pleura 50% (36–65%).

The next five sites most commonly involved were the adrenal gland, ovary, brain, opposite breast,

Table 4. Distribution of site of distant metastases among patients who had stage IV carcinoma of breast

Reference	Donegan (1970)[38]	Cutler (1969)[96]	Smalley (1976)[20,21]	Lee (1982)[22]
Period	1940–1965	1950–1961	?	1972–1980
Pt. No.	1,647	614	287	80
Note	First site	(920 sites)	All recurrent	First site
Lymph node	29%	27%	} 30%	} 15%
Skin	4%	17%		
Breast	3%	8%		
Bone	16%	34%	19%	29%
Bone, etc.	–	–	–	24%*
Lung	} 11%	18%	13%	11%
Pleura		15%	15%	4%
Liver	2%	8%	3%	4%
Brain	1%	2%	} 20%	4%
GI tract	1%	–		} 8%
Other	1%	3%		
Unknown	15%	–	–	–
	101%	132%	100%	100%

* Including bone and lung (4%), bone and pleura (10%), bone and liver (10%).

and soft tissue (skin and subcutaneous tissue). Adrenal gland(s) and ovary were involved in 21–41% (median) of the cases; brain, opposite breast, and soft tissue in 22–30%. All other organ sites not listed in Table 5 had metastatic breast cancer in 20% or less of the patients. Cifuentes and Pickren (103) listed that metastasis was present in the muscular system in 29% of the cases, but did not give any details.

Viadana et al. (106) found that *younger women had a more generalized disease whether they survived less or more than 5 years.* The median number of metastases at autopsy of patients below age 50 years was nine compared to a median of seven in the older group. Younger patients, especially those who survive less than 5 years, had a significantly higher incidence of metastasis than older patients in the bone (81% vs 65%), liver (80% vs 56%), thyroid gland (33% vs 15%), pituitary gland (28% vs 17%), and cerebrum (20% vs 12%). Metastasis in the choroid plexus and leptomeninges seemed to be more frequent in the younger patients also (3–7% vs 0–2%).

Viadana et al. (107, 108) reviewed records of 4,728 patients with adenocarcinoma who had autopsy during 1956–1965. They studied whether metastasis in a particular organ was more or less often associated with metastasis in another organ (metastasis in lymph nodes of the axilla or thorax were excluded). Analyzing 647 patients with breast carcinoma, the incidence of having isolated metastasis in lung at autopsy is about 4–6%, bone 5%, liver 2–12%, and brain 3%. The chance of having metastasis in any two organs is additive. The chance of involving lung, liver, and bone simultaneously is 42%, and involving lung, liver, and brain together is 26%. *When lung, bone, and liver were all free of metastasis (this happened in 15% of stage IV patients), the chance of having distant metastasis from breast primary was less than 3%,* except for the central nervous system (CNS incidence = 13%). The frequency of other metastasis increases as soon as one or more of these three major sites are seeded by the primary carcinoma.

The metastatic pattern of solid cancer can be interpreted either in terms of an anatomical proximity, such as increased pancreatic metastasis when liver or lung was involved, or in terms of hematogenous dissemination, such as significantly increased CNS metastasis when lung was involved

Table 5. Ten leading sites of metastatic involvement in breast carcinoma at autopsy.

Year	1950	1955	1971	1979	1980	1980	1982	
Author(s)	Abrams et al.	Sproul-Haagensen	Meissner and Warren	Cifuentes and Pickren	Cho and Choi	Hagemeister et al.	Amer	
Reference No.	(100)	(101)	(102)	(103)	(11)	(12)	(104)	
Period	1943–47	–	–	1959–74	1966–75	1973–77	1962–76	
Institution location	New York	New York	Boston	Buffalo	Philadelphia	Houston	Detroit	Median
Patient No.	167	100	432	676	141	166	368	value
Lung	77%	69%	57%	67%	60%	>75%	71%	71%
Pleura	65%	51%	–	50%	36%		48%	50%
Bone	73%	71%	49%	71%	54%	67%	74%	71%
Lymph node								
Abdomen	44%	>76%	>64%	39%	–	–	38%	>67%
Thorax	67%			54%	–	–	45%	
Liver	61%	65%	50%	62%	53%	71%	69%	62%
Adrenal gland	54%	49%	34%	41%	36%	30%	43%	41%
Ovary	23%	20%	12%	21%	15%	21%	–	21%
Skin tissue	19%	30%	29%	–	–	>36%	32%	30%
Breast	22%	–	–	–	14%		23%	22%
Brain	29%	22%	10%	18%	26%	22%	36%	22%

