

Survivorship in untreated breast cancer patients

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Abstract In any disease, the knowledge of the natural history of untreated cases provides a real background against which the real advantages of a new treatment itself are judged. Fortunately, in the present days, there are scant data on outcomes in patients with untreated breast cancer. In an attempt to provide this background against which the virtues of current curative and palliative treatments can be more accurately assessed, we have reviewed the literature regarding published untreated breast cancer series. Taking into consideration all the difficulties of analyzing reports written on the last half of the nineteenth century or on the first half of the twentieth century, in most reports, patients survived almost 3–4 years without any type of treatment. Worth mentioning, approximately 5–10 % of untreated patients lived longer than 10 years. Thus, the spectrum of clinical aggressiveness of untreated breast cancer varies between virulence and chronic disease. These facts should be taken into account when considering the value of current treatments for early-stage disease.

Keywords Breast cancer · Metastasis · Natural history · Cancer survivorship · Clinical outcome · Treatment

Introduction

Treatment of breast cancer has become a coordinated effort of specialists. The particular blend of surgery, radiotherapy and systemic chemotherapy and biological and hormonal therapies is used to control the local and systemic components of the disease. This strategy leads to substantial improvement in survival of women affected with breast cancer [1]. Overall 5- and 10-year relative survival rates after state-of-the-art treatment are approximately 85 and 78 %, respectively [2]. However, there is still an excess of death in breast cancer patients compared to the normal population [3–7]. This indicates that there is still scope for improvement and that increasing breast cancer survival rates remains a major priority for public health.

Many questions persist unanswered. Is breast cancer a necessarily fatal disease if not treated? Can some women live with their cancer and die of other causes? Can breast cancer be classified into two categories: curable and incurable? Moreover, if one is to judge of the efficacy of any type of treatment, it is essential to know the course of events if that treatment had not been used. If we do not know the character of a disease in the absence of treatment, how can we be sure that our interventions are of benefit to the patient? Fortunately, as almost all patients with breast cancer receive any form of specific therapy, the baseline “natural history of untreated breast cancer” is unlikely to emerge from modern studies. Thus, to obtain adequate information, one must turn to case records from the past assuming that the analysis of historical data from periods before effective therapies were available can fill that void

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of knowledge. For this purpose, we review here the natural history of untreated breast cancer patients in historical series of patients. We believe that this will help us to identify the remaining scientific challenges in breast cancer and prospects for the future.

Natural history of untreated breast cancer

For information about the natural history of untreated breast cancer, one must refer to publications of 60–100 years ago. At that time, breast cancer was considered as an external lesion, palpable on examination that attracted early attention by the presence of a lump and, compared to other cancers, it killed slowly [8–10]. Most patients were in their fourth to sixth decades [8–10]. Commonly, the lump had been present in the breast 3–12 months before diagnosis [8–10]. It was also considered that an easy diagnosis meant a bad prognosis and evidenced advanced disease. The presence of a lump, generally fixed in the breast substance, and usually hard but not always, was considered a sign of early disease, while retraction of the nipple, skin changes (e.g., adherence to the skin, satellite nodules, “pig skin,” or “peau d’orange”) and palpable, enlarged axillary glands were considered evidences of advanced disease. The usual evolution without treatment was for the tumor to infiltrate the skin (approximately 14–16 months after diagnosis), then to ulcerate (6 more months), followed by fixation to the chest wall (further 2 months) and invasion of the other breast if the patient was alive [8–14]. The average time for the appearance of enlarged axillary nodes was 15 months in those few women that presented with an “empty” axilla [14]. About 25 % of all these untreated women exhibited obvious distant metastases within a year. Death usually occurred after metastases were evident. However, some authors reported that a breast lump may have been recognized for many years prior to diagnosis, consistent with much slower evolution of disease [15].

