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Assessment of Breast Cancer Treatment Delay Impact on Prognosis and Survival: a Look at the Evidence from Systematic Analysis of the Literature

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Abstract

Introduction: Breast cancer has remained the most commonly diagnosed disease among women globally. Despite the advancement in biomedical sciences leading to improve survival outcomes, some patients endure longer wait periods prior to initiation of treatment.

Objective: To elucidate the impact of treatment delay on breast cancer patient's quality of life and survivorship. Second was to determine the optimal length of time (delay) between breast cancer diagnosis and start of first treatment in order to improve prognosis and general health and well-being of survivors.

Methods: Systematic search of the literature was conducted across five electronic databases: Pub Med, EMBASE, CINAHL, Scopus and Science Direct as well as the reference list of all articles retrieved.

Results: A total of 33 articles were included in the evidence based systematic review, which comprised of 255,366 observations. The results of the studies were categorized under five main themes as: study characteristics, cancer staging and classification, treatment delay time definition and interval, treatment regimen classification and delay impact on quality of life and survival. Analyzed wait times from diagnosis to the initiation of first therapy ranged from 7 days to a period of over 180 days. Combinations of standardized treatment including loco-regional radiotherapy, systemic chemotherapy surgery as well as hormonal therapy were examined. Even though some of the studies showed mixed results, overall, findings indicated that early detection, diagnosis and initiation of treatment within 90 days increase survival.

Conclusions: Evidence revealed that delaying the initiation of treatment for breast cancer more than 90 days after diagnosis has a detrimental effect on disease free and overall well-being of survivors.

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Keywords

- Breast cancer
- Treatment delay
- Treatment initiation
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ABBREVIATIONS

AJCC: American Joint Committee on Cancer; NBCCEDP: National Breast and Cervical Cancer Early Detection Program; SEER: Surveillance and Epidemiology End Results; TDT: Treatment Delay Time; TNM: Tumor, Nodes and Metastases; UK: United Kingdom; USA: United States of America; WHO: World Health Organization

INTRODUCTION

Breast cancer has remained the most commonly cancer diagnosed among women globally, although incidence rates in developed nations have been stable since 2003 [1-3]. While incidence rates are higher in Western countries, death rates are far much higher in developing countries such as those in Sub-Saharan Africa [1]. Overall, developing countries account for

approximately 50% of all breast cancer incidences and more than 60% mortalities annually [1].

In spite of advances in medical technology in most developed countries leading to early diagnosis and treatment, racial and ethnic breast cancer disparities in stage at presentation and treatment outcomes continue to widen. These disparities have mainly been attributed to organizational, structural, socioeconomic and sociopolitical underlying forces of the health care system [4-7]. For instance, studies investigating the geographical differences in late stage presentation of breast cancer in the developed world have shown that women living in areas of high socioeconomic disadvantage were more likely to be diagnosed at late stage of the disease resulting in poor treatment outcomes and survival [4,5]. In developing countries, delay in diagnosis and treatment has mainly been attributed to lack of human and financial resources to ensure timely diagnosis and treatment. Other factors include: lack of knowledge on breast cancer, family history and denial or superstition of the disease, access to affordable medical care and appropriate optimal resources for effective treatment [8-13].

Even though breast cancer treatment is multifaceted, in developed countries improvement in survival for patients have been attributed to sustainable medical programs that promote screening, early diagnosis and treatment [14]. Notwithstanding the increased outcomes in survival, cancer patients sometimes experience long wait times before initiation of first treatment or therapy [14-16]. There are two major types of delay. These are patient and system or provider or doctor delay. Patient delay refers to the period from first onset of symptoms to first medical consultation. System or provider delay is defined as the period from first consultation to definite diagnosis and treatment [15,17]. Although the impact of delay in starting cancer treatment after diagnosis is poorly defined, it is well known that early diagnosis and treatment influence better prognosis and overall quality of life of patients. As a result, any of these delays, may result in adverse prognosis for women with breast cancer [15,17-19].

According to the World Health Organization (WHO), early diagnosis of cancer greatly increases the chances for successful treatment for cancers such as breast, cervix, mouth, larynx, colon and rectum and skin [20]. Nonetheless, the optimal timing between breast cancer diagnosis and beginning of treatment are still uncertain. The purpose of this critical review was to conduct a qualitative analysis of published literature in English language on how time duration from the first presentation of breast cancer (diagnosis) to the start of first treatment affect recovery. The optimal goal was to elucidate the impact of treatment delay on breast cancer patient's quality of life and survivorship. In addition this evidence based systematic review tries to determine the optimum length of time (delay) between breast cancer diagnosis and start of first treatment in order to improve prognosis and general health and well-being of survivors.

