Cancer Surgery
ISSN: 2573-542X

Fentiman, Cancer Surg (Los Angeles, Calif.) 2016, 1:1
DOI: 10.4172/2573-542X.1000103

Review Article Open Access

Medico-legal Aspects of Delay in Diagnosis of Breast Cancer

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Received date: March 21, 2016; **Accepted date:** April 06, 2016; **Published date:** April 12, 2016

Abstract

Delayed diagnosis of breast cancer forms a substantial part of medical litigation and may sometimes result from communication failure in the multidisciplinary team. Review of such cases may result in improved patient pathways as a result of lessons learned. There is evidence that delay may significantly worsen prognosis. For a claimant to successfully pursue a case it is necessary for the medical experts to confirm that both negligence and causation have occurred. Methods are available whereby likely tumour size at the time of negligence and likelihood of axillary nodal involvement can be estimated. There are now various prognostic models that can be used to estimate the impact of delay on prognosis but as a result of improvements in treatment many cases will not meet the criteria for causation.

Keywords: Breast cancer; Delay; Prognosis; Sentinel node biopsy; Lymphoedema

Introduction

As a capricious and heterogeneous disease breast cancer may be difficult to diagnose and despite being appropriately treated may relapse unexpectedly. Governmental pressure to reduce waiting for women with breast cancer may lead some patients to suspect that very short delays may impact adversely on their prognosis. In this supercharged atmosphere of anxiety, communicational skills of breast surgeons may be constantly tested so that minor solecisms may translate into major patient dissatisfaction. With this background it is unsurprising that more patients are turning to litigation in an attempt to obtain satisfaction for what they perceive as medical negligence.

Requirements

In order for a case alleging medical negligence to be successful the claimant has to successfully negotiate at least 3 hurdles. Firstly, did the doctor(s) have a duty of care? Thus, was the defendant the claimant's general practitioner or a member of a hospital team to which a GP referral had been made? Incorrect advice given by a doctor to a friend or acquaintance does not make that individual liable since they do not have a duty of care.

Secondly were the history-taking/ clinical examination/ advice/ procedure negligent? Negligence is defined as an action which no responsible doctor would have taken. Under the normal circumstances where there are various courses of action, provided that there is a sensible body of medial opinion for a particular approach that is not negligent even though a medical expert might not agree with the defendant's allegedly negligent advice. An example of this is sentinel node biopsy where one body of opinion advocates a combination of tadio-isotope and dye whereas others use one or the other.

If the medical expert deems that negligence has occurred, such as failing to obtain a tissue diagnosis on a solid breast mass the next hurdle is determination of causation. For causation to be established it must be shown that as a result of the negligence the claimant has suffered an injury, that is, a significant worsening of prognosis, and/or a need for more extensive surgery or radiotherapy and or a requirement for more toxic systemic therapy and/or psychological damage. At present, in claims for delay in diagnosis of breast cancer it is necessary to prove that the claimants 10-year survival has changed from being >51% to <49%. Hence a reduction from 95% to 60% or from 45% to 25% will not meet the criteria for causation. Proportional damages are not granted at present.

Delay in Diagnosis

Controversy persists regarding the possible impact of delay on survival. In part this is a legacy from two different hypotheses concerning breast cancer: the first asserting that inadequate local treatment leads to more deaths from breast cancer, the second believing that breast cancer is a systemic disease at the time of diagnosis. Studies of the long term effect of breast cancer screening support the contention that detection of cancers at a smaller size and therefore earlier stage does influence overall survival. A systematic overview of published observational studies suggested that delays of 3-6 months from the onset of symptoms to the time of definitive treatment are clearly associated with lower survival rates.

In the same issue of The Lancet was another large study of 36 222 patients with breast cancer listed in the Yorkshire Cancer Registry which disagreed with the findings of the systematic review. Delays in GP referral of 3 months or more did not seem to be associated with decreased survival. A potential weakness in the study was the lack of data on patient's first noticing and presenting to the GP which effectively failed to eliminate lead-time bias.

Although there will be argument among experts as to the extent to which the patient's prognosis will have been affected by the delay there is fairly general agreement that a delay of <6 months is unlikely to have had a significant impact.

Causation

When Causation is being evaluated the test is whether, on a balance of probabilities, a particular event would have occurred. The crucial steps in terms of determining causation is to calculate the likely tumour size at the time of negligence and hence the likelihood of axillary nodal involvement. From this the estimated survival at the time of negligence and at the time of actual diagnosis can be derived. This seemingly simple step is beset with difficulties, particularly because the instruments used in the calculations were not designed for medico-legal purposes and were mostly attempts to place patients into prognostic groups for purposes of advising on adjuvant therapy.