Clinical outcome of untreated patients

In comparison with the other sites of cancer, and with the exception of cancer of the skin, the breast was considered the most favorable site, that is, the least rapidly lethal cancer [9, 10]. Estimates of duration of survival from different series of patients from widely separated geographic regions were remarkably similar (Table 1): The average survival from onset of symptoms was approximately 3 years [11–20]. Of note, some patients survived for many

Table 1 Mean survival of untreated carcinoma of the breast in different patient series

Source	N	Mean survival ^a	References
Gross	97	2.6	[14]
Lazarus-Barlow	243	3.2	[13]
Greenwood	651	3.2	[12]
Daland	100	3.3	[17]
Forber	64	3.2	[12]
Nathanson	100	2.5	[12]
Wade	27	2.7	[13]
Mackay	145	3.9	[19]
Beatson	61	3	[13]
Powell White	59	2.6	[13]
Carter-Braine	15	2.5	[13]
Wyard	273	3	[13]
Phillips	230	3.8	[23]
Bloom	250	3.2	[12]
Total	2,315	3.05	–

^a Expressed in years

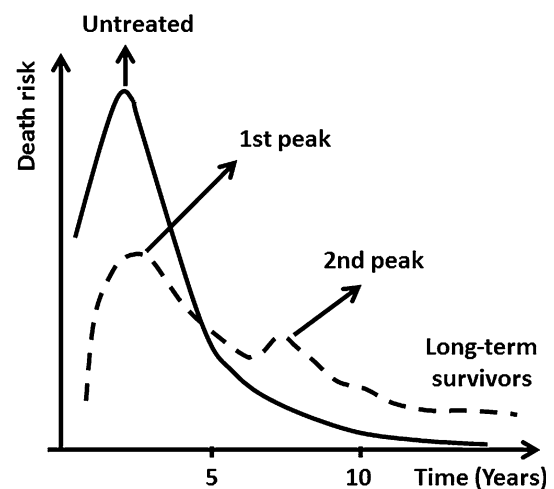


Fig. 1 Natural history of untreated and treated breast cancer patients. Hazard rate for death of breast cancer in untreated patients and patients undergoing mastectomy without or with adjuvant chemotherapy. (Dashed line) death-specific hazard rate of untreated patients; (dotted line) death-specific hazard rates for patients undergoing treatment. Adapted from [30, 61, 62]. For untreated breast cancer women, a single peak of death at about the 3rd–4th year, followed by a near constant plateau can be observed. In contrast, patients who undergo initial treatment (any type of surgery, with or without systemic adjuvant treatment) present a first peak of death at about the 3rd–4th year after treatment and a second, later peak near the 8th year

years without any specific treatment [11–13, 17, 20]. They usually had a breast tumor of moderate size with little or no ulceration, suffered no inconvenience from it, and apparently died of intercurrent disease Fig. 1.

Daland series

Daland reported a series of 100 patients including 98 women and 2 men [17]. None of these patients had received any type of treatment for the cancer. The average delay before medical consultation was 1.5 years. Daland recorded bone metastases (single or multiple) in 15 cases, lung or pleural metastasis in 18 cases and liver metastases in 11 cases. The bones involved were those commonly mentioned as the site of breast cancer metastases (e.g., spine, skull, ribs, etc.). Twenty-two patients had developed swollen arms during the course of the disease. Usually, this was accompanied by glandular metastasis, either axillary or supraclavicular. The average survival was 3.3 years (range 0.25–35 years). Deaths began as early as 3 months after diagnosis. There were 40 % alive at 3 years, while 22 % lived 5 years and 5 % lived 10 years. Two patients lived 13 years and another, more than 35 years. No case underwent spontaneous regression. Interestingly, in those patients in whom the cancer was detected early and in whom operation was advised and refused, the average duration of life was 3.5 years; those in whom the condition was inoperable at the first examination lived 2.4 years. Patients with swollen arms did not live quite as long as the average of the series (3 vs. 3.3 years, respectively). Patients with lung or pleural metastases lived 2.3 years on an average, while those who developed metastasis in the bone lived essentially no longer than the other patients without metastases, that is, 3.6 years. In ten cases where the tumor was examined histologically, there was no apparent relationship between the length of life and the degree of malignancy shown by the tumor.