(CNS incidence = 33%) (108). Their results provide strong evidence that a multistep or 'cascade' process is involved rather than by direct dissemination from the primary. Liver and lung play the principal roles in this cascade process (109).

b. Chemotherapy versus patterns of metastasis (especially CNS metastasis)

Amer (104) studied the pattern of metastasis in 368 breast cancer patients who had autopsy from 1962 to 1976. *At nearly all sites, the incidence of metastasis was higher among the 254 patients who had chemotherapy than the 452 who did not.* The following sites were significantly increased after cytotoxic treatment: other breast (27% vs 15%), retroperitoneum (31% vs 20%), paraaortic nodes (42% vs 29%), pleura (53% vs 37%), bone (80% vs 61%), meninges (48% vs 20%), and overall central nervous system (62% vs 35%).

In 1954, Lesse and Netsky (110) reported involvement of leptomeninge and/or dura in 75% of 71 breast cancer patients at autopsy; 50% had no parenchymal brain metastases. Tsukeda et al. (111) said the frequency of CNS metastasis per year actually showed a downward slope from 1959 to 1979 in their hospital. Among 30% of patients with CNS metastasis, 62% had involvement of brain, 54% cranial dura, 31% leptomeninges, and 10% spinal cord and dura. About 27% had cranial dura as the sole site of CNS metastasis, and 42% of the brain metastases were single lesions.

Amer (120) showed that the incidence of CNS metastasis, especially meningeal involvement, rose rapidly during the interval between 1967 and 1976 (44% to 78%), whereas the mean survival of the patients improved slightly from 17.6 to 20.4 months. Apparently two cytotoxic drugs were used concomitantly since 1966, three or more since 1968, and Adriamycin was added since 1972. Otherwise, the higher incidence of CNS metastasis among patients who received chemotherapy could not be explained on the basis of difference in patients' age, menopausal status, stage of disease, or disease-free intervals.

Yap et al. (112) reviewed 25 breast cancer patients with meningeal carcinomatosis seen over a 16-month period (1976–1977). The clinical diagnosis was documented at autopsy in 15 patients. All patients were receiving systemic chemotherapy at the time of diagnosis. None of the 25 patients had progression of systemic metastasis, while 12 were in partial or complete remission at the time of their CNS relapse. (Four had CNS involvement as the first manifestation of recurrent disease). They estimated that about 5% of their patients treated from 1973 to 1977 developed meningeal involvement.

Breast cancer has replaced gastric and lung cancer as the solid tumor most commonly associated with leptomeningeal spread since 1974 (113–115). Among 90 patients with leptomeningeal metastases from solid tumors treated from 1975 to 1980, Wasserstrom et al. (116) said the three most common primary sites were breast (51%), lung (26%), and melanoma (12%). In one autopsy series (115), leptomeningeal metastasis was the sole CNS abnormality in 3% of breast cancer patients. These findings suggest that most of the currently used chemotherapeutic agents does not cross the blood-brain barrier.

The prognosis of meningeal carcinomatosis has been considered poor; average survival after diagnosis was only six weeks in one review (113). The longest survivor recorded in the literature is a 37-year-old patient with meningeal spread of breast cancer who lived 2.5 years from the onset of neurologic symptoms (114). This patient was treated initially with whole-brain irradiation of 4,000 rads and intrathecal methotrexate (10 mg weekly at first and then less often). When this regimen failed, she had another response to oral CCNU (160 mg bimonthly). Yap et al. (112) used a more aggressive treatment regimen consisted of whole-brain irradiation (3–4,000 rads over two weeks), intrathecal methotrexate, and the insertion of an Ommaya shunt for the instillation of intraventricular methotrexate and/or Thiotepa at the completion of irradiation therapy. Six of their seven patients achieved a complete response, with disappearance of all tumor cells in the spinal fluid. The median survival of these seven patients was 22 weeks. Sondak et al. (113) even suggested that 'If meningeal metastasis continues to increase in breast cancer patients, prophylactic CNS treatment may become a consideration.'