MATERIALS AND METHODS

Search terms and databases

Systematic search was performed across the following databases. Pub Med (1951-2014), EMBASE (1966-2014), CINAHL (1982-2014), Scopus (1960-2014) and Science Direct (1997-2014) with the following keywords: "breast cancer" OR "breast neoplasm's" OR "breast tumor" AND "treatment delay" OR "treatment initiation" AND "survival" OR "survivors". In addition, secondary references were retrieved within the reference lists of publications that were included for review.

Eligibility criteria and study selection

Studies were considered eligible if they were in English language, included adult women, were peer-reviewed original research articles, included quantitative comparisons, and investigated the effect of treatment delay on recovery, recurrence and survival. Studies were removed during initial screening if they failed to meet any of these criteria. All returned citations across the searched databases were initially screened for duplicates, then for relevance by title and abstract.

RESULTS

Study selection

A total of 1,022 articles were retrieved from the following five databases: Pub Med, CINAHL, EMBASE, Scopus and Science Direct. Five additional articles were identified from other sources such as reference list and Google scholar search. After eliminating duplicates, 790 remained. After screening the abstracts for relevance, 557articleswere eliminated. Full text screenings of the remaining 233 articles/studies were conducted using the established inclusion criteria. A second thoroughly review of the studies further reduced the number to 105 after reading all articles. A total of 33 studies [21-53] were included in the evidence based systematic review, which included 255,366 observations (see Figure 1 for articles included based on eligibility criteria). The results of the final 33 studies were categorized under these main themes: (1) study characteristics, (2) cancer staging and classification, (3) treatment delay time definition and interval, (4) treatment regimen classification and (5) delay impact on quality of life and survival.

Study characteristics

Table 1 presents the study characteristics. Majority of the published studies were from the United States of America (USA), a total of ten [23,28,32,33,35,38,41-43,48]. There were six studies from Canada [29,37,49-52], three from Italy [22,24,26]. There were two studies from Korea [47,53], United Kingdom (UK) [39,45] and Turkey [21,44]. One study each was published from these countries; Denmark [25], Germany [27], Egypt [30], France [31], Sweden [36], Malaysia [40], Spain [34] and China [46]. Sample sizes in the studies ranged from 96 to 147,682. Patients of all ages were included in 28 of the studies [21-29,31,32,34-41,44-47,49-53], which comprised more than two thirds of the included studies. Three studies [33,42,43] included women 65 years and over while adolescents and young adults [48] and premenopausal women [30] had one each. All the studies included in this review used existing/secondary data sources such as cancer registry and surveillance and epidemiology end results (SEER) databases.

Breast cancer staging and classification

Cancer staging is done at the time of diagnosis, in order to determine the best therapy or treatment and/or measure