Wade series

Wade reported 27 untreated patients [13]. The series included one stage I (tumor localized in breast and movable, skin not involved, no metastases) and two stage II patients (as stage I, with metastases in axillary glands). The remaining 24 patients all came into stage III (any case more advanced than stage II). Mean survival for the whole series was 2.7 years, including a patient that survived for 13 years and another for 22 years. However, she drew the attention that when excluding these cases, most of the patients died around 1 year after the onset of symptoms. In fact, the shortest duration of life was 1 month. The largest number (21 patients) died between 1 and 1.2 years from the onset of symptoms. It will be noted that the patient who lived 13 years was only 35 at the time of onset, while the patient who lived 22 years was aged 50 at diagnosis. Spontaneous cure did not occur. Wade series also demonstrated an increasing expectation of life with advancing years until the age of 75 was reached. She also reviewed

the literature on untreated breast cancer up to the time of her report (777 cases in all) and found that the mean duration of life from the onset of symptoms was quite similar (3.1 years). However, in these series, it was not possible to prove any significant influence of age on prognosis for duration of life.

Bloom series

The study that has attracted the most attention over the years was that of Bloom and colleagues [11, 12]. Their data came from the records of 250 women for which the precise date of death was known, and an autopsy had been performed confirming the diagnosis of breast malignancy. None of the patients were treated by any form of surgery, nor in the later years, by radiotherapy. Nearly 75 % of the cases had a history longer than 1 year at the time of diagnosis, 24 % more than 3 years, and 12 % more than 5 years. The vast majority of cases were advanced when first seen (75 %). A lump in the breast was the initial symptom in 83 % of patients, and ulceration was present when first seen at hospital in 68 % [11, 12]. In 21 % of women, tumors were extensive, sometimes destroying the entire breast and excavating the chest wall to expose the pleura. To this picture was added ulceration of axillary-node masses and of skin nodules, cancer-en-cuirasse and gross edema of the upper limb. Although most of the patients finally died with extensive local disease or metastatic disease (95 %), he observed that some (5 %) survived for many years without specific treatment and died of an intercurrent disease [11, 12]. The mean survival from onset of symptoms was 3.2 years and the median survival, 2.7 years. The survival rates from the alleged onset of symptoms were 44 % at 3 years, 18 % at 5 years, 4 % at 10 years and 1 % at 15 years. Remarkably, few patients survived over 13–15 years and one person lived 18 years. Spontaneous regression was not observed in any cases in this series.

Of interest, histological material was available for analysis in 86 patients. Bloom and colleagues have observed that histological grade of malignancy was correlated with prognosis. The average survival from onset of symptoms for tumors of low malignancy (grade I) was 3.9 years and the 5-, 10-, and 15-year survival rates were 22, 9 and 1 %, respectively. For tumors of intermediate malignancy (grade II), the average survival was 3.2 years and the 5- and 10-year survival rates 22 and 3 %. The average survival for highly malignant (grade III) tumors was 1.8 years; there were no survivors at 5 years. In these series, age had little effect on prognosis although a somewhat lower mean survival was observed for the younger age groups.

A final review by Bloom and colleagues collected the series of Greenwood, Daland, Forber, Wade and its own

[11, 12]. The mean survival from onset of symptoms for over 1,100 collected untreated cases was 3.2 years. At 5 years, 22 % of grade I and also grade II cases were still alive, whereas all those with grade III tumors were dead. The corresponding figures at 10 years were 9 % for grade I and 3 % for grade II cases [11].

Other published series

Other clinical reports less detailed than the series of Daland, Wade and Bloom have also described the clinical outcome of untreated breast cancer patients. One of the first series was published by Gross and Boenning [14, 21]. They found that on average, a patient could live approximately 2.6 years after the lump first appeared. The average time for the appearance of enlarged axillary nodes was 1.2 years in those few cases that presented with an “empty” axilla. About 25 % of all these untreated cases exhibited obvious distant metastases within a year and 25 % after 3 years with only 5 % surviving more than 5 years. In 1924, Lazarus-Barlow and Leeming [15] reported 243 cases with a mean duration of life of 3.2 years. Of note, they observed that there was a tendency for the disease to last longer as it occurred later in life. Wyard [20] published 311 cases with a mean duration of life of 3 years (two lived over 30 years). In these series, the duration of life appeared fairly uniform throughout all the age periods. Similarly, Greenwood described 651 cases with an average duration of life from onset of symptoms of 3.2 years and the median duration of 2.3 years [16]. Greenwood has drawn attention to the fact that the small number of patients who have survived a very long time has pulled up the average survival period. Greenwood [16] cited 273 untreated cases from Wyard series (see above) with a mean duration of 3.3 years.