References

1. Silverberg E: Cancer Statistics, 1984. Ca-A Cancer J Clin 34: 7–23, 1982.
2. Pollack ES, Horm JW: Trends in cancer incidence and mortality in the United States, 1969–76. J Nat'l Cancer Instit 64: 1091–1103, 1980.
3. Fox MS: On the diagnosis and treatment of breast cancer. JAMA 241: 489–494, 1979.
4. Axtell LM, Asire AJ, Myers MH: Cancer patient survival, report number 5, DHEW Publication No (NIH) 77–992. Bethesda, National Cancer Institute, US Government Printing Office, 1976, pp. 157–163.
5. Brinkley D, Haybittle JL: A 15-year follow-up study of patients treated for carcinoma of the breast. Br J Radiol 41: 215–221, 1968.
6. Baum M: The curability of breast cancer. Br Med J 1: 439–442, 1976.
7. Hakulinen T, Teppo L: Causes of death among female patients with cancer of the breast and intestines. Ann Clin Res 9: 15–24, 1977.
8. Mueller CB, Ames F, Anderson GD: Breast cancer in 3,558 women: Age as a significant determinant in the rate of dying and causes of death. Surgery 83: 123–132, 1978.
9. Melnik Y, Slater PE, Katz L, Davies AM: Breast cancer in Israel, 1960–1975. II. Effects of age and origin on survival. Europ J Cancer 16: 1017–1023, 1980.
10. Klastersky J, Daneau D, Verhest A: Causes of death in patients with cancer. Eur J Cancer 8: 149–154, 1972.
11. Cho SY, Choi HY: Causes of death and metastatic patterns in patients with mammary cancer: Ten-year autopsy. Am J Clin Pathol 73: 232–234, 1980.
12. Hagemeister FB, Buzdar AU, Luna MA, Blumenschein GR: Causes of death in breast cancer: A clinicopathologic study. Cancer 46: 162–167, 1980.
13. Romsdahl MM, Sears ME, Eckles NE: Post-treatment evaluation of breast cancer. In: 'Breast cancer – Early and Late.' 13th Annual Clinical Conf on Cancer, 1968 at the University of Texas MD Anderson Hospital and Tumor Institute. Chicago, Year Book, 1970, pp 291–299.
14. Donegan WL cited by Kardinal CG in 'Cancer of the Breast.' Donegan WL and Spratt JS (eds), Philadelphia, Saunders, 1979, p 434.
15. Fisher B, Slack NH, Cavanaugh PJ, Cardner B, Ravdin RG: Postoperative radiotherapy in the treatment of breast cancer: Results of the NSABP Clinical Trial. Ann Surg 172: 711–730, 1970.
16. Bonadonna G, Brusamolino E, Valagussa P, Ross A, Brugnatelli L, Brambilla C, DeLena M, Tancin G, Bayetta E, Musumeci R, Verones U: Combination chemotherapy as an adjuvant treatment in operable breast cancer. New Engl J Med 294: 405–410, 1976.
17. Valagussa P, Tesoro Tess JD, Rossi A, Tancini G, Bonadonna G: Has adjuvant CMF altered the patterns of first recurrence in operable breast cancer with N+? Proceeding ASCO Abstracts 1: 413, 1980.
18. Lee RO, Lambley DG: Radical mastectomy in the treatment of breast cancer. Brit J Surg 58: 137–144, 1971.
19. Di Pietro S, Bertario L, Cantu G, Re A: An analysis of 800 breast cancer patients relapsed after radical mastectomy. Tumori 62: 99–112, 1976.
20. Smalley RW: Five clinical patterns of recurrence of cancer of the breast. Proc AACR-ASCO Abstracts 17: 172, 1976.
21. Kardinal CG: Chemotherapy, Chapter 12 in 'Cancer of the Breast.' Donegan WL and Spratt JS (eds.), Philadelphia, Saunders, 1979, pp 405–447.
22. Lee Y-TN: Breast carcinoma: Patterns of recurrent and metastasis after mastectomy. Am J Clin Oncol 7: 443–449, 1984.
23. Haagensen CD: The surgical treatment of mammary carcinoma, Chapter 34 in 'Diseases of the Breast': Philadelphia, Saunders, 1971, pp 669–733.
24. A report of the primary therapy of breast cancer study group: Identification of breast cancer patients with high risk of early recurrence after radical mastectomy. II. Clinical and pathological correlations. Cancer 42: 2809–2826, 1978.
25. Valagussa P, Bonadonna G, Veronesi U: Patterns of relapse and survival following radical mastectomy: Analysis of 716 consecutive patients. Cancer 41: 1170–1178, 1978.
26. Say CC, Donegan WL: Invasive carcinoma of the breast: Prognostic significance of tumor size and involved axillary lymph nodes. Cancer 34: 468–471, 1974.
27. Lee Y-TN, Chan LS: Surgical treatment of carcinoma of the breast: IV. Prognosis according to extent of involvement of the axillary lymph nodes. J Surg Oncol 27: 35–41, 1984.
28. Fisher ER, Redmond C, Fisher B: Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4) VI. Discriminants for five-year treatment failure. Cancer 46: 908–918, 1980.
29. Fisher B, Slack N, Katrych D, Wolmark N: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140: 528–534, 1975.
30. Fisher B, Bauer M, Wickerham L, Redmond CK, Fisher ER: Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. Cancer 52: 1551–1557, 1983.
31. Lee Y-TN, Chan LS: Surgical treatment of carcinoma of the breast; II. Prognostic factors influencing relapse rate. J Surg Oncol 25: 102–108, 1984.
32. Lee Y-TN, Terry R: Surgical treatment of carcinoma of the breast. I. Pathological finding and pattern of relapse. J Surg Oncol 23: 11–15, 1983.
33. Lee Y-TN: Surgical treatment of carcinoma of the breast. III. Pathological finding and probability of relapse. J Surg Oncol 25: 109–115, 1984.
34. Ansfield FJ: Adjuvant radiotherapy for breast cancer. JAMA 235: 67–68, 1976.