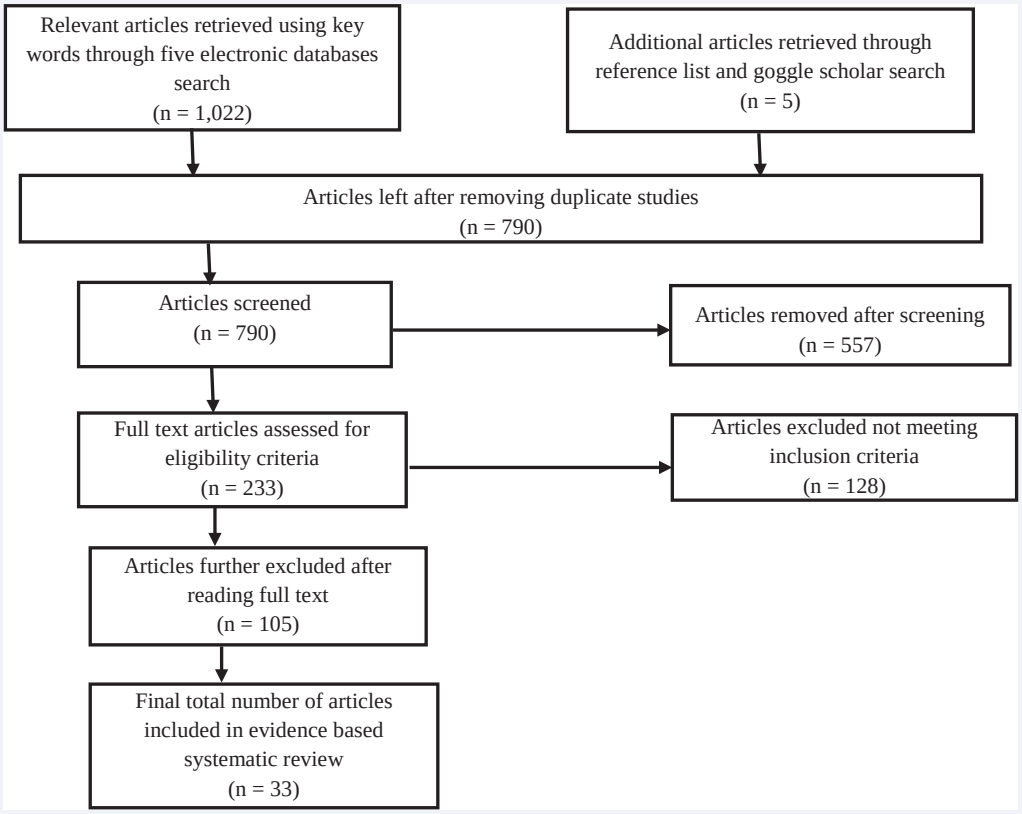

Figure 1 Flow Diagram of Study Eligibility Criteria for Inclusion and Exclusion.

Table 1: Data Source, Sample Population, Size and Country of Study.

Author and Year	Database Source	Study Population	Sample Size	Country
Alkis et al. 2011 [21]	Ankara Oncology Research and Training Hospital	Breast cancer patients who received chemotherapy between January 1995 and August 2002	642	Turkey
Barbieri et al. 2011 [22]	Regional Cancer Center of Basilicata	Patients diagnosed with breast cancer and treated with breast conserving surgery and radiotherapy between January 2000 and December 2006	387	Italy
Brazda et el. 2010 [23]	Parkland Memorial Hospital and The Simmons Comprehensive Cancer Center	Patients undergoing breast cancer treatment between August 2005 and December 2008	1,337	USA
Cefaro et al. 2007 [24]	Radiation Oncology Department in Chieti	Women diagnosed with early breast cancer between January 1, 1997 and December 31, 2001	969	Italy
Cold et al. 2005 [25]	Danish Breast Cancer Cooperative Group	Patients who received chemotherapy within 3 months of surgery between 1977 and 1999	7,501	Denmark
Colleoni et al. 2000 [26]	The International (Ludwig) Breast Cancer Study Group (IBCSG) Trial V	Premenopausal women with estrogen receptors (ER-) absent tumors diagnosed between 1978 and 1993	1,788	Italy
Corradini et al. 2014 [27]	Patients medical record and Munich Cancer Registry	Patients diagnosed and treated with breast cancer between 01, January 1990 and 31, December 2006	1,393	Germany
Eastman et al. 2013 [28]	Parkland Memorial Hospital and The Simmons Cancer Center	Patients diagnosed with triple negative breast cancer between January 2004 and January 2011	301	USA

Table 1: Data Source, Sample Population, Size and Country of Study.

Author and Year	Database Source	Study Population	Sample Size	Country
Froud et al. 2000 [29]	Breast Cancer Outcomes Unit (British Columbia Cancer Agency)	women with invasive breast cancer diagnosed between January 1, 1989 and December 31, 1993	1,962	Canada
Ghany 2013 [30]	Department of Clinical Oncology, Ain Shams University Hospital	Premenopausal women diagnosed with early stage breast cancer and ER-absent tumor between January 2005 and August 2008	103	Egypt
Gouy et al. 2005 [31]	Institut Gustave-Roussy	Women diagnosed with invasive breast cancer between January 1985 and October 1995	457	France
Hershman et al. 2005 [32]	Henry Ford Health System Tumor Registry	Women diagnosed with breast cancer between January 1, 1996 and December 31, 2001	472	USA
Hershman et al. 2006 [33]	SEER-Medicare database	Women, aged 65 years and older, who participated in Medicare, who were diagnosed with Stage I or II breast cancer from 1991 to 1999, and who received radiation within 1 year of their diagnosis of breast cancer	24,833	USA
Jara Sanchez et al. 2007 [34]	Breast Cancer Research Group (GrupoEspanol de Investigation en Cancer de Mama [GEICAM])	Patients with breast cancer treated from 1990 to 1997	2,782	Spain
Jung et al. 2011 [35]	University of Pittsburgh Medical Center and the University of Pittsburgh Cancer Institute Breast Cancer Program Physicians	Patients with metastatic breast cancer between January 1, 1999 and June 30, 2008	553	USA
Karlsson et al. 2011 [36]	International Breast Cancer Study Group	Patients treated with breast-conserving surgery to radiotherapy	964	Sweden
Lohrisch et al. 2006 [37]	British Columbia Cancer Agency	Women diagnosed with known pathologic nodal status between 1989 and 1998	2,594	Canada
McLaughlin et al. 2012 [38]	North Carolina Central Cancer Registry	Adult female North Carolina Medicaid enrollees diagnosed with breast cancer from January 1, 2000, through December, 31, 2002	1,786	USA
Mikeljevic et al. 2004 [39]	Northern and Yorkshire Cancer Registry	All female breast cancer patients diagnosed in the former Yorkshire Regional Health Authority area between 1 January1986 and 31 December 1998	7,800	UK
Mujar et al. 2013 [40]	University Malaya Medical Center	Breast cancer patients treated between 2004 and 2005	648	Malaysia
Nixon et al. 1994 [41]	Joint Center for Radiation Therapy	Breast cancer patients treated with conservative surgery and radiation therapy between 1968 and 1985	653	USA
Nurgalieva et al. 2013 [42]	The Surveillance, Epidemiology and End-Results	Women aged 65 years and older who were diagnosed with breast cancer between January1, 1992 and December 31, 2005	14,380	USA
Punglia et al. 2010 [43]	Surveillance, Epidemiology, and End Results Program-Medicare	Women aged 65 and over and diagnosed with breast cancer between 1991 and 2002	18,050	USA
Samur et al. 2002 [44]	Akdeniz University Faculty of Medicine	Breast cancer patients who were diagnosed and treated with adjuvant chemotherapy between 1995-2000	96	Turkey
Shannon et al. 2003 [45]	Royal Marsden Hospital	Patients treated with adjuvant chemotherapy for early breast cancer between January 1990 and June 2001	1,161	UK
Shi et al. 2012 [46]	Cancer Center of Sun Yat-sen University	Patients diagnosed with HER-2-positive advanced breast cancer (H2ABC) between September 2000 and December 2009	128	China
Shin et al. 2013 [47]	Korean Central Cancer Registry	Patients diagnosed and treated between 2006 and April 2011	2,967	Korea
Smith et al. 2013 [48]	California Cancer Registry	Adolescents and young adults (AYAs) breast cancer cases diagnosed from 1997 to 2006	8,860	USA
Vujovic et al. 1998a [49]	London Regional Cancer Center	Patients who were treated with breast-conserving surgery and breast irradiation, without adjuvant systemic therapy between January 1, 1985 and December 31, 1992	568	Canada