Gompertzian tumour growth postulates exponential growth with a fixed tumour volume doubling time (TVDT). This does not take into account apoptosis or necrosis or the heterogeneity of tumours and mixture of invasive and non-invasive components. The tumour volume doubling time has been calculated by, using measurements from at least two mammograms taken prior to diagnosis of breast cancer [1-3]. The study group comprised women aged 45-70 and so is of questionable application to both younger and older women. This also assumes that the mammographically visible lesion was the same as the true (pathological) tumour size. There was a significant difference between those aged <50 and those aged 50-70, as shown in Table 1.

Age group	Mean doubling time	Confidence limits
<50	80 days	44-147
50-70	157 days	121-204

Table 1: Age and growth rate of breast cancer [3].

For those aged <50 the mean TVDT was 80 days with 95% confidence intervals of 44-147 days. What is still being argued about is the relationship between tumour grade and TVDT. Since mitotic rate is a component of grade it is likely but not proven that grade I tumours will have TVDT towards the upper end of the scale and grade III cancers will be at the lower end but this remains contentious.

Having arrived at an estimate of TVDT volume at the time of actual diagnosis. The assumption can be made that the tumour is spherical so that the volume at diagnosis (V) is:

$$V = \frac{4\pi r^3}{3} \quad (\pi = 3.142,\ r = \text{radius})$$

Tumours are often spheroidal so that the volume is

$$V = \frac{4\pi \times r1 \times r2 \times r3}{3}$$

Say the tumour was grade III, 60 mm in diameter and 4 nodes positive at the time of diagnosis and there was a delay in diagnosis of 12 months. With this delay and a TVDT of 60 days the tumour would have undergone 365/60≅6 volume doublings. With a tumour diameter of 60 mm at the time of diagnosis, this gives a volume of 113 cm3. From this the tumour volumes and diameters at previous times can be estimated and this is shown in Table 2. The estimated tumour diameter 12 months previously is 15mm.

	Volume	Diameter
At diagnosis	113 cm^3	60 mm
1 volume halving	56.5 cm^3	48 mm
2 volume halvings	28.25 cm^3	38 mm
3 volume halvings	14.125 cm^3	30 mm
4 volume halvings	7.1 cm^3	24 mm
5 volume halvings	3.5 cm^3	19 mm
6 volume halvings	1.77 cm^3	15 mm

Table 2: Tumour volume halving and tumour diameters.

In a large study based on the Norwegian Breast Cancer Screening Program, Weedon-Fekjaer et al. [4] used a new estimating model to estimate tumour growth rates. Both tumour growth and the screen test sensitivity were used continuously increasing functions of tumour size using data from almost 400,000 women aged 50-69. What emerged was considerable variation in growth kinetics. A small proportion (5%) of cancers doubled in diameter in <0.2 months whereas in another 5% this took >6.3 years. The mean time for cancers to grow from 10 mmd to 20 mmd was 1.7 years. The fastest growth rates were seen in cancers in younger women indicating the need for caution in interpretation of tumour volume doubling times.

Since the tumour grade does not change with time, if it was grade III at the time of diagnosis it was also grade III at the time of negligence. With a tumour of known grade and estimated diameter the likelihood of axillary nodal involvement can be estimated. The data of Yiangou et al. [5-7] have often been used in this respect and these are summarised in Table 3. This indicates that in the group of patients with grade III cancers measuring 11-20 mm, only 35% had nodal involvement. Hence, on a balance of probabilities, the patient would have been node negative at the time of missed diagnosis. As another method, Cancer Math is able to estimate the likelihood of nodal involvement based on tumour size, type, grade, receptor status and patient age. In this case the likelihood is 34.3%, confirming the estimate that there would not have been axillary nodal involvement.

Tumour size (mm)	Grade I	Grade II	Grade III
0-5	0 (0)	0 (0)	0 (0)
6-10	3 (14)	9 (14)	3 (25)
11-20	12 (27)	79 (38)	37 (35)
21-50	8 (42)	114 (66)	84 (63)
>50	2 (100)	28 (90)	26 (87)

Prognostic Models

The prognostic system that has been used more than any other to determine prognosis in cases of delayed diagnosis is the Nottingham Prognostic Index (NPI). The NPI score is derived as follows:

NPI = 0.2 × tumour size + lymph node stage (1 = node negative, 2 = 1-3 nodes positive, 3 = 4+ nodes positive) + histological grade (1 = well differentiated, 2 = moderately differentiated, 3 = poorly differentiated)

At the time of diagnosis in this hypothetical case the components were:

Size-6cm, score-1.2; Nodes-4 positive, score -3; Grade-III, score-3; Total score-7.2.

Having obtained the NPI score the case can then be assigned to one of five prognostic groups as shown in Table 4. The score of 6.2 places the patient in the very poor prognostic group with an estimated 10-year survival of 38%. If a timely diagnosis had been made the components of the NPI score would have been, size-1.5 cm, score -0.3; Nodes-Negative, score-1; Grade-III, score-3; Total score-4.3.