Forber [18] also reported the mean duration of life from onset of symptoms in a series of 64 breast patients as 3.2 years. Of note, he found two cases with alleged survival of 40 and 41 years, respectively. Forber also quoted some unpublished data concerning 466 untreated breast cancer patients in which the mean natural duration of life was 4.2 years; when 45 cases with histories extending over 10 years were excluded, the mean duration was reduced to 2.5 years. Nathanson and Welch [22] likewise investigated the duration of life in 100 patients (97 female and 3 male) which included 50 of Daland’s original series. The average survival was 2.5 years with a crude 7-year survival rate of 10 %. Phillips [23] collected 230 cases with an average duration of life from onset of symptoms of 3.8 years. On the other hand, the report of Mackay described the clinical outcome of 145 well-documented cases [24]. The 5-year survival from first recorded symptom was 35 %, with a median survival of 3.9 years. The most surprising figure

was a near 70 % 5-year survival for the small group presenting with localized disease. Finally, Johnstone et al. [25] published an actuarial analysis of historical survival data of an amalgam of 1,022 patients from several historical series. Median survival time was 2.3 years. Actuarial 5- and 10-year survival rates were 19.8 and 3.7 %, respectively.

More recent series

More recently, Verkooijen et al. [26] detailed the prognosis of 37 non-operated breast cancer women that decided not to undergo surgery and did not receive any type of treatment. The disease-specific survival at 5 and 10 years was 64 and 39 %, respectively. Among six patients who refused surgery, Chang et al. [27] observed that five progressed to stage IV disease on follow-up evaluation, and one remained with stage II disease. The median length of time of follow-up evaluation was approximately 1 year. Han et al. [28] also reported that 11 women who omitted surgery experienced disease progression. The observed survival at 2.7 years of follow-up was 36.4 % with a median time to death of 3 years. In these series, the median tumor size at initial presentation was 2 cm and the median stage on initial presentation was II. Finally, Joseph et al. [29] reported a total of 155 patients that refused standard treatment and did not undergo any delayed surgery. The 5-year overall survival rate was 43 %. As 50 patients decided to undergo complementary and alternative medicine treatments instead of surgery, the authors compared the clinical outcome of these patients with those whose treatment details were not known. The 5-year overall survival was 57.4 % for women who received complementary/alternative medicine and 26.3 % for those whose treatment details were unknown.

Lessons from the untreated series

In any disease, the knowledge of the natural history of untreated cases provides a real background against which the real advantages of a new treatment itself are judged. Fortunately, in the present days, there are scant data on outcomes in patients with untreated breast cancer. In an attempt to provide this background, we have reviewed the literature regarding historical untreated breast cancer series. In spite of the inherent difficulties of analyzing reports written on the last half of the nineteenth century or on the first half of the twentieth century, it is surprising to find how close the agreement is between different published series, timely and geographically widely separated. This indicates that most of the published reports would thus reflect the real natural history of untreated breast cancer. It is of note that in most of the reports, patients survived

almost 3–4 years without any type of treatment. Furthermore, survival rates from onset of symptoms were around 15–18 % at 5 years and 5–10 % at 10 years. Although these figures seem very low compared to current survival rates, we need to consider that as most of the patients went into hospitals merely to die, these ancient reports mainly indicate the survival of advanced cases and not of the early ones. A further consideration is that many deaths in all these series could have been postponed for a time if certain non-specific modern therapeutic agents (e.g., antibiotics) had been available. In fact, the analysis of recent series shows that survival rates of untreated patients were higher (approximately 40 % at 5 years) compared to those of the older series [26, 28, 29]. At any rate, all these data indicate that in most patients, a survival of roughly 3–4 years is what would be expected without treatment, although around 5–10 % of patients would live longer than 10 years.

