Breast cancer recurrence: follow up after treatment for primary breast cancer

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Background: Breast cancer will affect one in 12 Australian women in their lifetime. After potentially curative treatment, it is usual for patients to be followed up for many years. However, controversies surround follow up, and its value is uncertain.

Aim: This study reviews the evidence and describes the role of routine follow up in the management of breast cancer in a tertiary hospital. By establishing how recurrence of breast cancer presents and identifying the proportion of patients with recurrence who were diagnosed as a consequence of regular follow up, the value of this system in detecting recurrence can be indirectly assessed.

Design: A retrospective review was undertaken of all patients attending the radiotherapy outpatient clinic for treatment of invasive breast cancer in 1997. Hospital records were reviewed to ascertain patient and tumour characteristics, treatment received, site of recurrence and its mode of detection, whether patients were symptomatic at the time of recurrence, and whether they presented at a scheduled appointment.

Results: Out of 286 patients who presented to the radiotherapy outpatient clinic, 220 were entered into the study. Recurrence was recorded in 42 patients (a complete dataset was available for 38 of these patients). In total, 74% (31/42) of recurrences were symptomatic, and 76% (32/42) presented at unscheduled appointments, the majority (17/32) of which were initiated by the patient. Only seven patients had asymptomatic recurrences.

Conclusion: Based on current evidence, long term routine hospital follow up after treatment for breast cancer appears to be inefficient in detecting recurrence.

Breast cancer is an important public health problem, affecting one in 12 Australian women in their lifetime. After potentially curative treatment for breast cancer it is common clinical practice for patients to be followed up for many years. However, controversies surround follow up, and its value is uncertain.

International figures suggest that about 30% of women will develop recurrence after treatment for primary breast cancer, figures for early stage disease being lower. The available data confirm that Australian recurrence rates are similar to the international average. Today, the combined effects of screening, early detection, and advances in treatment have resulted in increasing numbers of patients diagnosed with breast cancer in follow up clinics. At the same time, there is increasing pressure on resources from new referrals and urgent cases.

Follow up should include providing physical and psychosocial rehabilitation, monitoring treatment effectiveness and short term and long term toxicity, detecting recurrences and new cancers, and collecting data for research. Follow up schedules vary internationally. Guidelines issued by the American Society of Clinical Oncology in 1999 recommend monthly breast self examination, annual mammography of the preserved and contralateral breasts, and a history and physical examination every three to six months for three years, then every six to 12 months for two years, then annually. These recommendations are resource intensive.

Evidence that intensive follow up is of little value has come from randomised controlled trials and a Cochrane review. The Cochrane review of follow up strategies for women treated for early breast cancer (based on four randomised controlled trials) concluded that follow up programmes based on regular physical examinations and yearly mammography alone appear to be as effective as more intensive approaches based on regular laboratory and instrumental tests in terms of timeliness of recurrence detection, overall survival, and quality of life.

Routine follow up protocols in use today are based on two hypotheses: (i) that most recurrences are detected at an earlier stage through follow up; and (ii) that the earlier treatment of recurrences offers a better chance of cure; longer survival, or improvement in quality of life. However, current data suggest that neither of these hypotheses is correct and that postoperative follow up of patients with breast cancer is costly and time consuming and does not significantly extend survival.

Despite considerable effort to detect recurrent disease early, the evidence suggests that only a minority of recurrences are detected at an asymptomatic stage. It has also been found that most patients with recurrence have signs or symptoms as the first indicator of recurrence and that history and physical examination generally provide the first clues to recurrence.

Furthermore, most recurrences present at unscheduled appointments and not as a consequence of routine follow up appointments.

When analysing the presentation of recurrent breast cancer, a distinction has been made between locoregional and metastatic disease. Metastatic disease is incurable, and it has been demonstrated that no survival advantage is gained from diagnosing it at an asymptomatic stage by means of routine investigations.

Whether early detection of locoregional recurrence leads to a survival benefit, however, is still controversial, with the current evidence suggesting that early detection and
treatment of asymptomatic locoregional recurrence has no benefit to overall survival compared with treatment of symptomatic recurrence.15 19–22

Furthermore, the assumption that early detection of asymptomatic locoregional recurrence is associated with a better chance of controlling disease symptoms and thereby improving quality of life is also unproven. It should be noted, however, that this situation is different after breast conservation surgery, where salvage mastectomy is a well recognised treatment.23

There is no evidence as to what constitutes optimal follow up, and identification of an optimised follow up strategy will require long term prospective clinical trials. In the meantime, I sought to determine the value of routine hospital follow up indirectly by identifying the proportion of women with recurrent breast cancer who were asymptomatic and diagnosed directly as a result of routine outpatient attendance.