Group	Score	10 year survival
Excellent prognostic group	<2.4	96%
Good prognostic group	2.4-3.4	93%
Moderate prognostic group I	3.41-4.4	81%
Moderate prognostic group II	4.41-5.4	74%
Poor prognostic group	5.41- ≤ 6.4	55%
Very poor prognostic group	6.5-6.8	38%

This score places the case in the moderate prognostic group I with an estimated 10-year survival of 81%. Since the prognosis has fallen from 81% to 38% causation has been proved. There is however a problem with this analysis since it does not take into account other known prognostic variables or the influence of adjuvant systemic therapy.

In an attempt to include the effects of both adjuvant endocrine and adjuvant chemotherapy Ravdin et al. [8] devised the Adjuvant! Prognostic model which was available on the internet [8-12]. They used survival results from the Surveillance, Epidemiology and End Results (SEER) programme which had data on local treatment & prognostic factors. However details of adjuvant therapy and relapse status were unknown. In an attempt to control for this survival was adjusted downwards by 15% for stage I cases and 30% for stages II and III. To this adjusted survival they applied adjuvant results from 1998 Oxford overview which was used to estimate the increase in re-adjusted survival. Data was used only from women aged 35-59 so, that the model is underpowered to give survival rates for the young and old. Taking the hypothetical case being 45 at the time of negligence and 46 at the time of delayed diagnosis with an ER +ve tumour and in otherwise good health if the variables are entered into the Adjuvant! Model the estimated survival rates could be obtained unfortunately, access to Adjuvant! Online is temporarily disabled while it is being updated and it is hoped that is achieved by the end of April 2016.

Cancer Math is another useful prognostic model based on a set of web-based calculators, which estimates the risk of breast cancer death, reduction in life expectancy, and the impact of various adjuvant treatments. The size nodes and prognostic factors (SNAP) model of cancer metastasis used information on tumour size, nodal status, and other prognostic factors to accurately estimate of breast cancer lethality at 15 years after diagnosis.

Combining these 15-year lethality estimates with data on the breast cancer hazard function, breast cancer lethality was estimated at each of the 15 years after diagnosis. Accuracy of the calculators was tested against two large breast carcinoma datasets: 7,907 patients seen at two academic hospitals and 362,491 patients from the SEER national dataset. The calculators were found to be highly accurate and specific, as seen by their capacity for stratifying patients into groups differing by as little as a 2% risk of death, and accurately accounting for nodal status, histology, grade, age, and hormone receptor status.

When the hypothetical case's prognostic variables are entered into this model, at the time of actual diagnosis she is in a group with a 60% estimated 10-year survival. As a result of the cancer diagnosis her life expectancy has been reduced by 15.3 years. A diagnosis one year previously would have placed her in the group with a 90% survival at 10 years and a loss of 3 life years. The delay meant that she lost 12.3 life years.

Predict is an online breast cancer prognostic model. The prognostic effect of HER2 status has been incorporated in a new version (Predict +) based an analysis of data from 10 179 breast cancer patients from 14 studies. Predicted overall survival (OS) and breast cancer-specific survival (BCSS) for Predict+, Predict and Adjuvant online were compared with observed outcomes. All three models performed well for both OS and BCSS. Both Predict models provided better BCSS estimates than Adjuvant online. Among patients with HER2-positive tumours, Predict+ performed substantially better than the other two models for both OS and BCSS. According to Predict+, at the time of diagnosis she was in a group with 19% survival at 10 years, in the absence of adjuvant treatment, but giving a combination of chemotherapy and adjuvant therapy the 10-year survival increases to 52%. With an earlier diagnosis the 10-year survival would have been 90%.

Although the major part of the damages is for worsening of prognosis as a result of the delay, causation can also be established in relation to need for a change of treatment. In patients with breast cancer this may mean that mastectomy rather than breast conserving surgery was necessary. Additionally with nodal involvement radiotherapy to the supraclavicular fossa may be advised with an attendant increase in risk of arm lymphoedema and brachial plexopathy. In the hypothetical case she would have been node negative if a timely diagnosis had been made and therefore would have avoided an axillary clearance, this would place her at lifelong risk of lymphoedema. Evidence of the magnitude of the risk comes from a cohort of 923 women consecutively treated with mastectomy and complete axillary dissection at the Sloan Kettering Memorial Hospital between 1976 and 1978 who were observed intensively for 20 years. Circumferential arm measurements were taken using a validated instrument and at 20 years after treatment, 49% (128 of 263) developed lymphoedema.

Conclusions

As a result of working in multidisciplinary teams it is to be hoped that the number of cases of delayed diagnosis will reduce although there will always be some cancers that elude diagnosis at first presentation. Many of the problems of patient dissatisfaction can be avoided by good communication and an apology when required but some patients, irrespective of whether they have been managed correctly, will be angry as a result of either delay or unexpected relapse and institute legal proceedings. Since breast cancer mortality is falling, both as a result of earlier diagnosis and improvements in adjuvant systemic therapy for many patients even though there has been a delay there will not be causation as presently defined.

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