

**APPENDIX C.2 GENERAL SURGERY: BREAST CANCER
LITERATURE REVIEW**

Western Canada Waiting List Project

Literature Review – General Surgery: Breast Cancer

By

Cheryl M. Martin, Helen M. Roman-Smith, and David C. Hadorn

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1. Introduction

Prognostic indicators such as tumor size and stage are generally accepted to affect survival in breast cancer patients. The impact of other factors on survival is less clear. This review addresses several prognostic factors, with an emphasis on how delay of surgical treatment affects outcome. The review was conducted under the auspices of the Western Canada Waiting List Project for use by the general surgery panelists while developing priority criteria and associated criteria weights. Panelists will be asked to assess the extent to which the review provided meaningful assistance in this regard.

This report focuses on four major questions: (1) what impact does delay of surgery have on outcomes; (2) what is the severity of suffering and disability pre-operatively (baseline); (3) what is the degree of benefit from treatment with regard to suffering, disability, and/or extended life; and (4) which pre-operative variables predict the degree of benefit experienced by patients following surgery for breast cancer.

2. Search Strategy

A comprehensive search was completed to obtain relevant literature. The search consisted of the following:

- References were searched for with the use of the electronic databases Medline, Best Evidence, Cochrane Library, LegalTrac, HealthSTAR, and CancerLit.
- Recent review articles, practice guidelines, and consensus reports were searched for on the web by professional organizations such as the National Cancer Institute and Society of Surgical Oncology.
- In an ancestry analysis, references were obtained from bibliographies of articles retrieved through the computerized searches.
- Informal consultation with Western Canada Waiting List Project surgical panelists was used to request more information and ask whether they knew of additional data of which we should be aware.

See Appendix A for the search terms and limitations used to retrieve citations, and a list of the web sites accessed. Most terms searched electronically were limited to articles published between 1989 and 2000, and were written in English. Articles on delay were retrieved for years 1970 to 2000 to ensure an extensive coverage of the literature.

Approximately 3,300 citations were found from these searches. The abstracts of these citations were first screened to eliminate items not relevant to the review. Articles were retrieved and were screened once more for relevance to the four research questions mentioned above. A total of 130 references were cited in this report.

3. Condition and Treatment Description

3.1 Prevalence and incidence

Breast cancer is the most common cause of cancer death for women in Canada. The lifetime probability of a woman developing and dying from breast cancer is 10.7 percent and 4.0 percent respectively.[1] An estimated 19,200 new cases are expected to be diagnosed in Canada in 2000,

with 5,500 women dying of the disease in the same year.[2] Male breast cancer accounts for about one percent of all new cases and stage for stage, has a natural history similar to that in females.[3]

3.2 Risk factors

The causes of breast cancer remain unknown, but numerous factors have been associated with an increase in breast cancer risk (Table 1). Age, personal history of breast cancer and a family history of breast cancer have the greatest relative risks. Despite the recognition of these risk factors, approximately 50 percent of women who develop breast cancer have no identifiable risk factors beyond being female and aging.[4]

Risk Factor	Relative Risk
Any benign breast disease	1.5
Postmenopausal hormone replacement (estrogen ± progestin)	1.5
Proliferative breast disease without atypia	2.0
Menarche <12 yr.	1.1 – 1.9
Moderate alcohol intake (2-3 drinks per day)	1.1 – 1.9
Menopause >55 yr.	1.1 – 1.9
Sedentary lifestyle and lack of exercise	1.1 – 1.9
Age of first birth > yr. or nulliparous	2.0 – 4.0
First-degree relative with breast cancer	2.0 – 4.0
Postmenopausal obesity	2.0 – 4.0
Upper socioeconomic class	2.0 – 4.0
Personal history of endometrial or ovarian cancer	2.0 – 4.0
Significant radiation to chest	2.0 – 4.0
Older age	> 4.0
Personal history of breast cancer (in situ or invasive)	> 4.0
Proliferative breast disease with atypia	> 4.0
Two 1 st -degree relatives	5.0
Atypical hyperplasia and 1 st -degree relative	10.0

The incidence of breast cancer increases dramatically with increasing age; more than 65 percent of breast cancer cases are among women age 60 and older (Table 2).

Age	30	40	50	60	70	80
Female	0.3	1.3	2.2	2.8	3.2	2.4

3.3 Diagnosis and staging

Breast cancer is usually first detected as a palpable mass or as a mammographic abnormality, but it can also be manifested initially by nipple discharge, breast skin change, or breast pain. Suspicious palpable and mammographic breast lesions are investigated by biopsy. Most breast masses, especially those that are found in young premenopausal women are benign. Most (75 to 85 percent) of the masses found to be cancerous are invasive with the remaining 15 to 25 percent in situ. Carcinoma in situ is characterized by the proliferation of malignant cells within the ducts

or lobules of the breast without invasion of stromal tissue. The two major subtypes are ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).[3]

LCIS, unlike DCIS, is microscopic and lacks both clinical and mammographic signs. LCIS is also more likely to have bilateral involvement. The cells are grouped in a small, solid mass and have small, uniform, round to oval nuclei.[4]

All breast cancers are classified using a scheme that encompasses all attributes of the tumor that define its life history. The American Joint Committee on Cancer (AJCC) TNM classification is based on the premise that cancers of the same anatomic site and histology share similar patterns of growth and extension. The system is based on the size of the primary tumor (T), regional lymph node involvement (N), and distant metastasis (M) (Table 3). The combination of the T, N, and M classification indicates the extent of the disease at the time of clinical evaluation.

Table 3: The TNM system of staging of breast cancer [5]	
Tumor Size – T (Largest Diameter)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget’s disease of the nipple with no tumor
T1	Tumor <2 cm in greatest dimension
T2	Tumor >2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall* or skin (includes inflammatory carcinoma)
Nodal Involvement – N (Nodal Status)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed, not removed)
N0	No regional lymph node metastases
N1	Metastasis to movable ipsilateral axillary nodes
N2	Metastasis to ipsilateral axillary nodes fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph nodes
Metastases - M	
M0	No evidence of distant metastasis
M1	Distant metastases (including metastases to ipsilateral supraclavicular lymph nodes)

*The chest wall includes the ribs, intercostal muscles, and serratus anterior but not the pectoral muscle.

The stage grouping system is often used for the purposes of tabulation and analysis (Table 4). This grouping system was adopted to ensure, as far as possible, that each group is more or less homogeneous in respect of survival, and that the rates of these groups for each are distinctive.[5]

Table 4: Stage grouping system of staging of breast cancer: Conversion from TNM [5]			
Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1 ¹	N0	M0
Stage IIA	T0	N1	M0
	T1 ¹	N1 ²	M0
	T2	N0	M0

Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1 ¹	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes:

1. T1 includes T1mic;
2. The prognosis of patients with pN1a is similar to that of patients with pN0.

3.4 Treatment options

Effective means of treating breast cancer are widely available and may be used alone or in combination, depending on individual circumstances. Surgery is the most commonly used treatment for localized breast cancer. The surgical procedures most often used are lumpectomy with axillary node dissection and modified radical mastectomy. Lumpectomy with axillary node dissection entails excision of the tumor mass, including a clear margin of normal breast around the tumor, along with lymph nodes under the arm. Modified radical mastectomy entails complete removal of the breast, the underlying pectoral fascia, and some of the axillary nodes.[4]

The use of radiation therapy in the management of breast cancer has been increasing in recent years. For many early-stage cancers, radiation of the breast is used in combination with lumpectomy and surgical examination of the axillary lymph glands. In larger but still localized cancers, the breast, axilla, and chest wall may be irradiated following surgical treatment. A number of complications due to the spread of cancer to a distant site (e.g., pain) may be successfully treated with radiation. In these situations, hormone or drug treatment may be given as well.

Surgery and radiotherapy are very effective in removing or destroying cancerous tissue if it is known exactly where the cancer is and if adjacent normal organs and tissues can be preserved without injury. Chemotherapy, on the other hand, is distributed through the body and is capable of destroying cancer cells wherever they exist. Chemotherapy is often used, as adjuvant therapy where the primary tumor has been controlled by surgery or radiotherapy but a secondary tumor is known to exist. It is also used in some situations where the cancer is localized to one site. In a great many cases the growth of breast cancers has been shown to be dependent on the hormonal environment provided by the individual's body. Hormonal therapy provides another approach to suppress the growth of hormone-sensitive tumors. Sometimes suppression of tumor growth is achieved by reducing the level of appropriate hormones in the body through surgical removal or x-ray destruction of the organ that normally produces those hormones (such as the ovary or adrenal gland). Drugs are now also available that counteract the action of certain hormones. Tumor suppression is sometimes achieved by elevating the level of certain other hormones by providing them in the form of drugs.

3.5 Recurrence and survival

Observed and relative survival rates, based on the AJCC staging classification of 50,383 patients with breast cancer are listed in Tables 5 and 6, respectively. Relative survival rate refers to the ratio of the observed survival rate to the expected rate for a group of people in the general population similar to the patient group with respect to race, sex, and age. The data summarized in these tables were taken from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) for the year 1989[6]. Both the observed and relative survival rates progressively decline by years after diagnosis and by stage with stage IV disease declining the most dramatically.

Stage	n	Years after Diagnosis					
		0	1	2	3	4	5
0	5,686	1	0.99	0.97	0.95	0.94	0.92
I	21,604	1	0.98	0.96	0.93	0.9	0.87
IIA	10,412	1	0.97	0.93	0.88	0.83	0.78
IIB	5,673	1	0.97	0.89	0.81	0.74	0.68
IIIA	1,864	1	0.93	0.8	0.69	0.6	0.51
IIIB	2,035	1	0.88	0.7	0.58	0.49	0.42
IV	3,109	1	0.59	0.38	0.26	0.18	0.13

Stage	n	Years after Diagnosis					
		0	1	2	3	4	5
0	5,686	1	1	1	1	1	1
I	21,604	1	1	1	1	0.99	0.98
IIA	10,412	1	0.99	0.97	0.94	0.91	0.88
IIB	5,673	1	0.99	0.92	0.86	0.81	0.76
IIIA	1,864	1	0.95	0.83	0.72	0.65	0.56
IIIB	2,035	1	0.9	0.75	0.63	0.56	0.49
IV	3,109	1	0.61	0.4	0.28	0.2	0.16

Recurrence of breast cancer is dependent upon the stage of cancer at diagnosis and the treatment choice used, whether it is single or in combination.[7-10] A study that followed 407 patients between 1976-1987 with axillary node negative breast cancer treated by surgery alone showed a 10-year recurrence rate (RR) of 19 percent (95% confidence interval \pm 5%). Predictors of recurrence in order of strength were found to be: (1) tumor size ($p = 0.0006$); (2) histologic differentiation ($p = 0.017$); (3) age ($p = 0.046$) (Table 7). Groups with the highest risk for recurrence were patients with tumors less than two centimeters ($RR 32 \pm 12$), and patients with tumors 1.1-2 cm, poorly differentiated/ anaplastic tumors ($RR 24\% \pm 8$).[9]