35. Høst H, Brennhovd IO: The effect of post-operative radiotherapy in breast cancer. Int J Rad Oncol Biol Phys 2: 1061–1067, 1977.
36. Strender L-E, Wallgren A, Arndt J, Arner O, Bergström J, Blomstedt B, Granberg P-O, Nilsson B, Räf L, Silfverswärd C: Adjuvant radiotherapy in operable breast cancer: Correlation between dose in internal mammary nodes and prognosis. Int J Rad Oncol Biol Phys 7: 1319–1325, 1981.
37. Brincker H, Mouridsen HT, Andersen KW: Adjuvant chemotherapy with cyclophosphamide or CMF in premenopausal women with stage II breast cancer. Breast Cancer Research and Treatment 3: 91–95, 1983.
38. Donegan WL: Patterns and prognosis of advanced breast carcinoma. Missouri Med 67: 853–858, 1970.
39. Denoix P: Treatment of malignant breast tumors: Indications and results. Springer-Verlag, New York, 1970, pp 17–21.
40. Knight W, Livingston RB, Gregory EJ, McGuire WL: Absent estrogen receptor and increased recurrence rate in breast cancer. Proc Am Assoc Cancer Res – ASCO Abstracts 18: 271, 1977.
41. Lee Y-TN, Markland FS: Steroid receptors study in breast carcinoma. Med Ped Oncol 5: 153–166, 1978.
42. McGuire WL, Pearson OH, Segaloff A: Predicting hormone responsiveness in human breast cancer. In: McGuire WL, Carbone PP, Vollmer EP (eds): 'Estrogen Receptors in Human Breast Cancer.' New York, Raven Press, 1975, pp 17–30.
43. Lee Y-TN: Correlation of estrogen receptor with clinicopathologic factor and breast cancer prognosis. Breast 9(2): 6–11, 1983.
44. Skinner JR, Wanebo HJ, Betsill WL, Wilhelm MC, Drake CR, Macleod RM: Evaluation of the pathologic and prognostic correlates of estrogen receptors in primary breast cancer. Ann Surg 196: 636–641, 1982.
45. Clark GM, McGuire WL, Hubay CA, Pearson OH, Marshall JS: Progesterone receptors as a prognostic factor in stage II breast cancer. N Engl J Med 309: 1343–1347, 1983.
46. Lee Y-TN: Variability of steroid receptors in multiple biopsies of breast cancer: effect of systemic therapy. Breast Cancer Research and Treatment 2: 185–193, 1982.
47. Holdaway IM, Bowditch JV: Variation in receptor status between primary and metastatic breast cancer. Cancer 52: 479–485, 1983.
48. Singhakowinta A, Potter HG, Buroker TR, Samal B, Brooks SC, Vaitkevicius VK: Estrogen receptor and natural course of breast cancer. Ann Surg 183: 84–88, 1976.
49. Lee Y-TN: Correlation of estrogen receptor with site of recurrence or metastasis and breast cancer prognosis. Breast 10(1): 27–31, 1984.
50. Samaan NA, Buzdar AU, Aldinger KA, Schultz PN, Yang KP, Romsdahl MM, Martin R: Estrogen receptor: A prognostic factor in breast cancer. Cancer 47: 554–560, 1981.