Table 1: Data Source, Sample Population, Size and Country of Study.

Author and Year	Database Source	Study Population	Sample Size	Country
Vujovic et al. 2006b [50]	London Regional Cancer Center	Patients with node-negative invasive breast cancer who were treated with breast-conserving surgery and breast irradiation between January 1, 1985 and December 31, 1992	568	Canada
Vujovic et al. 2006c [51]	London Regional Cancer Center	Patients with node-negative invasive breast cancer were treated with breast conservative surgery and breast irradiation without adjuvant chemotherapy between January 1, 1985 and December 31, 1992	584	Canada
Vujovic et al. 2009d [52]	London Regional Cancer Center	Patients with breast carcinoma and treated between January 1, 1985 and December 31, 1992	397	Canada
Yun et al. 2012 [53]	Korea Central Cancer Registry	Patients who were registered in the KCCR from 2001 through 2005	147,682	Korea

Table 2: Definition of Treatment Delay, Treatment Category and Major Findings.

Author and Year	Definition of Treatment Delay Time (TDT)	Treatment Regimen/ Classification	Treatment Delay Interval	Cancer Stage/Type	Main Result or Finding
Alkis et al. 2011 [21]	Chemotherapy treatment stating date after surgery	Adjuvant treatments: (1) only hormonal – [tamoxifen or hormonal treatment], and (2) Chemotherapy + hormonal treatment)	(i) ≤44 days, and (ii) >44 days	TI, TII and TIII	Overall survival was significantly better in patients who received treatment within 44 days after surgery.
Barbieri et al. 2011 [22]	The period from definitive surgery to the day of the first radiation treatment	Radiation therapy	(i) <60 days, (ii) 61-120 days, (iii) 121-180 days, and (iv) > 180 days	T1, and T2NO	Delay had no impact on local relapse-free survival.
Brazda et el. 2010 [23]	Time between date of pathological diagnosis, usually via core needle biopsy, and the date of initial therapy, either surgical or systemic	Not stated	(i) 0-45 days, (ii) 46-90 days, and (ii) >90 days	All stages	No effect on overall survival, and time to treatment may not be a meaningful indicator of cancer care quality.
Cefaro et al. 2007 [24]	Interval between the date of surgery and the first date of radiation treatment	(1) Radiation therapy only, and (2) Radiation therapy + Chemotherapy	[1] Radiation therapy only: (i) <16 weeks, and (ii) ≥16 weeks [2] Radiation therapy + Chemotherapy: (i) >25 weeks, and (ii) ≥25 weeks	Early	No significant difference was found in local recurrence-free survival by surgery radiation interval.
Cold et al. 2005 [25]	Definitive surgery was defined as the date of the most extensive procedure ordinarily including axillary lymph node dissection, and could thus be preceded by a biopsy. Delays of chemotherapy were defined as time from definitive surgery to start of chemotherapy	Adjuvant chemotherapy	(i) 1-3 weeks, (ii) 4 weeks, (iii) 5 weeks, and (iv) 6-13 weeks	I, II and II	No evidence for a survival benefit due to early initiation of adjuvant chemotherapy within the first 2–3 months after surgery.
Colleoni et al. 2000 [26]	Time between definitive surgery and initiation of chemotherapy	Adjuvant chemotherapy	(i) 21 days, and (ii) >21 days	ER-absent tumors	Early initiation of chemotherapy did not significantly improve disease-free survival.
Corradini et al. 2014 [27]	Time interval between the date of surgery (date of first surgery in cases of multiple operations) and the date of first radiation treatment	(1) Radiotherapy plus adjuvant chemotherapy (CT+), and (2) Radiotherapy minus adjuvant chemotherapy (CT-)	CT+: (i) 0-15 weeks vs. ≥24 weeks CT-: (ii) 0-6 weeks vs. ≥7 weeks	0, I, II and III	A delay of radiotherapy was not associated with decreased local control or overall survival in the two groups.
Eastman et al. 2013 [28]	Number of days from pathologic diagnosis (typically via core needle biopsy) to first treatment whether local or systemic	Surgery (partial mastectomy and total mastectomy)	(i) 0–45, (ii) 46–90, and (iii) 90 days	All stages	No significant difference in locoregional recurrence free survival for patients comparing time to treatment of >45 days verses ≥45 days.