Table 7: Ten-year recurrence rate in node-negative breast cancer patients according to clinical parameters [9]				
Clinical parameters	# of patients	Recurrence Rate (% ± 95% C.I.)	p	
Tumor size (cm)				
<0.5	54	2 ± 4	0.0006	
0.6-1.0	58	6 ± 7		
1.1-2.0	125	16 ± 9		
2.1-5.0	132	29 ± 12		
>5.0	20	40 ± 31		
Histologic differentiation				
Well or moderate	129	13 ± 8	0.017	
Poor or anaplastic	253	24 ± 8		
Age				
Under 35	22	28 ± 20	Three groups 0.046	Two groups 0.027
35-50	113	22 ± 10		
Over 50	272	17 ± 7		
Up to 50	135	23 ± 8		

Nodal disease was found to be the most important single variable as a predictor of relapse.[8, 11] In a study of 416 patients, the annual rate of relapse of breast cancer was found to increase progressively over the first four years. The annual hazard rate for relapse for node positive patients in the first year was five percent; this increased to 10 percent and 14 percent in years three and four respectively. In contrast, in those patients who were node negative at diagnosis (n = 302; 73 percent), the hazard rate for relapse was 1 percent in year one, increasing to five percent in years three and four.[11] Reintgen and colleagues found in a multivariate regression analysis of clinical variables of 435 women, that the most important predictor of disease-free survival was lymph node status (p = 0.0046) and not tumor size.[8]

The use of combined treatment modalities has been found to decrease recurrence rates. Slotman and colleagues investigated the timing of radiotherapy in breast conserving treatment for early stage breast cancer. The recurrence rate determined for 508 patients with stage I-II invasive breast cancer, treated between 1980-89 with a lumpectomy and axillary lymph node dissection and postoperative irradiation, and adjuvant hormonal treatment (postmenopausal node-negative patients) or adjuvant chemotherapy (premenopausal node-negative patients). Breast cancer recurrence was detected in 17 patients (3.3 percent). The 5-year and 10-year recurrence rates were 5.7 percent and 10.3 percent for stage I, 16.2 percent and 33.2 percent for stage IIA and 32.7 percent and 73.9 percent for stage IIB (p < 0.001).[10] In a retrospective review of patients receiving the same type of surgery, the overall incidence of recurrence was not affected by the order in which chemotherapy and radiation were administered.[7]

The survival rates noted during this review are summarized in Appendix B.

4. Effects of Waiting for Treatment

4.1 Practice guidelines

At least ten clinical practice guidelines have been developed concerning the management of patients with breast cancer. Most of these guidelines addressed how to treat the patient, but not when treatment should be initiated or the consequence of delay. The National Comprehensive Cancer Network (NCCN) Guidelines for the Treatment of Breast Cancer (updated 1997), for example, made no mention of when treatments should be undertaken in relation to diagnosis.[12] The Canadian consensus document “Clinical practice guidelines for the care and treatment of breast cancer” also did not recommend a time period in which treatment should begin (other than suggesting that a patient may take one to two weeks to decide on the type of treatment preferred).[13]

Nor did any of the following guidelines address the appropriate timing of surgery or consequences of delay:

- the “Standard for Diagnosis and Management for Invasive Breast Carcinoma” adopted by the American College of Radiology[14];
- “Surgical Management of Early Stage Invasive Breast Cancer (Stage I and II)” from the Cancer Care Ontario Practice Guideline Initiative[15];
- the NIH Consensus Statement “Treatment of Early-Stage Breast Cancer”[16];
- Clinical Practice Guidelines For The Management Of Early Breast Cancer: Second Edition (1999) from Australia’s National Health and Medical Research Council[17];
- “Breast Cancer Surgical Practice Guidelines” from the Society of Surgical Oncology[18];
- “Practice Guidelines for Breast Cancer” produced by the University of California Cancer Consortium Breast Cancer Clinical Pathways Committee[19].

Two guidelines discussed the question of timing of surgery, if only briefly. In Breast Cancer in women – a national clinical guideline, published by the Scottish Intercollegiate Guidelines Network in 1998, the only reference to timing for surgery was a comment that treatment delays of less than three months were unlikely to be associated with a measurable difference in survival.[20]

A more specific recommendation provided in “The British Association of Surgical Oncology Guidelines for surgeons in the management of symptomatic breast disease in the UK (1998 revision)” indicated that an operation for diagnostic purposes should take place within two weeks of the decision to operate. The guideline further recommended that an initial therapeutic operation be performed within three weeks of the decision to operate. The maximum acceptable wait for therapeutic surgery was considered to be four weeks, unless there was a therapeutic reason for delay.[21]

4.2 Definition and causes of delay

It is generally accepted that cancer should be detected as early as possible. However, the delay of diagnosis or the initiation of treatment can occur for a number of reasons. The first signs of breast cancer may be discovered by patients, or found incidentally by the doctor or through a screening program and delay can be associated with each activity. Similarly, delays may also

occur between the first consultation with the primary-care physician to a hospital referral or between the first hospital visit and the start of definitive treatment. Hospital delay is of interest to the legal profession, and claims for delay in diagnosis of breast cancer are common, rising in number and expense.[8]

Patient delay is defined as the interval between the first symptom or sign of breast cancer recorded by the patient and first visit to the doctor. Patient delay is extremely variable ranging from several days to years. It was found that younger women sought medical advice earlier than did the older patients ($p < 0.0001$). The median patient's delay was 10 days in patients younger than 40 years compared to 20 days in patients older than 80 years.[22] It has been cited that delay is due to a complex interaction of unconscious psychological processes inherent within the individual, while others have attributed it to the nature and sequence of physical symptoms and/or signs.[23] Afzelius et al. believed that the reason for the shorter period for younger women was due to a more rapid progression of disease in younger women and a higher awareness of breast disorders. The longer delay was found with older patients was ascribed to a cohort effect, which at any age would lead to a delay in this age group. It was indicated that older patients may be less inclined to seek medical advice for breast disorders, especially in the presence of other concurrent diseases related to aging. [22]

Doctor delay is generally defined as the interval between the first visit and the time of definitive surgery or biopsy if this was the only intervention. Doctor's delay decreased with patient age ($p < 0.0001$). A median of 31 days in patients younger than 40 years was recorded compared to 19 days in patients aged 80 years or more.[22] The reason for this may be that the diagnostic work-up is more difficult in younger patients due to a higher frequency of dense and lumpy breast tissues in this age group.

A limitation of studies of delay is that the information about first symptom or sign of breast cancer, and thus patient's delay, is generally not as accurate as the information of doctor's delay. The time of first symptom may be difficult to establish since patients usually make no record of the exact date and, therefore, many patients might misjudge the delay. Another limitation is related to lead-time bias, the systematic error arising when follow-up of groups does not begin at comparable stages in the natural history of a condition.[24] For this reason measurement of survival is generally from the time that a patient first notices symptoms, rather than from the time of diagnosis.

Appendix C summarizes the key points of the articles reviewed on delay that are discussed below in greater detail.

4.3 Influence of delay on survival

A comprehensive review of observational studies (worldwide) was completed by Richards and colleagues in 1999 to study the influence of delay on survival among patients with breast cancer [29]. Eighty-seven studies (101,954 patients) published between 1907 and 1996 with direct data linking delay (including delay by patients) and survival were identified and reviewed. Each study was assigned to one of three classifications for the purpose of analysis: category I, in which actual survival rates at five years after diagnosis were available for groups with delays of less or more than three months, less or more than six months, or both; category II, in which actual

survival rates at five years were not reported in the paper, but in which the investigators reported other analyses (e.g., univariate actuarial analyses, multivariate Cox's regression analyses, or both), all published after 1970; or category III, which consisted of studies that did not fall into the first two categories, including a few studies with no data but in which the investigators commented on the relation between delay and survival (e.g., increasing delays seemed to have no adverse effect on survival).

Statistical analysis of the 38 category I studies (n = 53,912) revealed that patients with delays of three months or more had 12 percent lower five-year survival than those with shorter delays (odds ratio for death 1.47 [95% CI 1.42-1.53]) and those with delays of three to six months had seven percent lower survival than those with shorter delays (1.24 [1.7-1.30]). In category II, 13 of 14 studies with unrestricted samples (i.e., encompassing all age groups, all stages, and all pathological subtypes; n = 21,753) showed a significant adverse relation between longer delays and survival, whereas four of five studies of only patients with operable disease showed no significant relation. In category III, all three studies with unrestricted samples (n = 12,312) supported the primary hypothesis that longer delays between onset of symptoms and diagnosis or treatment are associated with worse survival rates among patients with breast cancer.

Richards and colleagues tested a secondary hypothesis that patients with longer duration of symptoms would generally present with more advanced disease. All the thirteen relevant studies supported this hypothesis. The group also wanted to look at whether relation between delay and stage would account for the poorer survival anticipated among patients with longer delays. Eight studies showed a significant relation between delay and tumor size but one study showed no significant association between these variables. Three studies with unrestricted samples significantly reported on the relation between delay and survival within individual stages. In each study, longer delays were associated with lower survival rates when all patients were included in analyses, but longer delay was not associated with poorer survival among patients with stage I disease. In a fourth study, which was restricted to patients with a stage III disease, longer delays were associated with better survival rates. In four studies, multivariate analyses showed that delay was a significant adverse prognostic factor when stage was excluded from the model, but not when stage was included.

The authors of this review concluded that delays of three to six months are associated with lower survival. They claimed that these effects could not be accounted for by lead-time bias, and that efforts should be made to keep delays by patients and providers to a minimum. For the purposes of this paper, thirty-three original studies were reviewed that addressed the question of the impact of delay of surgery on outcomes. Fourteen studies found that delay worsened survival prospects and 16 (three from the same study project on different patient types) did not. An additional, ten studies indicated that delay affects tumor characteristics or progression of disease. Highlights from these studies are presented below.

4.3.1 Delay worsens survival

Several studies have found that a longer delay before treatment may reduce the patient's survival. In a study of 1,784 cases of histologically confirmed breast cancer diagnosed from 1969 to 1974 and followed through 1976, those patients in whom surgery was performed within two months had significantly better survival (estimated 50th percentile survival from graph = 63 months; p <

0.001) than those who delayed three to six months or more than six months (estimated 50th percentile survival from graph = 41 months for both groups).[25]

A study conducted by Richards et al.[26] evaluated the influence of delay presentation and treatment on survival among 2,964 patients of all stages of cancer who were referred to hospital between 1975 and 1990 in England. These patients were followed for a median of 12.5 years. The investigators found that longer delay in presentation were significantly associated with worse survival ($p < 0.0001$). At ten years following diagnosis, the all-cause survival rates for different delay groups were as follows: 51 percent (delay < 12 weeks); 44 percent (delay 12-26 weeks), and 40 percent (delay > 26 weeks). At 20 years, the survival rates were 33 percent, 26 percent, and 24 percent, respectively. When only breast cancer mortality was considered, the comparable survival rates at ten years were 58 percent, 51 percent, and 47 percent, respectively, and those at 20 years were 48 percent, 40 percent, and 32 percent, respectively. The impact of delay in presentation on survival remained highly significant ($p = 0.003$), but the survival curves only started to diverge markedly after about four years.