PATIENTS AND METHODS

I conducted a retrospective cross sectional study of patients who attended a tertiary hospital radiotherapy outpatient clinic in 1997 with a diagnosis of invasive breast cancer. Ethical approval to conduct the study was obtained from the hospital ethics committee, and the study was conducted with due attention to patient confidentiality.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and tumour demographics and treatment received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>All patients (n = 220)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>90 (41)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>130 (59)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal including no special type</td>
<td>164 (75)</td>
</tr>
<tr>
<td>Infiltrating lobular</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Tubular or cribriform</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Mucinous or colloid adenocarcinoma</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Other carcinoma of mixed type</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Papillary</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medullary</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>Well differentiated, low grade, G1</td>
<td>47 (21)</td>
</tr>
<tr>
<td>Intermediate, medium grade, G2</td>
<td>74 (34)</td>
</tr>
<tr>
<td>Poorly differentiated, high grade, G3</td>
<td>74 (34)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>119 (54)</td>
</tr>
<tr>
<td>≥2 cm but &lt;5 cm</td>
<td>75 (34)</td>
</tr>
<tr>
<td>At least 5 cm</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Nodes</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>118 (54)</td>
</tr>
<tr>
<td>1–3 positive nodes</td>
<td>37 (17)</td>
</tr>
<tr>
<td>≥4 positive nodes</td>
<td>40 (18)</td>
</tr>
<tr>
<td>Nodes not examined</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oestrogen receptor</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>145 (66)</td>
</tr>
<tr>
<td>Negative</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>214 (97)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>188 (85)</td>
</tr>
<tr>
<td>Hormonal</td>
<td>125 (57)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>75 (34)</td>
</tr>
</tbody>
</table>

Out of a total of 286 patients who presented, 220 patients were entered into the study. The remaining 66 patients were excluded because they had metastasis at the time of diagnosis. Data on 220 patients were examined to determine the pattern of recurrence over a five year follow up period. Full five year follow up on 65 patients was available from their hospital outpatient records; for the remainder, the patient’s surgeon or oncologist was contacted to achieve a five year follow up.

The management and frequency of follow up visits were determined by the specialist, protocol at the time, and clinical indications, but visits generally occurred at intervals of six months for two years and then annually to five years. Annual mammography was performed; no other investigations were routinely undertaken.

Recurrences were classified as locoregional if they occurred in the ipsilateral breast or in the axillary or supraclavicular lymph nodes, and as distant metastasis if they occurred at any other site. Tumours in the contralateral breast were recorded separately. These may have been new primary cancers or metastases from the previous primaries.

Recurrences were classified as symptomatic if the patient presented with a relevant complaint. Clinic visits were classified as scheduled if they corresponded to a routine follow up appointment, irrespective of whether the patient had symptoms. If patients were referred back to the clinic between routine appointments then these visits were classified as unscheduled. No attempt was made to quantify counselling or support requested or delivered at clinic visits.

Analyses identified the site of recurrence, the recurrence rate, whether the recurrence was symptomatic or
asymptomatic, the first indicator of recurrence, whether it was identified at a scheduled or an unscheduled visit, the referral pattern for unscheduled visits, and what proportion of recurrences were detected as a result of follow up in the clinic (that is, diagnosed by a clinic doctor at a scheduled visit in an asymptomatic patient).

The patient and tumour characteristics at diagnosis and the treatment given are shown in table 1. The characteristics of patients with recurrence are also shown. However, because of the small numbers and because this was not an aim of the study, I will not draw any further conclusions about prognostic indicators of recurrence.

RESULTS

Recurrence was recorded in 42 patients (19%) (a complete dataset was available for 38 of these patients), with a disease free interval ranging from 10 months to five years. Patients with recurrence were categorised according to the site of recurrence (table 2). Overall, 25 patients developed metastatic disease; the most common site of metastasis was bone. Table 3 details the recurrence rate at intervals of six months. Most recurrences occurred in the second or third year after diagnosis. The recurrence rate varied between 0.5% and 7.9% with no clearly consistent pattern.

The most common first indicator of recurrence (table 4) was patient symptoms or the finding of an abnormality on self examination (31/42), with the majority of patients presenting with pain. Specialist examination picked up two cases, and a routine mammogram was the first indicator of recurrence in five cases.

Table 5 categorises recurrence by visit type, presence or absence of symptoms, and site of recurrence. Of those patients whose disease recurred, 74% were asymptomatic, and 76% of recurrences presented at unscheduled appointments. Looking at the referral pattern for unscheduled visits (table 6), it is seen that 53% were initiated by the patient, and 31% of patients were referred by their general practitioners. Only seven patients had asymptomatic recurrences; five of these were detected by mammography, and only two were detected by physical examination in the outpatient clinic (representing 1% of the 220 patients followed up).