51. Stewart JF, King RJB, Sexton SA, Mills RR, Rubens RD, Hayward JL: Oestrogen receptors, sites of metastatic disease and survival in recurrent breast cancer. Europ J Cancer 17: 449–453, 1981.
52. Qazi R: Estrogen receptors determine pattern of relapse in breast cancer. Proceeding ASCO Abstracts 1: 7, 1982.
53. Lee Y-TN: Therapeutic castration for advanced breast cancer. Am J Surg 122: 42–49, 1971.
54. Donegan WL, Perez-Mesa CM, Watson FR: A biostatistical study of locally recurrent breast carcinoma. Surg Gynec Obstet 122: 529–540, 1966.
55. Chu FCH, Lin F-J, Kim JH, Huh SH, Gearmatis CJ: Locally recurrent carcinoma of the breast: Results of radiation therapy. Cancer 37: 2677–2681, 1976.
56. Bedwinek JM, Fineberg B, Lee J, Ocwieza M: Analysis of failures following local treatment of isolated local-regional recurence of breast cancer. Int J Rad Oncol Biol Phys 7: 581–585, 1981.
57. Bedwinek JM, Munro D, Fineberg B: Local-regional treatment of patients with simultaneous local-regional recurrence and distant metastases following mastectomy. Am J Clin Oncol 6: 295–300, 1983.
58. Valagussa P, Bonadonna G, Veronesi U: Patterns of relapse and survival in operable breast carcinoma with positive and negative axillary nodes. Tumori 64: 241–258, 1978.
59. Spratt JS: Locally recurrent cancer after radical mastectomy. Cancer 20: 1051–1053, 1967.
60. Bruce J, Carter DC, Fraser J: Patterns of recurrent disease in breast cancer. Lancet 1: 433–435, 1970.
61. Gilliland MD, Barton RM, Copeland EM: The implications of local recurrence of breast cancer as the first site of therapeutic failure. Ann Surg 197: 284–287, 1983.
62. Bedwinek JM, Lee J, Fineberg B, Ocwieza M: Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. Cancer 47: 2232–2235, 1981.
63. Lee Y-TN: Carcinoembryonic antigen as a monitor of recurrent breast cancer. J Surg Oncol 20: 109–114, 1982.
64. Lee Y-TN: Serial tests of carcinoembryonic antigen in patients with breast cancer. Am J Clin Oncol 6: 287–293, 1983.
65. Devitt JE: The enigmatic behavior of breast cancer. Cancer 27: 12–17, 1971.
66. Pearlman NW, Jochimsen PR: Recurrent breast cancer: Factors influencing survival, including treatment. J Surg Oncol 11: 21–29, 1979.
67. Langlands AO, Prescott RJ, Hamilton T: A clinical trial in the management of operable cancer of the breast. Br J Surg 67: 170–174, 1980.
68. Papaioannou AN, Tanz FJ, Volk H: Fate of patients with recurrent carcinoma of the breast: Recurrence five or more years after initial treatment. Cancer 20: 371–376, 1967.
69. Bonadonna G, Valagussa P: Dose-response effect of adjuvant chemotherapy in breast cancer. New Engl J Med 304: 10–15, 1981.
70. Tancini G, Bonadonna G, Marchini S, Bajetta E, Val-