At ten years from the onset of symptoms, a five percent difference in survival was observed between patients with delays of less versus more than 12 weeks (52 percent vs. 47 percent). At 20 years, the difference in absolute survival rate was 10 percent (34 percent vs. 24 percent). When deaths from causes other than breast cancer were excluded, similar survival differences according to delay were observed. At ten years, the survival rates were 57 percent and 53 percent, respectively, and at 20 years they were 48 percent and 33 percent. When survival was measured from the date of diagnosis, those with longer delays within each stage tended to have better survival, though none of the differences reached statistical significance. When survival was measured from the onset of symptoms, these trends were more marked and reached significance among patients in stages II ($p = 0.01$), III ($p = 0.001$), and IV ($p \leq 0.001$). For patients with ductal carcinomas, delays of 12 or more weeks in presentation had an adverse impact on survival in each tumor grade (grade I, $p = 0.05$; grade II, $p = 0.001$; grade III, $p = 0.007$).

After analyzing the records of 1,591 women with histologically confirmed primary breast cancer diagnosed in the years 1945, 1950, 1955, 1960, 1965, 1970, or 1975, Elwood and Moorehead determined that patients with long delays between the appearance of first symptom and diagnosis had a poorer survival from the date of diagnosis, with a relative survival rate at five years of 57 percent compared with 70 percent in the short delay group. Within stage categories, however, there were no consistent or statistically significant differences in survival between the long and short delay groups.[27]

In some cases delay was only associated with survival under certain conditions. Feldman et al. divided cancers into five classes to determine the relationship of survival in breast cancer to delay in treatment. Class 0 included in situ carcinomas (Tis). Class I cancers included tumors up to five centimeters with no nodal involvement (T1-2; N0). Class II included tumors the same size as Class I but with nodal involvement (T1-2; N1-3) Class III included were larger tumors, node positive with no metastases (T3-4; N1-3). Lastly, Class IV included invasive carcinoma with metastases (M1). The study ($n = 664$) found that patient-induced delay in treatment of more than three months was associated with poor overall ($p < 0.05$) and disease-free survival ($p <$

0.01) in patients diagnosed from 1975 to 1979 with Class III disease. Class III patients with delay less than three months had a four-year overall survival rate of 76 percent, compared to 51 percent for patients in the three to 11 months group and 45 percent in the >12 months group. Disease-free survival was 68 percent for the short delay group, in comparison to 34 percent and 37 percent, respectively. The presence of symptoms other than a lump was associated with longer delay and poorer survival in patients with Class II and III disease.[28]

In an early study of 1,840 patients diagnosed between 1954 and 1965, Sheridan et al. reported survival rates for different delay periods for stage I and II disease.[29] As shown in Table 8, delay was not associated with poorer survival among patients with stage I disease. However, increasing delay among patients with stage II resulted in a greater deterioration.

Duration from first symptom to treatment	Stage I	Stage II
< 4 wks.	74%	65.8%
5 – 12 wks.	76%	55.9%
3 – 6 mo.	85%	59.5%
6 – 9 mo.	83%	-
> 9 mo.	73%	46.8%

In a study of 621 cancer patients (including 101 patients with breast cancer (16.3 percent)) referred to an oncology clinic in Israel in 1974, delay of at least six weeks between first symptom and diagnosis for all stages was associated with poorer survival at 96 months: 45 percent for patients without delay and 32 percent having experienced delay (values estimated from graph).[30] Both Neale et al. and Dohrmann et al. reported that delays over six months negatively affected survival.[31, 32] Neale examined 10-year survival following breast cancer diagnosis among 1,261 women treated in Texas between 1949 and 1968. Ten-year survival was found to be inversely related to delay in seeking treatment ($p < 0.001$) with the cumulative proportion surviving 47 percent, 38 percent, and 25 percent for less than three months, three to six months, and more than six months delay, respectively. In the Dohrmann study, 435 patients underwent surgery for breast cancer between 1950 and 1980. Of these patients, symptom duration data and tumor staging was available for 353 patients. Cancer-specific survival time was better for the total patient series and for those treated by potentially curative operation when symptoms had been present for one week or less as compared with those who had symptom duration of six months or more, $p = 0.007$. Survival prospects were also better in those patients who had symptoms from one week to one month as compared with those who had six months or more symptom duration, $p = 0.005$. An M.D. Anderson study on the differences in 10-year survival rates of white, black, and Hispanic breast cancer patients ($n = 1983$) operated on between 1949 and 1968 found that ethnicity, socioeconomic status, stage of disease, and delay in seeking treatment all affected survival when considered separately.[33]

In a study of 7,608 patients conducted by Afzelius et al., regression analysis demonstrated that, in addition to age, both patient- and doctor-induced delay had prognostic value. If the patient delay was more than two months, the mortality was 24 percent higher than for a short or intermediate delay ($p < 0.0001$). If a doctor-induced delay was less than 15 days, the mortality was 13 percent higher than for longer delays ($p = 0.0002$). The prognostic value of delay in terms

of excess mortality increased to 34 percent for a long patient delay compared to a shorter delay and to 19 percent for a short doctor delay compared to a longer delay when omitting age from the model.[22]

The results of the Afzelius study give an example of a trend that has been found in a few other studies, in that there appears to be a subgroup of patients with short delay that have a worse survival rate. Two reasons have been suggested for this phenomenon. One is the ability of the doctor to recognize and recommend immediate surgery for the patients with the worst diagnoses, and the other is the theory that certain types of tumors progress very rapidly.[23, 29, 34, 35]

The following table (Table 9) is a summary of the studies that found longer delay associated with decreasing survival. The “worst survival period” indicates the time period that had the worst survival statistics (i.e. patients who had surgery delayed for over 1.5 months had worse survival statistics [either disease-free, overall or both] than patients with less than 1.5 months of delay.)

Table 9: Period of worst survival				
Number of Patients	Worst Survival Period (months)	Year	Variable (if any)	Reference
412	> 1.5	1984		[30]
1784	> 3	1979		[25]
664	> 3	1983	Class III only	[28]
7608	> 3	1994		[22]
?	> 6	1982		[32]
1261	> 6	1986		[31]
2964	> 6	1999		[26]
1840	> 9	1971	Stages II & III only	[29]
1591	> 12	1980		[27]
189	> 12	1990		[36]
18313 = Total				

4.3.2 Delay does not worsen survival

A number of studies have determined that delay does not affect outcome. In the review conducted by Richards et al., seven studies identified did not support their hypothesis that longer delays between onset of symptoms and diagnosis or treatment are associated with worse survival rates among patients with breast cancer. Six of the seven studies had restricted samples (four of operable patients only; one of locally advanced disease only; one of patients older than 65 years). These studies ranged in size from 184 to 1539 patients (median 258 patients) and only one involved more than 1000 patients. The lack of a relation between delay and survival in these studies might, therefore be related to the size of the studies or to restrictions by stage.[37]

It is not uncommon for patients operated on immediately to have the poorest survival, but these patients frequently have some of the diagnoses with the worst prognoses. A review by Facione has also called into question the practice of using multivariate analysis to determine the effect of delay.

In a retrospective analysis of 36,222 women, Sainsbury, Johnston, and Haward found that patients with delays of less than 30 days between family-physician referral and treatment had

worse survival than patients in any other time period ($p < 0.001$). The authors concluded that delays of longer than 60 days did not significantly impair survival, and delays of more than 90 days were unlikely to impact survival. Patients receiving treatment within 30 days had worse survival statistics.[35] In a study on node-negative patients, patients whose tumor was detected within six months before surgery ($n = 701$) had a recurrence rate of 21 percent. Those who had surgery between six and twelve months after detecting the mass ($n = 121$) had a 23 percent recurrence rate, and those waiting over 12 months ($n = 83$) had a 25 percent recurrence rate ($p = 0.433$; log-rank = 0.64). The differences were not significant.[38] Fisher, Redmond, and Fisher[39] found that there was a trend toward a reduction in treatment failure rate in patients whose symptom period was greater than 9 months.

Neave, Mason, and Kay, in a study on 1,675 breast cancer patients, found no difference in survival among patients experiencing different lengths of delay, although the variables tumor size, skin attachment, and nipple retraction were more common in the group with longer delay, and histologically grade III tumors were more common in patients with shorter delay.[23]

Charlson found that out of 685 breast cancer patients, those with delays of three months or more from the time of first symptom to treatment had a more advanced clinical stage than those with shorter delays; however, within each stage, prognosis was not affected by delay. Progression of disease did not invariably occur among patients with longer delays. The author estimated that the number of patients in the cohort who would have benefited by a reduction in delay was a maximum of five percent.[40] Machiavelli et al. had results similar to Charlson. In a study on 596 patients with breast cancer, patients with a delay of less than three months had a higher 10-year survival rate than those in the longer delay groups ($p = 0.034$), but within each stage no statistically significant difference in survival according to delay was observed.[41] In four additional studies (three of which were a series of studies on node-negative, node-positive, and metastatic patients), delay was not found to be associated with survival.[42-45]

In a literature review on delay, Facione refers to the Charlson and Machiavelli studies finding that delay is insignificant to survival, and states that “the ill-conceived use of statistical methods of data analysis might be the culprit responsible for this dangerous and illogical inference.” She claimed that multiple regression analyses that include the variables of tumor stage, tumor size and delay, particularly hierarchical regressions where tumor stage is introduced as the first covariate, will tend to show that delay “contributes no additional explained variance.”[46] However, this explanation is unlikely to account for all of the findings described above, showing that delay in treatment is not necessarily related to outcome.