Table 2: Definition of Treatment Delay, Treatment Category and Major Findings.

Author and Year	Definition of Treatment Delay Time (TDT)	Treatment Regimen/ Classification	Treatment Delay Interval	Cancer Stage/Type	Main Result or Finding
Froud et al. 2000 [29]	The number of weeks between the final breast conserving surgery date and the commencement of RT	Radiation therapy	(i) 0-5 weeks, (ii) 6-8 weeks, (iii) 9-12 weeks, and (iv) ≥13 weeks	T1, T2, and T3	No statistically significant relationship between ipsilateral breast recurrence and delay interval.
Ghany 2013 [30]	Time between surgery and adjuvant chemotherapy start	Chemotherapy (CT)	(i) >21 days, and (ii) ≥21 days	I, II, and IIIA	Delay of adjuvant CT for more than 3 weeks after definitive surgery in premenopausal patients with early breast cancer stage and ER-absent tumors was associated with poor survival.
Gouy et al. 2005 [31]	Not defined	Adjuvant therapy	Only mean days reported	T2, T3, and T4	Survival was not different in patients.
Hershman et al. 2005 [32]	Not defined	Adjuvant chemotherapy	(i) 1 week, (ii) 2 weeks, and (iii) >2 weeks	I, and II	Delays did not reduce survival.
Hershman et al. 2006 [33]	Not defined	Radiation therapy (RT)	(i) (i) Less than 1 month, (ii) 1-2 months, (ii) (iii) 2-3 months, and (iv) greater than 3 months	(iii) I and II	Early initiation of RT was not associated with survival. Although delays of >3 months are uncommon, they are associated with poor survival.
Jara Sanchez et al. 2007 [34]	The time interval between surgery and chemotherapy	Adjuvant chemotherapy	(i) <3 weeks, (ii) 3-6 weeks, (iii) 6-9 weeks, and (iv) >9 weeks	I, II, IIIa, and IIIb	There was no differences in disease-free survival nor 5-year overall survival.
Jung et al. 2011 [35]	Time in days between the date of diagnosis of initial breast cancer metastasis and the date of the initiation of first treatment. The date of firstmetastatic breast cancer diagnosis was identified as the date of first metastatic biopsy or chemotherapy scan, whichever came first	(1) Chemotherapy, (2) Hormonal therapy, (3) immunologic therapy, (4) vaccine therapy, and (5) biologic therapy	(i) Less or equal to 4 weeks, (ii) more than 4 weeks to less or equal 12 weeks, and (iii) more than 12 weeks	IV	Delays of over 12 weeks in receiving treatment for metastatic breast cancer were related to adverse survival outcomes.
Karlsson et al. 2011 [36]	Not defined	Radiation therapy	Not defined	Not stated	RT interval was not significantly associated with disease-free survival or overall survival.
Lohrisch et al. 2006 [37]	Time between most recent definitive surgery and start of adjuvant chemotherapy	Adjuvant chemotherapy	(i) 0-4 weeks, (ii) >4-8 weeks, (iii) >8-12 weeks, and (iv) >12-24 weeks	I, II and III	Adjuvant chemotherapy is effective up to 12 weeks after definitive surgery.
McLaughlin et al. 2012 [38]	Number of days from biopsy confirmed cancer diagnosis in the North Carolina Central Cancer Registry (CCR) to the day of first record of treatment in either the CCR or claims.	(1) Surgery, (2) Radiotherapy, (3) Chemotherapy, and (4) Hormonal or biologic therapy	(i) 0-29 days, (ii) 30-59 days, and (iii) greater than 60 days	All stages	Waiting greater or equal 60 days to initiate treatment was associated with a significant 66% and 85% increased risk of overall and breast cancer related death, respectively, among late-stage patients.
Mikeljevic et al. 2004 [39]	Date of first surgery to thedate of start of radiation treatment	Radiation therapy	(i) 1–4 weeks, (ii) 5–6, (iii) 7–8, (iv) 9–12, (v) 13–19 and (vi) 20–26 weeks	II, II and III	Delaying the initiation of RT for 20–26 weeks after surgery is associated with decreased survival in patients treated with conservation surgery.
Mujar et al. 2013 [40]	Time between the pathological diagnosis date to the date of primary treatment	(i) Surgery , (2) chemotherapy, (3) hormonal therapy	(i) Less or equal 2 weeks, (ii) more than 2 weeks, (iii) less or equal 1 months, (iv) more than 1 month, (v) less or equal 2 months, and (vi) more than 2 months	All stages	Time to primary treatment after a diagnosis of breast cancer had no impact on overall survival.