agussa P, Veronesi U: Adjuvant CMF in breast cancer: Comparative 5-year results of 12 vs. 6 cycles. Proceeding ASCO Abstracts 1: 86, 1982.
71. Lee Y-TN: Adjuvant chemotherapy (CMF) for breast carcinoma: Patient's compliance and total dose achieved. Am J Clin Oncol 6: 25–30, 1983.
72. Levine JF, Coleman CN, Cox RS, Gordon RR, Rogoway WM, Martinez A, Stockdale FE: The effect of postoperative and primary radiation therapy on delivered dose of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy in breast cancer. Cancer 53: 237–241, 1984.
73. Stjernswärd J: Decreased survival related to irradiation postoperatively in early operable breast cancer. Lancet 2: 1285–1286, 1974.
74. Nevin JE, Baggerly JT, Laird TK: Radiotherapy as an adjuvant in the treatment of carcinoma of the breast. Cancer 49: 1194–1200, 1982.
75. Fisher B, Glass A, Redmond C, Fisher ER, Barton B, Such E, Carbare P, Economon S, Foster R, Fralick R, Lerner H, Levitt M, Margolese R, McFarland J, Plotkin D, Shibata H, Volk H: L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: An update of earlier findings and a comparison with those utilizing L-PAM plus 5-Fluorouracil (5-FU). Cancer 39: 2883–2903, 1977.
76. Fisher B, Redmond C, Wolmark N, Wieland S: Disease-free survival at intervals during and following completion of adjuvant chemotherapy: The NSABP experience from three breast cancer protocols. Cancer 48: 1273–1280, 1981.
77. Chlebowski RT, Weiner JM, Luce J, Hestorff R, Lang JE, Reynolds R, Godfrey T, Ryden VMJ, Bateman JR: Significance of relapse after adjuvant treatment with combination chemotherapy or 5-Fluorouracil alone in high-risk breast cancer. Cancer Res 41: 4399–4403, 1981.
78. Ahmann DL, Frytak S, O'Fallon JR, Hahn RG, Scanlon PW, Ingle JN, Payne WS, Rubin J, Bisel HF, Creagan ET, Edmonson JH: A preliminary assessment of factors associated with recurrent disease in a surgical adjuvant clinical trial for patients with breast cancer with special emphasis on the aggressiveness of therapy. Am J Clin Oncol 5: 371–381, 1982.
79. Henderson IC: Chemotherapy of breast cancer: A general overview. Cancer 51: 2553–2559, 1983.
80. Tormey DC, Weinberg VE, Holland JF, Weiss RB, Glidewell OJ, Preloff M, Falkson G, Falkson HC, Henry PH, Leone LA, Rafla S, Ginsberg SJ, Silver RT, Blom J, Carey RW, Schein PS, Lesnick GJ: A randomized trial of five and three drug chemotherapy and chemoimmunotherapy in women with operable node positive breast cancer. J Clin Oncol 1(2): 138–145, 1983.
81. Paterson AHG, Agarwal M, Lees A, Hanson J, Szafran O: Brain metastases in breast cancer patients receiving adjuvant chemotherapy. Cancer 49: 651–654, 1982.
82. Zimm S, Wampler GL, Stablein O, Hazra T, Young HF: Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. Cancer 48: 384–394, 1981.
83. Romsdahl MM, Montague ED, Ames FC, Richards PC, Schell SR: Conservation surgery and irradiation as treatment for early breast cancer. Arch Surg 118: 521–528, 1983.
84. Findlay P, Goodman R: Radiation therapy for treatment of intraductal carcinoma of the breast. Am J Clin Oncol 6: 281–285, 1983.
85. Amalric R, Santamaria F, Robert F, Seigle J, Altschuler C, Kurtz JM, Spitalier JM, Brandone H, Ayme Y, Pollet JF, Burneister, Abed R: Radiation therapy with or without primary limited surgery for operable breast cancer: A 20-year experience at the Marseilles Cancer Institute. Cancer 49: 30–34, 1982.
86. Osborne MP, Ormiston N, Harmer CL, McKinna JA, Baker J, Greening WP: Breast conservation in the treatment of early breast cancer: A 20-year follow-up. Cancer 53: 349–355, 1984.
87. Lagios MD, Richards VE, Rose MR, Yee E: Segmental mastectomy without radiotherapy: Short-term follow-up. Cancer 52: 2173–2179, 1983.
88. Robbins GF, Shah J, Rosen P, Chu F, Taylor J: Inflammatory carcinoma of the breast. Surg Clin No Am 54: 801–809, 1974.
89. Barber KW, Dockerty MB, Clagett OT: Inflammatory carcinoma of the breast. Surg Gynec Obstet 112: 406–410, 1961.
90. Droulias CA, Sewell CW, McSweeney MB, Powell RW: Inflammatory carcinoma of the breast: A correlation of clinical, radiologic and pathologic findings. Ann Surg 184: 217–222, 1976.
91. Morris DM: Mastectomy in the management of patients with inflammatory breast cancer. J Surg Oncol 23: 255–258, 1983.
92. Fracchia AA, Evans JF, Eisenberg BL: Stage III carcinoma of the breast: A detailed analysis. Ann Surg 192: 705–710, 1980.
93. Rao DV, Bedwinek J, Perez C, Lee J, Fineberg B: Prognostic indicators in stage III and localized stage IV breast cancer. Cancer 50: 2037–2043, 1982.
94. Bedwinek JM, Ratkin GA, Philpott GW, Wallack M, Perez CA: Concurrent chemotherapy and radiotherapy for nonmetastatic, Stage IV breast cancer: A pilot study by the Southeastern Cancer Study Group. Am J Clin Oncol 6: 159–165, 1983.
95. Pearlman NW, Guerra O, Fracchia AA: Primary inoperable cancer of the breast. Surg Gynec Obstet 143: 909–913, 1976.
96. Cutler SJ, Asire AJ, Taylor SG: Classification of patients with disseminated cancer of the breast. Cancer 24: 861–869, 1969.
97. Swenerton KD, Legha SS, Smith T, Hortobagyi GN, Gehan EA, Yap H-Y, Gutterman JU, Blumenschein GR: Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res 39: 1552–1562, 1979.