Without any doubt, it is clear from the analysis that in most patients, any type of therapy improves survival. This benefit is estimated in approximately 4–5 years or more compared to untreated patients (Fig. 1; Table 2) [30]. However, many breast cancer patients will continue to succumb to the disease within the first 3–4 years following the initial diagnosis, similar to what is observed in untreated patients (Fig. 1; Table 2); this indicates that these patients are marginally benefiting from early diagnosis and current standard therapies [30–39]. Already in yesteryears, McKinnon, Fox and others suggested that breast cancer could be classified into two types: incurable with a short (3–4 years) survival and curable with a long (5–10 or more years) survival [40–42]. Currently, and thank to the advancement of breast cancer treatment, most of the patients moved from the first group (most in untreated series) into the second group. But we still do not know why so many women continue to die in that 4-year period despite that they were diagnosed and subsequently treated for an early-stage disease. A possible explanation is that this is related to a biological phenomenon called “concomitant resistance” [32, 43]. At any rate, it remains a great challenge to prospectively identify these early-stage

breast cancer patients with a low chance of surviving when treated with current standard therapy and, to also find new therapeutic strategies to increase the survival of this patient subgroup [30, 44–46].

Another interesting observation is that a small group of women with far-advanced breast cancer had an indolent disease and showed long-term survival without any type of treatment. This is surprising, mostly knowing that long-term survival rate of treated patients varies between 10 and 40 % [3, 42, 47–52]. The fraction of untreated long-term survivors could be considered as small, but indicates that the chance for survival without treatment truly exists. A first consideration is that it is difficult to determine whether long-term survival in treated series of patients result truly from the treatment strategy or the underlying indolent nature of breast cancer. For example, it is currently known that long-term survivors in treated series of patients can be found in all clinical or molecular subtypes of breast cancer, including those related to worse prognosis (e.g., ER-, HER2+ , triple-negative, etc.) [33, 48, 49, 53–55]. These could indicate that unknown tumor biology processes, rather than molecular subtypes or the choice of therapy, determine the survival trends. A second consideration is that as it seems that long-term survival is not only related to treatment, a watchful behavior could only just be enough for some patients. Thus, identification of patients that would survive for long time and that may not need any type of treatment is a research priority; moreover, if we consider that therapy can induce adverse effects years after completion of therapy, which can considerably decrease long-term quality of life [56]. A better knowledge of tumor biology in these patients is needed. The role of the immune system is one of the main aspects to investigate as it was recently published that cytotoxic T cell tumor infiltration is associated with longer survival independently of the ER or HER2 status [57]. Long-term survival could also be related to high levels of circulating estrogen in some patients. Although paradoxical because estrogen is recognized to stimulate breast cancer growth, laboratory and clinical data support a mechanism of estrogen-induced apoptosis under the correct environmental circumstances [58, 59].

Table 2 Patterns of mortality of untreated and treated carcinoma of the breast in different patient series

Source	N	First mortality peak ^a	Second mortality peak	References
Bloom	250	3rd	–	[12]
Demicheli	1,173	3rd–4th	8th–9th	[60]
Karrison	1,547	3rd–4th	8th	[34]
Jerez	3,811	2nd	9th	[35]
Sant	1,991	4th	7th–8th	[36]
Baum	–	2nd–3rd	5th–7th	[37]
Gao	2,105	2nd–4th	9th	[39]

^a Expressed in years

Implications for breast cancer patients

The natural history of breast cancer of untreated patients indicates that the spectrum of clinical aggressiveness varies between virulence (most of the patients dying at 3rd–4th years) and chronic disease (5–10 % of long-term survivors). If we compare this to the current situation, we can conclude that the clinical outcome of breast cancer patients was colossally improved. Thank to the advancement of breast cancer treatment, patients can be now ascribed to three distinct groups: (i) patients who succumb to the disease early; (ii) patients in which the survival will be substantially prolonged; and (iii) patients who continue to survive the disease for many years. The behavior of breast tumors is such that each group seems to have a nature all its own. For the first group, it seems that current treatment modalities only delay death for a short period. For the intermediate group, being this most populated, treatment offers a real survival benefit of 4–5 years. For the last group, standard treatment is not offering any major benefit; these patients should be treated with new and less toxic therapeutic modalities or, if in the future they could be identified, even a watchful strategy could be considered. Substantial efforts are needed to understand breast tumor biology of these three different patient populations with the aim of improving clinical outcome (particularly for the first group). Furthermore, all these facts should be taken into account when considering the value of current treatments for breast cancer.

Conflict of interest Carlos M. Galmarini is currently an employee and stockowner of PharmaMar. Olivier Tredan and Felipe C. Galmarini declare no conflict of interest.

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