4.4 Other factors related to delay

Besides survival, several other factors have been associated with delay of treatment, including stage of disease, tumor size, and lymph node involvement at diagnosis. The risk of nodal involvement was almost doubled for patients with a greater than 6-month delay (compared with patients with less than three month’s delay; adjusted by age) who also had between three and four times the risk of being diagnosed with advanced disease.[47]

In reviewing the records of 1,014 patients, delay in diagnosis was found to average 11 months (range three months to more than six years) in one doctor’s practice. Tumors of patients with

delay were significantly larger than tumors of patients without delay (2.3 vs. 1.8 cm), but nodal involvement was no more frequent. The cancers of patients with delay were similar to those of patients without delay. Pathology, tumor differentiation, and estrogen receptor status were all comparable.[48] A study on the symptom to diagnosis interval (SDI) in seven different types of cancer, found that only in breast cancer was the status of the tumor significantly affected by the duration of symptoms.[49]

Robinson, Mohilever, and Borovik found that delay in diagnosis of over six weeks affected the likelihood of being diagnosed with an advanced stage of disease in 523 patients. Women with no delay were more likely to be diagnosed at stage I (52 percent) than those with delay (35 percent). Of the patients without delay, 42 percent were diagnosed with stage II cancer and five percent with stage III cancer, as compared to 52 percent and 12 percent of delayed patients, respectively.[50]

Of 1,784 cases of histologically confirmed breast cancer, a larger proportion of patients who delayed two months or less before seeking treatment were diagnosed as having localized disease compared to those delaying three to six months or more than six months. However, 50 percent of those waiting three to six months were diagnosed with regional involvement as opposed to 41 percent of those waiting two months or less, and 49.5 percent of those waiting more than six months. Twenty-five percent of patients waiting more than six months compared to 6 percent of patients waiting two months or less demonstrated distant metastases at the time of diagnosis.[25] In a study by Gould-Martin et al. on 274 patients diagnosed with breast cancer, increased relative risks for regional disease were observed with increasing intervals between self-discovery of tumor or onset of symptoms and first contact with physician. This relationship persisted for up to five months.[34]

Nettleton et al. analyzed the data from a study published by Silverstein et al. on the correlation of the size of primary breast cancer with the incidence of positive axillary nodes in order to determine the risk of axillary nodal metastases due to delayed treatment of breast cancer during pregnancy. The data included 939 patients with stage T1 and T2 breast cancer who underwent conservative surgical treatment of the primary tumor and axillary node dissection. At the time of diagnosis, a patient with a 2.5 mm tumor was calculated to have a 1.4 percent risk of axillary metastases. A 1-month delay in treatment for an early-stage primary breast cancer with a 130-day doubling time increased the risk of axillary lymph node involvement by 0.9 percent, making the total risk (risk at diagnosis + 1-month risk) 2.3 percent. A 3-month delay increased the risk by 2.6 percent, and a six-month delay by 5.1 percent. For breast cancer with a 65-day doubling time, a 1-month delay increased the risk by 1.8 percent, a three-month delay by 5.2 percent, and a six-month delay by 10.2 percent. Patients with tumors averaging 35.5mm had a 45.7 percent risk of axillary metastases with a 65-day doubling time, compared to 59.3 percent risk after nine months with the 65-day doubling time. With a 130-day doubling time, the risk was 44.8 percent at one month and 51.6 percent at nine months.[51]

In a review of court cases designed to determine the patient and physician factors that lead to breast cancer malpractice litigation, 24 cases provided the TNM stage at diagnosis. According to linear regression analysis, no correlation was noted between the increasing delay in diagnosis and the advancing TNM stage ($p = 0.91$). In eight cases, size of the tumor was plotted against

the months of diagnostic delay. Linear regression analysis showed no statistically significant correlation between tumor size and final diagnosis and diagnostic delay ($p = 0.91$).[52]

In a literature review, Caplan and Helzlsouer[53] reported on an article by Pilipshen et al.[54], which followed patients treated by radical or modified radical mastectomy. Those delaying more than six months were about twice as likely to have tumors of at least four centimeters and 40 percent more likely to have axillary metastases than patients delaying six months or less.

4.5 Delay of radiation

Several studies have tested the impact of delay of radiation therapy on survival. In a study on the impact of delaying irradiation after chemotherapy on patients with node-positive cancer, Hartsell et al. determined that delays over 120 days increased the risk of relapse. The five-year actuarial survival rates were 87 percent and 82 percent for the early and delayed groups, respectively ($p = 0.39$). The disease free survival and distant disease free survival rates were 85 percent and 85 percent for the early group, compared with 69 percent and 81 percent for the delayed group ($p = 0.04$ and 0.34 , respectively). For the 42 patients receiving delayed irradiation, there were six local recurrences, for a 5-year actuarial rate of 14 percent ($p = 0.05$).[55]

In a study on the effect of delaying radiation after chemotherapy, Buchholz et al. found that local control rates (the percentage of patients who did not have local recurrence) were 98 percent for the early radiation group compared to 76 percent for the delayed group at eight years. The difference was significant at a value of $p = 0.004$. Overall survival was 80 percent for the early group compared to 52 percent for the delayed radiation patients ($p = 0.016$). Eight-year actuarial disease-free survival rates for the early patients and the delayed patients were 71 percent and 48 percent, respectively ($p = 0.008$).[56] Among patients who received breast-conserving surgery with and without chemotherapy, local and systemic failure rates were determined based on timing of irradiation. Those who did not receive chemotherapy had higher local and systemic failure rates if radiation was undertaken more than seven weeks after surgery. In the group that did receive chemotherapy, local, regional, and systemic failures only occurred in women with a delay of radiation exceeding 24 weeks. There were no differences in survival rates.[57] Slotman et al. also found delay of radiotherapy to be an independent factor predictive of recurrence in 508 patients with stage I and II invasive cancer.[10]

Two studies did not find an association between delay of radiation therapy and lower survival rates. Leonard et al., in a study on 262 patients, could not identify any surgery-radiotherapy interval that resulted in increased local recurrence if radiotherapy was delayed for administration of adjuvant chemotherapy.[58] Vujovic et al. found that patients treated with radiation within 12 weeks of surgery had a local recurrence rate of 7.8 percent (34/436), compared to a rate of 3.8 percent for the patients treated after 12 weeks (5/132).[59]

5. Baseline Health Status Measures

5.1 Function

The effect of breast cancer on function has not been frequently studied. At best, function-related factors may be included in an overall quality of life assessment. The McCorkle and Young Symptom Distress Scale (SDS) includes the domains of fatigue and mobility in its assessment.

Cimprich used the SDS to assess 74 newly-diagnosed breast cancer patients prior to surgery (see Table 10). The affect of a cancer diagnosis on mobility was low in all patients (mean of 1.3 out of a worst possible five). Fatigue was noted to be more of a problem by the patients, following insomnia and mood disturbance.[60] See Appendix D for a description of measurement tools.

Worst 5 - Best 1 Variable	Pre and Postmenopausal Mean (SEM*)	Premenopausal Mean (SEM)	Postmenopausal Mean (SEM)
n	74	25	49
Appearance	1.68 (0.11)	1.92 (0.24)	1.55 (0.12)
Bowel disturbance	1.73 (0.12)	1.88 (0.24)	1.65 (0.13)
Fatigue	2.41 (0.12)	2.68 (0.20)	2.27 (0.20)
Insomnia	2.88 (0.14)	3.00 (0.20)	2.81 (0.20)
Loss of appetite	1.8 (0.12)	2.20 (0.30)	1.59 (0.10)
Loss of concentration	2.24 (0.13)	2.60 (0.30)	2.06 (0.20)
Mobility	1.30 (0.08)	1.32 (0.11)	1.29 (0.11)
Mood disturbance	2.72 (0.10)	3.12 (0.10)	2.51 (0.10)
Nausea	1.37 (0.08)	1.68 (0.20)	1.21 (0.80)
Overall distress	19.35 (0.70)	21.8 (1.30)	18.1 (0.80)
Pain	1.31 (0.07)	1.44 (0.12)	1.24 (0.12)

* SEM refers to the standard error of the mean or the standard error

5.2 Pain

Breast pain is reported as a symptom in about 10 percent of patients with breast cancer.[3] In the Cimprich study, the overall pain score was 1.31 out of five, with premenopausal women scoring a mean 1.44 and postmenopausal women scoring 1.24. Other discomforting problems assessed by the SDS were bowel disturbance and nausea (See Table 10).[60]

5.3 Psychological

The psychological affects of breast cancer are more frequently studied, but the period between diagnosis and surgery has seen little research. Again, the Cimprich study provides some information. On the SDS, patients found that psychological problems were the most difficult to handle while awaiting surgery, with insomnia (2.88) and mood disturbance (2.72) rating the worst scores. After fatigue (2.41), loss of concentration (2.24) was the next most often reported difficulty. In all domains, premenopausal women had more difficulty dealing with a cancer diagnosis than did their older counterparts. (See Table 10) [60]

Three studies used the Profile of Mood States (POMS) to evaluate the psychological status of patients between diagnosis and surgery. Rather than developing high and low scores for the individual scales on the POMS, the creators of this tool, McNair, Lorr, and Droppleman, produced mean comparison groups using college women and psychiatric outpatients. With the exception of the “vigor” scale, a higher score indicates worse status. For the purposes of comparing breast cancer patients to a normal population, the college women scores are included in Table 11.[61] A second comparison group of healthy women has been extracted from a study by Anderson, Anderson and deProsse.[62]

Cimprich[60] evaluated 51 patients, 39 of whom were postmenopausal and 12 were premenopausal. Table 11 shows the POMS scores for each group. Cimprich noted that premenopausal patients had notably higher scores than postmenopausal patients. Two other studies, Romsaas et al. and Stanton and Snider[63, 64], also assessed patients after diagnosis and before surgery, and the scores of these three groups have been averaged in Table 11 in the “All” column. All patients who were awaiting surgery at the time of evaluation with the POMS assessment had much worse (higher) scores in the areas of depression-dejection and tension-anxiety than those in the healthy women group, but were not much different than the college women evaluated by the creators of the POMS. All women waiting for surgery had a much worse (lower) score for vigor than did either of the comparison groups or the postmenopausal women.

Table 11: Comparison of average preoperative Profile of Mood States (POMS) mean scores for diagnosed breast cancer patients and other groups.					
For all scales except “vigor,” Worst = high score; Best = low score. For “vigor,” Worst = low score; Best = high score. (Maximum and minimum scores are not used for this questionnaire.)					
	Preoperative Patients Diagnosed with Breast Cancer			Comparison Groups	
Scales	All*	Premenopausal (< 55 years)	Postmenopausal (≥ 55 years)	Healthy Women	College Women
n	109	12	39	60	516
Anger-hostility	8.4	9.9	5.4	8.7	9.3
Confusion-bewilderment	8.6	10.8	8.5	5.8	11.7
Depression-dejection	14.88	17.2	10.8	6.9	14.8
Fatigue	9.15	9.5	7.4	6.5	10.7
Tension-anxiety	16.36	19.3	16.0	8.8	13.9
Vigor	9.45	11.3	16.8	19.0	15.6
Total mood disturbance**	44.57	55.4	31.2	17.7	44.8
Reference(s)	[60, 63, 64]	[60]	[60]	[62]	[61]

*See Appendix E for the scores used to calculate the “All” category in Table 11.

**Total mood disturbance = anger + confusion + depression + fatigue + tension – vigor.

Separately, a study by Seckel and Birney examined the relationship among stress, age, and social support in 30 women scheduled for biopsy. The authors determined that patients who perceived having less social support reported greater anxiety while awaiting surgery. In addition, the patients tended to have increased stress with aging until age 40, then stress decreased with increasing age, which agrees with the data found by Cimprich in the pre- and postmenopausal patients.[65]

5.4 Other quality of life measures

Of the studies reviewed which measured quality of life between the time of diagnosis and surgery, there were no other elements studied which would indicate a worse status for the patient

during this specific time period and which were specifically the result of the knowledge that surgery was pending.