Table 2: Definition of Treatment Delay, Treatment Category and Major Findings.

Author and Year	Definition of Treatment Delay Time (TDT)	Treatment Regimen/ Classification	Treatment Delay Interval	Cancer Stage/Type	Main Result or Finding
Nixon et al. 1994 [41]	The time interval between last breast surgery (either excision or reexcision of the tumor, but not axillary dissection if it was performed separately) and the start of radiation therapy	Radiotherapy	(i) 0-4 weeks, (ii) 5-8 weeks, and (iii) 9-12 weeks	I, and II	No significant effect on disease recurrence was noted.
Nurgalieva et al. 2013 [42]	The days from the most definitive resection of the primary site of the first administration of chemotherapy	Adjuvant chemotherapy	(i) >3 months, and (ii) <3 months	I, II and III	Survival was significantly worse for patients who initiated chemotherapy in more than 3 months.
Punglia et al. 2010 [43]	The number of days between the start date and the last breast cancer conserving surgery	Radiation therapy	(i) <6 weeks, and (ii) >6 weeks	0, I, and II	Starting radiotherapy after 6 weeks was associated with absolute increase in local recurrence.
Samur et al. 2002 [44]	Time to surgery was time from initial biopsy to the time of definitive surgery. Time to chemotherapy as time from definitive surgery to the onset of chemotherapy, and time to treatment (total) as time from initial biopsy to the onset of chemotherapy	Mastectomy and adjuvant chemotherapy ±radiotherapy	Surgery: (i) up to 3 days, (ii) 3-8 days, (iii) 8-16 days, (iv) ≥16 Chemotherapy: (i) >35 days, (ii) ≥35 days Total treatment: (i) >43 days, (ii) ≥43 days	Not stated	Delay in surgery up to several weeks has no detrimental effect on outcome. Also, up to several months of delay in chemotherapy does not have a major impact on prognosis and delay should not be a reason for omitting adjuvant therapy.
Shannon et al. 2003 [45]	The time from surgery till the first day of administration of first cycle of treatment	Adjuvant chemotherapy	(i) <21 days and (ii) ≥21 days	Not stated	No significant difference in 5-year disease-free survival.
Shi et al. 2012 [46]	Not defined	Trastuzumab therapy	Not defined	H2ABC	The delayed use of trastuzumab has no negative effect on the overall survival of patients.
Shin et al. 2013 [47]	Time from diagnosis to surgery	Curative surgery	(i) ≤1 week, (ii) >1 to 4 weeks, (iii) >4-8 weeks, (iv) >8-12 weeks, and (v) >12 weeks	Local or regional stage	No clear pattern of increased risk was observed with delays between 4 and 12 weeks.
Smith et al. 2013 [48]	The number of weeks between date of diagnosis and date of definitive treatment. The date of diagnosis was the date of pathologic diagnosis. The date of definitive treatment was the date of (i) earliest definitive surgery and (ii) definitive chemotherapy given as the first course of treatment	3 groups: (1) Surgery only, (2) Surgery and neoadjuvant chemotherapy, and (3) Surgery and chemotherapy	4 groups: (i) less than 2weeks, (ii) 2 to 4 weeks, (iii) 4 to 6 weeks, and (iv) more than 6 weeks	All stages	Young women with breast cancer with a longer TDT have significantly decreased survival time compared with those with a shorter TDT.
Vujovic et al. 1998a [49]	Time intervals between breast surgery and breast irradiation	Breast irradiation (Radiation therapy)	(i) 0-8 weeks, (ii) >8-12 weeks, (iii) >12-16 weeks, and (iv) >16 weeks	T1, and T2N0	Delay in start of breast irradiation beyond 12 and up to 16 weeks does not increase the risk of recurrence in node-negative breast cancer patients.
Vujovic et al. 2006b [50]	The number of days from definitive breast surgery to the start of breast irradiation	Radiation therapy	(i) 0-8 weeks, (ii) >8-12 weeks, and (iii) >12 weeks,	T1, and T2N0	Patients with positive resection margins have higher local recurrence rates that become apparent when breast irradiation is delayed.
Vujovic et al. 2006c [51]	Time intervals between breast surgery and breast irradiation	Breast irradiation	(i) 0-8 weeks, (ii) 8-12 weeks, (iii) 12-16 weeks, and (iv) >16 weeks	T1, and T2N0	No statistically difference between the groups in local recurrence or disease-free survival.