98. Hortobagyi GN, Smith TL, Legha SS, Swenerton KD, Gehan EA, Yap H-Y, Buzdar AU, Blumenschein GR: Multivariate analysis of prognostic factors in metastatic breast cancer. J Clin Oncol 1: 776–786, 1983.
99. George SL, Hoogstraten B: Prognostic factors in the initial response to therapy by patients with advanced breast cancer. J Natl Cancer Inst 60: 731–736, 1978.
100. Abrams HL, Spiro R, Goldstein N: Metastases in carcinomas: Analysis of 1000 autopsied cases. Cancer 3: 74–85, 1950.
101. Sproul cited by Haagensen CD: The natural history of breast carcinoma. In 'Diseases of the Breast,' 2nd ed. Philadelphia: W.B. Saunders Co., 1971, p 426.
102. Meissner WA and Warren S: Sites of metastases at autopsy. In: Anderson WAD 'Pathology.' St. Louis: C.V. Mosby Co., 1971, Vol 1, p 538.
103. Cifuentes N, Pickren JW: Metastases from carcinoma of mammary gland: An autopsy study. J Surg Oncol 11: 193–205, 1979.
104. Amer MH: Chemotherapy and pattern of metastases in breast cancer patients. J Surg Oncol 19: 101–105, 1982.
105. Lee Y-TN: Breast carcinoma: Pattern of metastasis at autopsy. J Surg Oncol 23: 175–180, 1983.
106. Viadana E, Cotter R, Pickren JW, Bross IDJ: An autopsy study of metastatic sites of breast cancer. Cancer Res 33: 179–181, 1973.
107. Viadana E, Au K-L: Patterns of metastases in adenocarcinomas of man: An autopsy study of 4,728 cases. J Medicine 6: 1–14, 1975.
108. Viadana E, Bross IDJ, Pickren JW: An autopsy study of some routes of dissemination of cancer of the breast. Br J Cancer 27: 336–340, 1973.
109. Bross IDJ, Viadana E, Pickren J: Do generalized metastases occur directly from the primary? J Chronic Dis 28: 149–159, 1975.
110. Lesse S, Netsky MG: Metastasis of neoplasms to the central nervous system and meninges. Arch Neurol Psychiatr 72: 133–153, 1954.
111. Tsukada Y, Fouad A, Pickren JW, Lane WW: Central nervous system metastasis from breast carcinoma: Autopsy study. Cancer 52: 2349–2354, 1983.
112. Yap H-Y, Yap B-S, Tashima CK, DiStefano A, Blumenschein GR: Meningeal carcinomatosis in breast cancer. Cancer 42: 283–286, 1978.
113. Little JR, Dale AJD, Okazaki H: Meningeal carcinomatosis: Clinical manifestations. Arch Neurol 30: 138–143, 1974.
114. Olson ME, Chernik NL, Posner JB: Infiltration of the leptomeninges by systemic cancer: A clinical and pathologic study. Arch Neurol 30: 122–137, 1974.
115. Sondak V, Deckers PJ, Feller JH, Mozden PJ: Leptomeningeal spread of breast cancer: Report of case and review of the literature. Cancer 48: 395–399, 1981.
116. Posner JB, Chernik NL: Intracranial metastases from systemic cancer. Adv Neurol 19: 579–592, 1978.
117. Wasserstrom WR, Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastases from solid tumors: Experience of 90 patients. Cancer 49: 759–762, 1982.