6. Surgical Outcomes

6.1 Function

The only pre- and postoperative comparison of function encountered during the review was that performed by Stanton and Snider using the Profile of Mood States (POMS). In Table 12, fatigue and vigor were compared among patients over 40. (Note that for fatigue a high score is worse, but for vigor a high score is better.) The changes in these domains between pre- and postoperative scores were not major.[64]

6.2 Pain

Of the studies reviewed, no data was available on the difference between pain for breast cancer patients before and after surgery.

Scales	Preoperative Mean (SD)	3 Weeks Postoperative Mean (SD)
n	36	36
Anger-hostility	5.90 (8.91)	4.57 (7.50)
Confusion-bewilderment	5.53 (5.69)	4.45 (10.54)
Depression-dejection	13.37 (12.50)	9.00 (11.74)
Fatigue	10.33 (7.11)	9.83 (6.66)
Tension-anxiety	12.97 (8.01)	8.57 (8.76)
Vigor	10.10 (6.18)	11.48 (6.68)

6.3 Psychological

One study evaluated the mental status of breast cancer patients prior to and after surgery (see Table 12). Patients indicated similar improvements in the scales of depression-dejection and tension-anxiety, with an increase in score of approximately 4.4 points. Other changes showed improvements in the patients' status, but were not large differences.

7. Prognostic Indicators of Treatment Benefit

7.1 Age/menopausal status

Age is frequently tested as a prognostic indicator for survival. Not all studies find the association significant. In some studies, age was only associated with recurrence. Vujovic et al. found that patients under 40 years had increased risk of recurrence. Under univariate analysis, age was a significant prognostic factor associated with local recurrence and disease-free survival. Age was also a significant factor for disease-free survival under multivariable analysis.[59] In another study, younger patients were more likely to have local failure.[66] In a group of 407 axillary node negative breast cancer patients having received surgery alone, age ($p = 0.046$) was a significant predictor of outcome. Patients under 35 had a higher recurrence rate.[9] Of 3,585 patients entered into a study on adjuvant therapies, postmenopausal patients had a greater hazard of recurrence ($p = 0.0009$) for the entire 12-year follow-up interval.[67] In a study by Merchant et al., no differences were observed regarding disease-free or overall survival between the two

groups of < 65 and ≥ 65 patients, but at both five and ten years, there was a statistically significant improvement in local control for older patients (numerical values not reported).[68]

Other studies have found age to be a predictor in the overall survival rates or risk of death. In a study by Byrne et al., the five-year survival rate for patients under 40 was 74.8 percent. For patients between 40 and 79, survival rates ranged from 82.7 to 85.2 percent. After 80 years of age, survival decreased to 40.9 percent.[69] Among 611 patients with breast cancer, under multivariate analysis, age older than 74 years was significantly and independently associated with a shorter disease-specific survival as compared with patients younger than 75 years.[70]

La Rosa et al. found that relative survival at one year from diagnosis was stable up to 69 years (between 0.97-0.91). After 69 years, the prognosis progressively worsened with increasing age. At five years from diagnosis, the highest relative survival values referred to women under 35 years of age (0.83). Thereafter chances of survival generally diminished with increasing age up to 0.59 in women of 75 and over. There was a difference among women of 45-49 years (0.81) and 60-64 years (0.76), for whom the prognosis was six percent and 13 percent better respectively, than the preceding age groups.[71]

Patients not receiving adjuvant cytotoxic treatment had a significantly increased risk of dying with decreasing age (adjusted relative risk: 45-49 years: 1(baseline); 40-44 years: 1.12 (95% confidence interval 0.89 to 1.40); 35-39 years: 1.40 (1.10 to 1.78); < 35 years: 2.18 (1.64 to 2.89)). Young patients receiving adjuvant cytotoxic therapy did not show the same increase of risk.[72]

Numerous studies have reported on both rates of disease recurrence and death with regard to age. In a study on age as a prognostic factor for breast cancer, patients under 33 years ($n = 67$) had the worst actuarial overall survival rate of 67.8 percent at five years compared to patients in groups of 34 to 40 years and over 40 years. The youngest patients also had the lowest disease-specific survival rate of 68 percent, compared to 76.5 percent for the 34-40 group and 84.6 percent for the over 40 group. The disease-free survival was, again, worst for the youngest patients at 52.7 percent compared to 60.4 percent and 70 percent for the older groups.[73]

In 980 patients with stage I and II breast cancer who underwent excisional biopsy, axillary dissection, and radiation, younger women (≤ 35) were found to have a statistically significant decreased 8-year actuarial relapse-free survival, 53 percent compared to 67 percent for women between 36 and 50, and 74 percent for women 50 and over ($p = 0.009$). The younger group also had lower cause-specific survival (73 percent vs. 84 percent vs. 90 percent, $p = 0.02$), freedom from distant metastasis (76 percent vs. 75 percent vs. 83 percent, $p = 0.02$), and a significantly increased risk of breast recurrence (24 percent vs. 14 percent vs. 12 percent, $p = 0.001$), and regional node recurrence (seven percent vs. one percent vs. one percent, $p = 0.0002$).[74]

In reviewing data on 125,000 breast cancer patients, Yancik, Ries, and Yates determined that patients with localized disease could expect a relative survival rate of about 99 percent regardless of age at one year. After five years, 90 percent of the women in the age groups between 45 and 85 years continued to survive. Rates for those in the age groups younger than 45 and 85 years or older had lower survival rates by three to seven percentage points. Survival rates for localized

disease decline in the eighth year post-diagnosis to 84 percent. Women younger than 35 years had the lowest 8-year survival rate.[75]

Bonnier et al. reported on 1,266 patients treated for breast cancer. The three groups were: <35 (Group A), premenopausal >35 (Group B), postmenopausal <70 (Group C). Metastasis-free survival and overall survival were significantly poorer for the <35 group. Group A also had higher risk of local recurrence.[76]

For the premenopausal patients, long-duration chemotherapy significantly increased both disease-free survival and overall survival compared with the short-duration treatment. For the postmenopausal patients, while differences in terms of disease-free survival were highly significant, those in terms of overall survival appeared late during follow-up and were not statistically significant.[77]

Younger patients displayed better survival than older patients. However, patients under 45 demonstrated good survival for about 25 to 26 months, after which survival began to decline, eventually becoming similar to patients over 55.[25]

Age has also been associated with cancer characteristics that can ultimately increase survival rates. In developing a series of Markov-chain models to estimate tumor progression rates and sensitivity, Duffy et al. determined that tumor progression to the clinical phase, and with respect to node status and tumor size, is faster in the age group 40-49 than in older age groups.[78] Callies et al. found that younger patients with a tumor size of T1 and T2 had a significantly better prognosis than older patients with the same tumor stage. Influence of age became significantly weaker in patients with a T3 or T4 tumor. In patients with a primarily M1 stage, very little dependence on age was shown.[79]

In seven additional studies, age was found to be a prognostic indicator for survival [59, 73, 80-84]. Eight additional studies did not find age to be a significant indicator (three of which are part of the same study series on different types of patients) [43-45, 85-89].

7.2 Axillary lymph node involvement

The number of axillary lymph nodes involved has frequently been found to be a significant prognostic indicator. In an analysis by Wheeler et al., there was a significant difference in disease-free survival rate in patients presenting with node-negative disease compared with those presenting with node-positive disease ($p < 0.0001$). Multivariate analysis showed that nodal stage was the most important single prognostic indicator. Patients with node-negative disease at diagnosis had a five-year disease-free survival rate of approximately 82 percent (95% CI 78-86) compared with a 64 percent (95% CI 55-73) for node-positive patients.[11]

In patients having unilateral invasive ductal breast cancer in stages I-III, positive node status was found to significantly increase the risk of developing local-regional recurrence, distant recurrence, or death.[84] In 903 stage I and II cancer patients, nodal status had a strong affect on survival and distant relapse, and a lesser, but significant, affect on local relapse.[90] Buzdar et al. found nodal status to be a significant predictor for disease-free survival, but not for overall survival.[85]

Markiewicz et al. found that for node-positive patients, outcome at five and 10 years, respectively, were 86 percent and 70 percent for overall survival, 78 percent and 67 percent for disease-free survival, and 82 percent and 69 percent for freedom from distant metastases. For node-negative patients, outcomes at five years were 94 percent for overall survival, 94 percent for disease-free survival, 94 percent for freedom from distant metastases.[91]

An additional 15 studies associated nodal status with disease-free or overall survival [8, 35, 45, 56, 67, 69, 73, 76, 86, 87, 92-96]. Three studies [44, 81, 97] did not associate lymph node involvement with survival. Two additional studies [94, 97] connected the number of lymph nodes examined to survival.

7.3 Estrogen/progesterone receptors

There have been mixed results in efforts to determine if estrogen and progesterone receptor (ER and PR, respectively) status have an effect on survival. Quiet et al. determined that patients with a negative or borderline ER status had a statistically improved DFS period ($p = 0.008$) compared to those with positive ER status. DFS was worse in premenopausal patients with ER-positive tumors as compared to ER-negative tumors. In postmenopausal patients, ER status was not a predictor of long-term survival.[38] In a study of 1,266 patients treated for breast cancer, multivariate analysis revealed that ER status was a significant predictor of survival. PR status was not correlated with survival.[76] In 3,585 patients entered into a study on adjuvant therapies, up through year five, ER-negative patients had a higher hazard of recurrence. Beyond year five, the hazard rate was higher for ER-positive patients ($p = 0.0002$).[67]

In five other studies [73, 87, 93, 94, 97], ER status was a predictor of survival, but in eight studies [9, 43, 45, 81, 85, 86, 88, 92] the factor was not associated with survival. For progesterone receptor status, four studies [45, 56, 73, 87] found the factor to be significant and four [9, 43, 88, 92] did not.

7.4 Tumor size

Tumor size is one of the prognostic indicators most consistently associated with survival. Of the 25 studies reviewed, which tested the impact of tumor size, only one did not report it to be a predictor of recurrence or death. Quiet et al. found that tumor size was the strongest predictor of outcome in node-negative breast cancer. For tumors less than 20 mm, the 20-year DFS rate was 79 percent, as compared to 64 percent for patients with tumors over 20 mm ($p < 0.001$). The median time to recurrence was 48 months for tumors less than one centimeter, 44 months for tumors between 2.1 and 3.0 cm, and 37 months for tumors between 4.1 and 5.0 cm. Patients with smaller tumors developed metastatic disease later than patients with larger tumors.[38] In a group of 407 axillary node negative breast cancer patients having received surgery alone, large tumor size ($p = 0.0006$) was the most significant predictor of outcome.[9]

In a report on treatment results of 508 patients with stage I and II invasive breast cancer, patients with T2 tumors had a shorter survival than those with T1 tumors ($p < 0.001$).[10] In 24,740 breast cancer patients, actuarial five-year relative survival rates varied from 45.5 percent for tumor diameters equal to or greater than five centimeters with positive axillary nodes to 96.3 percent for tumors less than two centimeters and with no involved nodes.[98] Perrone et al.

found that tumor size was closely associated with the number of metastatic nodes and significantly and independently affected DFS and OS in a univariate analysis. P values for the stratified analyses were all less than 0.0001.[99]

Nineteen other studies indicated that tumor size was a predictor of survival [8, 43-45, 59, 67, 69, 73, 76, 87, 90, 92, 94-97, 100-102].