Table 2: Definition of Treatment Delay, Treatment Category and Major Findings.

Author and Year	Definition of Treatment Delay Time (TDT)	Treatment Regimen/ Classification	Treatment Delay Interval	Cancer Stage/Type	Main Result or Finding
Vujovic et al. 2009d [52]	Intervals from the date of clinical presentation to that of definitive surgery	Definitive breast surgery	(i) 0-4 weeks, (ii) >4-12 weeks, (ii) >12 weeks	TI, and T2N0	Intervals greater than 12 weeks to surgery might be associated with decreased survival.
Yun et al. 2012 [53]	The time between the date of cancer diagnosis and the date of the initiation of definitive treatment	Surgery (± radiotherapy or chemotherapy)	(i) Less than 1 month, and (ii) greater than 1 month	Not stated	Regardless of cancer site, surgical patients in low- to medium-volume hospitals showed significantly worse survival. For patients in low- to medium-volume hospitals, treatment delay was associated with worse survival for all types of cancer.

outcome for the patient. There were great variations in the cancer staging system used for the studies included (Table 2). Although majority of the studies clearly stated the staging system such as the American Joint Committee on Cancer (AJCC) tumor, nodes and metastases (TNM) or clinical or pathologic, early or late, other studies did not state it. More than two-thirds (12) of the studies [25,27,30,32-35,37,39,41-43] used the number staging system (0, I, II, III etc.). Eight studies [21,22,29,31,49-52] used the AJCC TNM staging classification. Five studies [23,28,38,40, 48] simply reported using all stages. Four studies [36,44,45,53] did not mention the staging system analyzed. Another two studies (24, 47) reported using early, local and regional breast cancer treatment operable classification while the final two studies [26,46] stated using the hormone receptor status.

Treatment delay time definition and interval

Variation in definition of treatment delay or interval length was evident in the studies. A third of the studies included in this critical review 33.3% (11 out of 33) defined treatment interval as the time period from biopsy and/or diagnosis date to the start of first treatment in general or either in surgery, chemotherapy, radiation, or hormonal therapy [23,25,28,35,38,40,44,47,48,52,53]. Ten studies representing 30.3% of the total number of eligible articles defined it as the interval between the date of surgery and the first date of radiation [22,24,27,29,39,41,43,49-51]. Six other studies (18.2%) defined it as time between surgery and beginning of first chemotherapy treatment [21,26,30,34,37,42]. On the other hand, one study (3%) simply defined it as the interval between surgery and treatment [45] while five studies (15.2%) did not provide any definition of the interval delay used in their assessment [31-33,36,46].

Further, there was a general lack of understanding on what constitute treatment delay interval. Some studies classified the interval period in days, weeks or even months. In spite of this disagreement, more than half of the studies eighteen (55%) defined the interval period in weeks (0 week – more than 26 weeks) [24,25,27,29,32,34,35,37,39-41,43,47-52]. Additional nine (27%) studies [21-23,26,28,30,38,44,45] categorized the delay interval in days (0 day – more than 180 days), while three studies [33,42,53] classified the treatment delay interval between diagnosis and initiation of treatment in months (0 month – greater than 3 months). One (3%) study [31] defined the delay intervals in mean days. Two (6%) studies [36,46] did not provide any information on the treatment delay interval examined. However, after converting all the delay intervals to days, the length of wait period to the initiation of first treatment varies from as low as 7 days to a period of over 180 days.