The one study reviewed that did not associate tumor size with survival[86], was a retrospective analysis on 966 patients who had tumors under the size of five centimeters. The study was designed to determine the clinical significance of local recurrence after simple mastectomy and node biopsy for primary operable breast cancer without postoperative irradiation or systemic adjuvant therapy.

7.5 Histopathologic grade

The histopathologic grade or differentiation of the tumor indicates the extent to which a tumor resembles the normal tissue at the cancer site. Joensuu, Pylkkanen, and Toikkanen conducted a study on 265 node negative patients with tumor size less than or equal to two centimeters and treated with mastectomy and axillary lymph node dissection without adjuvant therapy. At 20-years, no patients with a well-differentiated pT1a-b tumor died during follow-up, but the survival rate after correction for intercurrent death was 81 percent in patients with Grade 2-3, pT1a-b tumors or pT1c tumors.[101]

Under both univariate and multivariate analysis, grade was a significant prognostic factor associated with disease-free survival in the study by Vujovic et al.[59] In a study on patients having unilateral invasive ductal breast cancer in stages I-III, high grade was found to significantly increase the risk of developing local-regional recurrence, distant recurrence, or death.[84]

In six additional studies, histopathologic grade was associated with survival [9, 43, 45, 69, 73, 76, 86]. Three studies did not support the association.[56, 87, 92].

7.6 Stage of disease

Stage has frequently been found to significantly affect survival. In a study by Neale, Tilley, and Vernon, survival curves indicated that stage at diagnosis may be the most important variable in predicting survival. Within the first year, women with metastatic disease evidenced greater mortality than those diagnosed in-situ. After 10 years, about 60 percent of women with localized disease were still living, about 30 percent with regional disease remained alive, and virtually all of the metastatic cases had died.[31] In patients having unilateral invasive ductal breast cancer in stages I-III, Broet et al. found that high clinical stage significantly increased the risk of developing local-regional recurrence, distant recurrence, or death.[84]

Except for Stage IV disease, the survival rates for each individual stage in a study by Henson, Ries, and Carriaga were similar regardless of the number of years lived after diagnosis. At the time of diagnosis, however, patients with Stage I-III cancers had a 93 to 100 percent probability of surviving the first year, while Stage IV patients only had a 64 percent probability of survival in the first year.[72] In a study by Byrne et al., breast cancer survival among women with in situ

breast cancer was 98.6 percent at five years. Patients with invasive disease had a rate of 81.4 percent. Women with Stage III cancer had the poorest survival rate at 51.4 percent.[69]

In six other studies [11, 25, 82, 93, 103-105], stage was significantly associated with survival. Two studies [81, 85] did not find a relationship between stage and outcome.

7.7 Margins of resection

Of five studies reviewed, four found the margin of resection to be a prognostic indicator for survival. Hartsell et al. determined that local recurrence was more common in patients with widely negative margins of excision. In a multiple regression analysis, margin of excision (negative vs. close/unknown/positive) was the only factor that predicted local recurrence ($p = 0.04$).[55] In a report on treatment results of 508 patients with stage I and II invasive breast cancer, patients with close and positive pathological margins had a significantly higher risk of breast recurrence, 8.3 percent and 9.7 percent, respectively, compared to 2.6 percent for patients with negative margins.[10] Vujovic et al.[59] and Fortin et al.[66] also found the resection margin to be associated with survival, but Buchholz et al. did not[56].

7.8 Adjuvant chemotherapy

Studies on chemotherapy, radiation therapy, and, more recently, tamoxifen have been carried out to determine the affect of these treatments on recurrence and death.

Haffty et al. conducted a study on 548 patients to determine the impact of adjuvant systemic chemotherapy and adjuvant hormonal therapy on local relapse in the conservatively treated breast cancer. Patients who underwent conservative surgery, axillary dissection, and radiation therapy to the intact breast were likely, at least in the short term, to have a lower breast relapse rate if they received adjuvant systemic chemotherapy.[81]

In a study by Gelber, Cole, and Goldhirsch, on premenopausal patients, the long-duration chemotherapy significantly increased both disease-free survival and overall survival compared with the short-duration treatment. For postmenopausal patients, while differences in terms of disease-free survival were highly significant, differences in overall survival appeared late during follow-up and were not statistically significant.[77] In a study of 1,124 positive-node breast cancer patients aged ≥ 50 years, Fisher et al. determined that patients had a better disease-free survival rate at three years with prolonged tamoxifen use and short-course chemotherapy (Adriamycin and cyclophosphamide) than from prolonged tamoxifen therapy alone (84 percent vs. 67 percent; $p = 0.0004$).[106]

Five other studies [72, 107-110] showed a relationship between adjuvant chemotherapy and improved recurrence and survival rates.

Bonnier et al. did not find a significant association between adjuvant chemotherapy and survival[76], and Broet et al. reported that for patients having unilateral invasive ductal breast cancer in stages I-III who received chemotherapy, the rate of metastases or death was increased (RR = 1.22).[84]

7.9 Adjuvant radiation therapy

Diab et al. found that among 618 breast cancer patients with 10 or more positive axillary lymph nodes, radiation therapy to the loco-regional area lowered failure rates and improved overall survival. The adjusted 5-year loco-regional failure rate was 13 percent with radiation and 38 percent without radiation ($p = 0.0001$). The adjusted five-year distant failure rate was 48 percent with radiation and 58 percent without radiation ($p = 0.02$). The adjusted five-year overall survival rate was 56 percent with radiation and 42 percent without radiation ($p = 0.001$).[111]

In a study on 1,708 premenopausal patients who had undergone mastectomy for stage II or III cancer, the group who received chemotherapy plus irradiation had reduced local/regional recurrence and longer survival in comparison to the group that received chemotherapy alone.[112]

Boyages et al. conducted a meta-analysis of published studies to identify the factors that may be predictive of local recurrence after management of ductal carcinoma in situ by mastectomy, conservative surgery (CS), or conservative surgery plus radiation therapy (RT). The analysis yielded a summary recurrence rate of 22.5 percent (95% CI = 16.9-28.2) for studies using CS alone, 8.9 percent (6.8-11.0) for CS plus RT, and 1.4 percent (0.7-2.1) for studies involving mastectomy alone. Local recurrence among patients treated by CS alone was approximately 20 percent, and one-half of the recurrences were invasive cancers. For most patients, RT reduced the risk of recurrence after CS alone by at least 50 percent.[113]

Three additional studies [80, 114, 115] also showed that adjuvant radiation therapy reduced recurrence and death rates.

7.10 Tamoxifen

Muss[116] conducted a meta-analysis of randomized trials to determine if tamoxifen improves relapse-free and overall survival for postmenopausal women, including those older than age 70 years. Tamoxifen therapy was shown to significantly decrease the annual odds of recurrence (28 percent) and death (21 percent) in women over 70. The reduction was seen in both estrogen-receptor positive (36 percent decrease) and estrogen-receptor negative (16 percent decrease) patients. Over two years of tamoxifen therapy was also associated with greater benefit. Horobin et al. found that 113 patients aged 70 and older treated with tamoxifen alone had an actuarial five-year survival rate of 49.4 percent. Of the 38 women who had a complete response, the rate was 92 percent.[117]

In a study on patients diagnosed in 1974 and 1984, tamoxifen was recommended in the 1984 group for postmenopausal women with involved lymph nodes or lymphatic, vascular, or neural invasion unless their tumors were negative for estrogen receptors. The seven-year disease-specific survival for women from 50 to 89 years in 1984 ($n = 977$) was 70.4 percent compared to 63.2 percent in the 1974 group ($n = 711$). The actuarial overall survival seven years after diagnosis for the 50 to 89 group diagnosed in 1984 ($n = 986$) was 58.3 percent compared to 56 percent for the 1974 group ($n = 717$).[110]

In comparing chemotherapy alone and chemotherapy plus tamoxifen, Taylor et al. found that disease-free survival favored chemotherapy plus tamoxifen, but overall survival rates did not

differ.[97] Fisher and Redmond, in a study on 2,844 estrogen receptor positive patients, compared postoperative tamoxifen for five years to placebo. The tamoxifen group had a significant improvement in disease-free survival (82 percent vs. 72 percent at five years; $p < 0.000005$) regardless of age, surgery type, tumor size, ER status, or PR status. There was no significant difference in overall survival.[118] The Scottish Cancer Trials Breast Group found that adjuvant tamoxifen given for a minimum of five disease-free years had a beneficial effect overall and in both premenopausal and postmenopausal node-negative patients.[119]

Comparisons of two vs. five years of tamoxifen therapy have shown that the longer treatment interval increases time to relapse, but treatment over five years does not appear to make a difference. In a comparison of two years versus five years of tamoxifen treatment in women 50 years and older, patients who received the longer treatment demonstrated a statistically significant delay in the time to relapse.[120] After five years of tamoxifen treatment, a group of 194 patients was randomized to continue tamoxifen or be in an observation group. At five years after randomization no statistically significant differences were noted in either time to relapse or survival between the two groups.[121]

7.11 Miscellaneous

Numerous prognostic indicators for breast cancer have been studied. Table 13 lists other predictors that were encountered during this review, as well as citations of the articles which found the indicators significant or non-significant in relation to disease-free or overall survival.

Table 13. Miscellaneous prognostic factors studied for effect on breast cancer survival		
Prognostic Indicator Examined	Significant	Non-Significant
[3H]thymidine labeling index	[89]	
Absence of axillary lymph node dissection		[80]
Body Mass Index	[97, 102, 122]	
Conservative vs. radical surgery	[88, 96]	[9, 43-45, 56, 76, 80, 87, 90, 123]
Distant Metastases	[35, 92]	
Estrogen Replacement Therapy	[124]	[125]
Ethnicity	[122, 126]	
Extensive Intraductal Component	[59]	
Fibrotic Focus	[100]	
HER-2/neu gene		[88]
Histological Type		[73, 80, 87]
Low levels of serum albumin and hemoglobin	[122]	
Lymphatic Vessel Invasion	[59, 86]	
Marital Status	[31]	[25]
Microcalcifications		[88]
Mitotic activity status	[95, 96]	
Table 13. Miscellaneous prognostic factors studied for effect on breast cancer survival (cont.)		
Noninflammatory v. inflammatory	[82]	
Nuclear atypia	[88, 100]	
Oral contraceptives	[93]	[87, 127]

p53		[88, 89]
Palpability		[88]
Patients meeting high-dose consolidation chemotherapy criteria	[128]	
Phenotype A		[129]
Phenotype B	[129]	
Ploidy	[95]	[88]
Post-op MTX 5-FU followed by leucovorin	[118]	
Response to Chemotherapy	[44]	
Site of Metastasizing	[44]	
Skin/Fascia/Nipple Invasion	[99, 100]	
S-phase		[88]
Symptoms present at initial diagnosis	[80]	
Tumor Location		[43]
Tumor necrosis	[97, 130]	
Urinary neopterin	[92]	
Year of diagnosis		[88]

8. Conclusion

There has been little effort to develop standards to recommend the appropriate timing of surgical treatment for patients with breast cancer. This is despite the fact that longer delays between the onset of symptoms and diagnosis or treatment are associated with worse survival rates, except for those with stage I disease. Patients with a longer duration of symptoms tend to present with larger tumors and with a more advanced stage of disease. In addition, the presence of symptoms other than a lump has been shown to be associated with poorer survival in breast cancer patients.

Although studies differ in their conclusions regarding the impact of delay in treatment for breast cancer, there is no doubt that the time between diagnosis and treatment of breast cancer can be very stressful for women. Insomnia, mood disturbances, depression, and tension have been identified as primary problems facing preoperative breast cancer patients. Tension and depression appear to be reduced once surgery has taken place; therefore, every effort should be taken to ensure a short waiting period for surgical treatment.

Stage of disease and tumor size are primary predictors of disease-free and overall survival in breast cancer patients, further indicating the need for prompt diagnosis and surgical treatment. Other significant prognostic indicators include age, axillary lymph node involvement, histopathologic grade, margins of resection, the type of adjuvant therapy used, among many others. Some of the more promising indicators of survival that are beginning to be examined involve genetic factors.

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Breast Cancer Literature Review Appendix A: Search Terms

Relevant literature was obtained through electronic database searches of Medline, Best Evidence, Cochrane Library, LegalTrac, CancerLit, and HealthSTAR. The following search terms and limitations were used to retrieve citations.

Medline:

The Medline search was limited to articles published between 1989 and 2000 (unless otherwise noted). Articles were included if they were written in English, or had an English abstract. The following subject headings were combined with breast neoplasms* not mass screening* not population surveillance using an “and” connector.

The majority of terms were “exploded” to include all narrower terms. When exploded searches yielded a more than a hundred articles, the strategy was modified to “focus” the search to limit the search to those articles in which the subject heading is considered the major point of the article. In the list of search terms an asterisk refers to a focused search whereas “exp.” refers to an exploded strategy. For example “cost-benefit analysis* or (exp. 1999-2000) refers to the focused search for age factors for the years 1989-2000, combined with (or) an exploded search of age factors for the years 1999-2000.

- Absenteeism
- Activities of daily living*
- Age factors*
- Age of onset* or (exp. 1999-2000)
- Aging*
- Consensus development conferences
- Cost allocation
- Cost-benefit analysis* or (exp. 1999-2000)
- Cost control
- Cost savings
- “Costs and cost analysis”*
- Decision making*
- Decision support techniques* (1996-2000)
- “Delay\$”
- Delivery of health care* (1999-2000)
- Disability evaluation
- Disease management
- Disease progression* or (exp. 1999-2000)
- Economic value of life
- Employment
- Evaluation studies* (1999-2000)
- Geriatric assessment
- Health care costs*
- Health care rationing
- Health planning*
- Health priorities
- “Health services needs and demand”*
- Health status*
- Health status indicators
- Jurisprudence
- Karnofsky performance status
- Liability, legal
- Life expectancy
- Malpractice
- Medical futility
- Models, theoretical* (1998-2000)
- Mortality* (1999-2000)
- Multivariate analysis* or (exp.1999-2000)
- Neoplasm staging*
- Nutritional status
- “Outcome and process assessment (health care)”*
- “Outcome assessment (health care)”*
- Pain* (1997-2000)
- Pain measurement
- Patient acceptance of healthcare* (1999-2000)
- Patient satisfaction*

- Patient selection*
- Policy making
- Practice guidelines*
- Predictive value of tests*
- Preoperative care*
- Quality-adjusted life years
- Quality of life* (1999-2000)
- Questionnaires*
- Reference standards
- “Referral and consultation”*
- Reoperation* or (exp.1999-2000)
- Risk factors (exp.1999-2000 & review articles)
- “Self assessment (psychology)”
- Severity of illness index* or (exp.1999-2000)
- Sex factors* or (exp.1999-2000)
- Sick leave
- Socioeconomic factors* (review articles)
- Surgical procedures, elective
- Surgical procedures, operative (economics, standards, statistics & numerical data, trends, utilization, mortality)* (1998-2000)
- Survival analysis* or (exp.1999-2000 & review articles)
- Survival rate* or (exp.1999-2000 & review articles)
- Time factors* or (exp.1999-2000 & review articles)
- Treatment failure (1999-2000)
- Treatment outcome*
- Waiting lists
- Work capacity evaluation

Best Evidence:

Records from 1991 to issue 4/1999 were searched using the following terms:

- Breast cancer
- Waiting lists
- Rationing

CancerLit:

The records from 1989 to January, 2000 were searched using the following terms:

- Breast cancer
- Delay
- Wait
- Pregnant/pregnancy
- Disease Progression

Cochrane Systematic Reviews:

Issue 4/1999 was searched using the following terms:

- Breast cancer
- Waiting lists
- Rationing

LegalTrac

Publications from 1980 to March, 2000 were searched using the following terms:

- Breast cancer
- Cancer
- Cancer – care and treatment

HealthSTAR:

The records from 1975 to January, 2000 were searched using the following terms:

- Breast neoplasms
- “Delay\$”
- Health care rationing
- Health priorities
- “Prioritisation”
- “Prioritization”
- Surgery
- Time factors
- Waiting Lists
- Outcome
- Quality of life
- Guidelines
- Time factors
- Survival

Websites:

Information from the following websites was used in this review:

NIH Consensus Development Program: Consensus Statements
Treatment of Early Stage Breast Cancer
http://odp.od.nih.gov/consensus/cons/081/081_intro.htm

American College of Radiology
Standard for Diagnosis and Management for Invasive Breast Carcinoma
www.acr.org/departments/stand_accred/standards/html_standards/html_files/collaborative/invas_breast_carc.html

National Health and Medical Research Council (Australia)
Clinical Practice Guidelines For The Management Of Early Breast Cancer: Second Edition (1999)
<http://www.health.gov.au/nhmrc/advice/pdfcover/eabrscof.htm>

University of California Cancer Consortium Breast Cancer Clinical Pathways Committee
Practice Guidelines for Breast Cancer
cancer.mednet.ucla.edu/CancerJournal/html/breast.htm

Scottish Intercollegiate Guidelines Network
Breast Cancer in Women - A National Clinical Guideline
www.show.scot.nhs.uk/sign/html/Html29.htm

Breast Cancer Literature Review Appendix B: Summary of Survival Rates

The following table summarizes the survival rates noted in the articles reviewed.

n	Year of analysis	Disease-Free	Overall	Observed	Relative	Crude	Actuarial Local Control	Absolute	Metastases-Free	Actuarial	Variable (if any)	Reference
	1			89%	91%							[71]
416	1	98%										[11]
	3			75%	79%							[71]
416	3	88%										[11]
	5		63%								Diagnosed 1986-90	[35]
	5			64%	71%							[71]
692	5		81%									[103]
416	5	77%										[11]
4,051	5		83%									[69]
471	5						93%	82%				[66]
6,185	5		84%						76%		Invasive ductal cancer stages I-III	[84]
508	5	88%	86%								Stages I and II	[10]
	5	94%	93%								Stage I	[10]
	5	84%	81%								Stage IIA	[10]
	5	67%	66%								Stage IIB	[10]
283	5	41%									>= 10 pos. nodes; doxorubicin treatment	[85]

n	Year of analysis	Disease-Free	Overall	Observed	Relative	Crude	Actuarial Local Control	Absolute	Metastases-Free	Actuarial	Variable (if any)	Reference
2,163	5				80%	69%					White patients, 1981	[104]
283	7	37%									>= 10 pos. nodes; doxorubicin treatment	[85]
2,163	7				77%	62%					White patients, 1981	[104]
	8		51%								Diagnosed 1986-90	[35]
	10			47%	59%							[71]
471	10						87%	66%				[66]
6,185	10		71%						66%		Invasive ductal cancer stages I-III	[84]
407	10	70%	71%								Node -; surgery alone	[9]
508	10	75%	70%								Stages I and II	[10]
	10	90%	86%								Stage I	[10]
	10	67%	60%								Stage IIA	[10]
	10	26%	24%								Stage IIB	[10]
435	10									80%	Invasive Cancer	[8]

* Patients are assumed to have received surgery and adjuvant therapy according to guidelines unless otherwise noted.

Breast Cancer Literature Review Appendix C: Articles Related to Delay Affecting Survival

Reference	Title	Methods summary	n=	Comments
Afzelius, [22]	Patient's and doctor's delay in primary breast cancer. Prognostic implications	In a study of patients with primary breast cancer, patient's and doctor's delay were examined in relation to age, tumor size, grade of anaplasia, and number of positive lymph nodes.	7,608	Overall, when corrected for age, the prognostic value of delay in terms of mortality increased by 24% for a long patient's delay compared to a shorter and by 13% for a short doctor's delay compared to a longer.
Charlson, [40]	Delay in the treatment of carcinoma of the breast	The prognostic impact of pretreatment delays was examined in an inception cohort of patients with carcinoma of the breast.	685	Patients with delays of three months or more had a more advanced clinical stage than those with shorter delays; however, within each stage, prognosis was not affected by delay. Patients with delays of three months or more had a worse over-all prognosis than those with short delays because they had a less favorable distribution by anatomic stage and they had more adverse changes in clinical state. Nonetheless, progression of disease did not invariably occur among patients with longer delays. Patients with long delays, but without adverse changes had an excellent prognosis.
Dennis, [42]	Analysis of survival and recurrence vs. patient and doctor delay in treatment of breast cancer	Patients with cancer of the breast treated with radical mastectomy were reviewed.	237	Coefficients of correlation between patient's and doctor's delay vs. survival were not significant at $p < 0.05$. No significant relationship between delay and time of recurrence was found.
Dohrmann, [32]	Symptom duration, tumor staging and survival in patients with carcinoma of the breast (Abstract)	Between 1950 and 1980, patients were operated upon for carcinoma of the breast. Symptom duration data were available for 402 patients. Fifty-three of the patients had preoperative symptoms for less than one week; 113, for one week to one month; 144, for one to six months and 92, for six months or more.	435	With increasing preoperative symptom duration, there was an increase in the incidence of Stage IV tumors, $p = 0.003$, and a reduction in Stage I tumors, $p = 0.006$. Cancer specific survival time was better for the total patient series and for those treated by potentially curative operation when symptoms had been present for one week or less as compared with those who had symptom duration of six months or more, $p = 0.007$.