Treatment regimenclassification

Of the total 33 articles included in the review, ten (30.3%) reported on standard radiation treatment option for breast cancer patients [22,29,33,36,39,41,43,49-51] and nine (27.3%) studies focused on combinations of standardized treatment like surgery, radiation, chemotherapy and hormonal types [21,24,27,35,38,40,44,48,53]. Eight (24.2%) reported on the impact of delaying chemotherapy treatment on survival [25,26,30,32,34,37,42,45] whereas three (9.1%) described the effect of survival in terms of delay of undergoing breast conserving surgery, partial or modified radical mastectomy [28,47,52]. Brazda et al [23] did not provide information of the type of treatment regimen while Gouy et al [31] and Shi et al [46] reported on any kind of adjuvant treatment and hormonal therapy.

Treatment delay impact on quality of life and survival

Although not all studies included in the review mentioned either the cancer stage at diagnosis, defined treatment delay, treatment regiment, or associated treatment delay interval examined, all indicated the impact of breast cancer treatment delay on the patient's quality of life and survival. Of the nine studies that measured the delay interval in days, three noted that delaying the onset of treatment significantly affect overall survival [21,30,38]. The treatment delay wait period analyzed ranged between 21 and 84 days. Six studies reported no statistically difference [22,23,26,28,44,45]. However, three studies that measured the delay in months (0 > 3 months) all started that initiating treatment more than one month after breast cancer diagnosis is significantly associated with poor quality of life and survival [33,42,53]. Results of the eighteen studies that assessed interval delays in weeks (0 - >= 26 weeks) also varies significantly. Whereas ten studies [24,25,27,29,32,34,40,41,49,51] noted no substantial difference between early initiation of treatment and late initiation on recovery, recurrence and survival, seven [35,37,39,43,48, 50,52] reported statistical difference. One study

[47] stated no clear pattern of increased risk was observed in those who initiated early and late treatment.

DISCUSSION

According to the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) benchmark, there should be no more than 60 days between identification of an abnormal or suspicious mammogram screening test and diagnosis, and no more than 60 days between diagnosis and initiation of treatment [54]. Early initiation of treatment are highly encouraged because treatment delays of more than 90 days may result in poorer treatment out comes and overall survival for the patients [33,37,38,42,55-57]. After converting all treatment delay time intervals to days, 13 studies [21,30,33,35,37-39,42,43,48,50,52,53] collaborated previous findings that delay in the initiation of first treatment significantly impact increased risk of overall quality of life and breast cancer related deaths in patients. In spite of the NBCCEDP recommendation and previous studies [55-58] indicating poorer survival among women receiving treatment more than 90 days after diagnosis, majority of the studies included in this review suggested no statistical difference in patients who initiated treatment early compared to those who waited long in terms of general quality of life, recurrence and or survival. In all a total of 17 studies [22-29,31,32,34,40,41,44,45,49,51] reported this conclusion. The statistically non-significant delay time intervals reported for these studies ranged from as low as 21 days to over 180 days.

However, a critical examination of all17 study results taking into account the NBCCEDP benchmark for treatment delay revealed discrepancies in the results of these studies (17). For instance, ten [26,28,29,31,32,34,40,41,44,45] (59%) out of the 17 studies which concluded there was no statistically significant difference in recurrence of cancer and disease free survival quality of life between those who initiated early treatment and delayed it, compared delay intervals that were not long enough. These studies examined delay intervals (7 days verses90 day wait period) which were actually within the NBCCEDP recommended benchmark. Only seven [22-25,27,49,51] (41%) of the 17 studies investigated treatment delay that was outside the NBCCEDP standard treatment delay guideline (7 day verses over 175 day period). Taking this evidence into account, overall, this review suggests that early initiation of breast cancer treatment is associated with higher quality of life and general survival. In all twenty-three [21,26,28-35,37-45,48,50,52,53] (77%) out of 30 studies which clearly mentioned the treatment delay interval investigated supported this conclusion.

There are a number of limitations that are associated with this evidence based systematic review. First the search strategy was limited to English language publications and thus, some studies may have been overlooked which were indexed in other languages or which appeared in electronic databases that were not retrieved. As all the included studies were observational, it is possible that there is a risk of selection or self-report bias. The possibility of publication bias needs to be considered because studies which have null results tend not to be published.

CONCLUSIONS

The aim of this study was to examine the impact of treatment delay on breast cancer survivorship, as well as to determine appropriate length of time (delay) between breast cancer diagnosis and start of first treatment in order to improve general quality of life for survivors. Overall, this systematic review of the literature suggests that delaying the initiation of treatment or therapy for breast cancer more than 90 days after diagnosis has a detrimental effect on disease free and overall well-being of survivors. Although some studies reported that delaying initiation of treatment does not impact survival, a critical analysis of those studies revealed that the length of delay interval analyzed, fell within the benchmark of NBCCEDP standard. Subsequently, considering the evidence, it is clear that to enhance quality of life for breast cancer patients, it is important not to wait more than 90 days after diagnosis to begin treatment.

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