Reference	Title	Methods summary	n=	Comments
Elwood, [27]	Delay in diagnosis and long-term survival in breast cancer	The records of all women with a histologically confirmed primary breast neoplasm who received their primary treatment at the main referral center in British Columbia and were diagnosed in the years 1945, 1950, 1955, 1960, 1965, 1970, or 1975 were reviewed.	1591	An analysis of survival from the date of first symptom showed that long-term survival was greater in patients with a shorter delay between the appearance of symptoms and diagnosis.
Feldman, [28]	The effects of patient delay and symptoms other than a lump on survival in breast cancer	Examined the relationship of survival in breast cancer to delay in treatment and the presence of symptoms. Data were analyzed for patients diagnosed from 1975-1979 at 15 hospitals in one city.	664	Delay was associated with poor survival for patients with Class III disease. The presence of symptoms other than a lump was associated with longer delays and poorer survival in patients with Class II and III disease.
Fisher, [39]	A perspective concerning the relation of duration of symptoms to treatment failure in patients with breast cancer	Measures of association between the duration of symptoms and 7 clinical and 33 histologic characteristics in patients with clinical stage I and II invasive cancer were performed.	1,539	The relative frequency of highly malignant (histologic grade 3) cancers and tumor necrosis decreased when the duration of symptoms exceeded 9 mo. However, tumor size, clinical stage II disease, nipple involvement, and microscopic evidence of involvement of the skin overlying the tumor were significantly increased with longer periods of duration of symptoms. There was a trend toward a reduction in treatment failure rate in patients whose symptoms period was greater than 9 mo.
Machiavelli, [41]	Relation between delay and survival in 596 patients with breast cancer	Evaluated the influence of delay between first symptom and first treatment upon survival. The medical records of patients with breast cancer were reviewed.	596	Patients in the less than 3 months delay group had a better distribution by clinical stages and a 10-year survival rate higher than those in the longer delay groups ($p = 0.034$). However, within each stage no statistically significant difference in survival according to delay was observed. A Cox multivariate analysis revealed that performance status and stage of disease were independent predictors of survival, but not delay.

Reference	Title	Methods summary	n=	Comments
Neale, [31]	Marital status, delay in seeking treatment and survival from breast cancer	Examined 10-year survival following a breast cancer diagnosis among women after adjusting for the effects of age, socio-economic status (SES), stage of disease and delay in seeking treatment for symptoms.	1261	Marital status, age, SES, delay, and stage were all univariate predictors of survival.
Neave, [23]	Does delay in diagnosis of breast cancer effect survival?	Breast cancer patients in the Auckland regional area were divided into two major groups according to delay in diagnosis greater or less than six weeks.	1675	Overall there was no difference in survival, although the variables tumor size, skin attachment, and nipple retraction were more common in the group with longer delay, and grade III tumors in those with short delay. Three important prognostic variables (the presence of tumor steroid receptors, positive axillary nodes, and distant metastases at diagnosis) were equally distributed and had a similar effect on survival within the two delay groups. However, in a subgroup of women with negative axillary nodes, short delay was associated with poorer survival, independent of tumor size.
Quiet, [38]	Natural history of node-negative breast cancer: a study of 826 patients with long-term follow-up	Examined the long-term outcome of patients with node-negative breast cancer to address the following questions: (1) Is node-negative breast cancer a disease that is curable by local modalities? (2) Are there predictors of disseminated disease in node-negative breast cancer? (3) Are there subgroups of tumors that have different times to recurrence?	826	Delay did not cause significant differences in survival.

Reference	Title	Methods summary	n=	Comments
Richards, [26]	The influence on survival of delay in the presentation and treatment of symptomatic breast cancer	Examined the possible influence on survival of delays prior to presentation and/or treatment among women with breast cancer. Duration of symptoms prior to hospital referral was recorded for women who presented with any stage of breast cancer to one hospital between 1975 and 1990. The impact of delay on survival was measured from the date of diagnosis and from the date when the patient first noticed symptoms to control for lead-time bias.	2964	Survival measured both from the date of diagnosis ($p < 0.001$) and from the onset of the patient's symptoms ($p = 0.003$) was worse among women with longer delays. Multivariate analyses indicated that the adverse impact of delay in presentation on survival was attributable to an association between longer delays and more advanced stage. However, within individual stages, longer delay had no adverse impact on survival.
Richards, [37]	Influence of delay on survival in patients with breast cancer: a systematic review	Identified 87 studies with direct data linking delay (including delay by patients) and survival. Tested the main hypothesis that longer delays would be associated with lower survival, and a secondary hypothesis that longer delays were associated with more advanced stage, which would account for lower survival.	101,954	Delays of 3-6 months were associated with lower survival.
Robinson, [30]	Delay in diagnosis of cancer. Possible effects on the stage of disease and survival	New cancer patients were referred to the Northern Israel Oncology Center in 1974 and in 1980. The stage of disease, delay in diagnosis, the responsibility for the delay, and the survival of those referred in 1974 were investigated.	2299	Only in the breast cancer group without delay in diagnosis, however, were there significantly more patients at an early stage than at an advanced stage of disease.

Reference	Title	Methods summary	n=	Comments
Rudan, [43]	Breast cancer prognosis. I. Prognostic factors in patients with node-negative (N0) breast cancer	Predictors of breast cancer survival were investigated among node-negative breast cancer patients treated at one facility between 1969-1988. Selected prognostic factors included patient age, delay in treatment, tumor size, histologic grade of malignancy, estrogen receptor status, progesterone receptor status, tumor site, and type of surgical treatment.	196	Among these predictors, only tumor size and pathohistologic grade of malignancy caused significant differences in 5-year overall survival rates. Delay did not significantly affect survival.
Rudan, [45]	Breast cancer prognosis. II. Prognostic factors in patients with node-positive (N1-3) breast cancer	Predictors of breast cancer survival were investigated among node-positive (N1-3) breast cancer patients treated at one facility between 1969-1988. Selected prognostic factors included patient age, delay in treatment, tumor size, type of lymph-node affection, pathohistological grade of malignancy, estrogen receptor status, progesterone receptor status, tumor site, and type of surgical treatment.	282	Among these predictors, only tumor size, type of lymph-node affection, malignancy grade, and progesterone receptor status revealed a significant impact on a 5-year overall survival rates. Delay did not significantly affect survival.

Reference	Title	Methods summary	n=	Comments
Rudan, [44]	Breast cancer prognosis. III. Prognostic factors in patients with distant metastases (M1) at the time of diagnosis	Predictors of breast cancer survival were investigated among patients who had distant metastases at the time of diagnosis (M1). All of these patients were treated at one facility between 1969-1988. Selected prognostic factors included patient age, delay in treatment, tumor size, type of lymph node affection, response to palliative surgical treatment and administered chemotherapy or hormonal therapy, and site of metastasizing.	66	The most important predictor was the response to chemotherapy ($p < 0.001$), followed by site of metastasizing ($p < 0.05$) and primary tumor size ($p < 0.05$). Palliative surgical treatment, apart from improvement of life quality, played no role in determining the survival among breast cancer patients with a distant disease. Delay in treatment was not a significant predictor.
Sainsbury, [35]	Effect on survival of delays in referral of patients with breast-cancer symptoms: a retrospective analysis	Conducted a retrospective analysis of patients with breast cancer listed in the Yorkshire Cancer Registry. Data on delay after family-physician referral, hospital visit, and start of treatment were available, as well as on tumor grade and stage of presentation.	36,222	There was no evidence that provider delays of longer than 90 days adversely influenced survival. Patients who presented early and were treated in less than 30 days had significantly worse outcomes
Sheridan, [29]	The effects of delay in treatment of survival rates in carcinoma of the breast	Analyzed cases to see whether any significant statistical evidence could be obtained showing that a delay in the institution of treatment injures the chances of the patient, and to explore why and where such delays may occur.	1840	Survival ratios for Stage I patients with delay of less than four weeks were low and very similar to Stage I patients with delay of over 9 months. Patients in this group with delays of 5 weeks to 9 months had better survival rates. For Stage II patients, those with delays of less than 4 weeks had the best survival rates, and patients waiting over 9 months had the worst survival.

Reference	Title	Methods summary	n=	Comments
Vernon, [33]	Ethnicity, survival, and delay in seeking treatment for symptoms of breast cancer (Abstract)	Examined differences in 10-year survival rates from breast cancer among white, black, and Hispanic women controlling for the effects of age, socioeconomic status, stage of disease, and delay in seeking treatment for symptoms. Breast cancer patients treated at one facility between 1949 and 1968 were followed for 10 years.	1983	Ethnicity, SES, stage of disease, and delay were all found to affect survival when considered separately. Black patients were less likely to survive than either white or Hispanic patients whose survival experience appeared to be similar. Multivariate analysis that used a Cox regression technique showed that ethnic differences remained when age, SES, stage, and delay were included in the model. In contrast, the authors could not detect an effect of delay on survival when ethnicity and all other variables were included.
Wilkinson, [25]	Delay, stage of disease and survival from breast cancer	Reviewed breast cancer cases reported in a local tumor registry to examine the effect of delay, age, availability of physicians, stage of disease, and marital status upon length of survival.	1784	Regression analysis showed stage of disease, length of delay, and age to be significant predictors of survival. Delay by patients was found to affect survival through its influence upon the extent of disease at the time of diagnosis.

Breast Cancer Literature Review Appendix D: Quality of Life Measurement Tools

The following table documents the quality of life measurement tools mentioned in the literature reviewed

Tool	Worst – Best	Description	Details – Subscales
Profile of Mood States (POMS)	204 - -32	Patients rate themselves for each adjective on a five-point scale ranging from 0 (not at all) to (extremely) to describe how they have been feeling during the previous week. The positive factor of vigor creates a reverse scored subscale, making the range of possible scores 204 to -32.	A list of 65 adjectives measuring five negative mood factors (tension-anxiety, depression-dejection, anger-hostility, fatigue, and confusion-bewilderment) and one positive mood factor (vigor). Internal consistency reliability coefficients range from 0.87 to 0.95 for the various subscales of the POMS. Test-retest reliability for the scales range from 0.65 to 0.74.
McCorkle and Young Symptom Distress Scale (SDS)	50 - 10	Responses are made on a five-point Likert scale of 1 (best) to 5 (worst), providing a total possible score of 10 to 50.	Assesses ten symptoms: nausea, loss of appetite, insomnia, pain, mobility, bowel pattern, fatigue, loss of concentration, changes in appearance, and mood.

Breast Cancer Literature Review Appendix E: Scores Used For Calculation in Table 11.

Preoperative Profile of Mood States (POMS) scores used to calculate the “all” category in Table 11			
Scales	All Patients Mean (SEM)	All Patients Mean (SD)	All Patients Mean (SD)
n	51	36	22
Anger-hostility	6.43 (0.92)	5.90 (8.91)	12.95 (12.92)
Confusion-bewilderment	9.02 (0.85)	5.53 (5.69)	11.15 (6.87)
Depression-dejection	12.31 (1.54)	13.37 (12.50)	18.95 (15.01)
Fatigue	7.92 (0.94)	10.33 (7.11)	9.2 (6.43)
Tension-anxiety	16.76 (1.29)	12.97 (8.01)	19.35 (8.04)
Total mood disturbance	36.90 (5.31)	Not reported	58.8 (46.22)
Vigor	15.55 (0.93)	10.10 (6.18)	12.8 (6.04)
Reference	[60]	[64]	[63]