DISCUSSION

In this study recurrence was recorded in 42 patients (19%). These data, like those of others, show that most recurrences (74%) are symptomatic and that signs and symptoms are the most frequent indicator of recurrence.

Boekhorst et al reported that only 37% of recurrences were detected while they were asymptomatic, and Loong et al found that only 24 out of 115 patients with recurrence were diagnosed before they became symptomatic. In a study by Pandya et al the first indicator of recurrence was symptoms in 36%, patient self examination in 18.3%, physical examination by the physician in 19.4%, abnormal blood chemistry in 12%, bone scans in 8%, chest radiographs in 5.1%, and mammograms in 1.1%.

In this study 76% of recurrences were diagnosed at unscheduled appointments, which were often initiated by the patient. Similar results were obtained in other studies: after a median follow up period of 76 months, Loong et al reported that 55% of local recurrences and 70% of metastatic recurrences were detected by interim referral, and Churn and Kelly found that 64% of local recurrences were detected at interim referral.

This study found that only two recurrences were detected directly as a result of routine follow up, representing 1% of the 220 patients being followed up. This pilot study was limited by assessing follow up in only one outpatient clinic (hospital based follow up usually occurs over a few different clinics) and by small numbers, incomplete data collection, low statistical power, and retrospective data collection. However, my findings are in accordance with those of larger studies.

Morris et al discovered that only 1% of routine visits contribute to the detection of recurrence following potentially curative treatment of breast cancer, compared with 27% of interval visits. Holli and Hakama found that recurrence was detected in 14.7% of spontaneous visits compared with 2.9% of regular visits conducted according to the recommended follow up schedule. They concluded that a woman is 5.1 times more likely to detect a recurrence herself than to have one detected during organised follow up. In this situation, educating patients about the indicators of relapse might be beneficial. Persistent pain and bone tenderness are common indicators of treatment failure, and patients should be taught to report such findings to their physician.

The possible detection of a contralateral primary is also regarded as an important component of follow up. The incidence of contralateral primaries is approximately 0.8% per year, and the survival of those with a localised contralateral...
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contribute directly to detecting contralateral tumours.16 17 21 of other studies, which found that routine clinic visits did not
difference in survival between patients who complied with
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attributed to lead time bias and length bias. More impor-
tmatic recurrence with that of those who had symptomatic
recurrence after mastectomy for early breast cancer.20 21 Both groups reported better overall survival for patients
compared the survival of patients who developed asymptomatic
recurrences. However, this was
tumour.26 In this study four patients developed contralateral
metastases from the previous primaries. All four tumours,
however, were diagnosed during unscheduled visits. This is
similar to the series reported by Loong et al and to the results
of other studies, which found that routine clinic visits did not
contribute directly to detecting contralateral tumours.16 17 21

while there was no very consistent pattern, the highest
recurrence rates in this study were in the second and third
years after diagnosis. Although this finding is supported by
others,17 19 it may be a result of selecting women who had five
years follow up recorded in their notes.

This study did not assess the survival benefit of follow up.
Tomin and Donegan and Dewar and Kerr retrospectively
compared the survival of patients who developed asymptomatic
recurrence with that of those who had symptomatic
recurrence after mastectomy for early breast cancer.20 21 Both groups reported better overall survival for patients
with asymptomatic recurrences. However, this was
attributed to lead time bias and length bias. More impor-
tantly, Tomin and Donegan’s paper showed that there was no
difference in survival between patients who complied with
the schedule of follow up examinations and those who
deviated from the schedule. These findings are in accordance
with those of Boekhorst et al and others.15 19 22 Thus, current
evidence suggests that early detection and treatment of
asymptomatic locoregional recurrence has no benefit to
overall survival compared with treatment of symptomatic
recurrence.

The need for psychosocial support for women with breast
cancer is increasingly recognised.23 Psychological morbidity,
particularly anxiety, is common, occurring in up to 30% of
patients within a year of diagnosis.23-24 In busy clinics these
problems may be under-recognised. Psychological morbidity
can be overlooked if it is not deliberately addressed. This
support may be better and more consistently provided by
general practitioners than by regular visits to an outpatient
clinic.23 There is evidence that, although some patients do
gain reassurance from clinic visits, a reduced frequency
of follow up is preferred and that patients may be willing
to accept follow up in primary care, particularly if provision
is made for prompt specialist review should the need
arise.10 29

A randomised controlled trial by Grunfeld et al found that
follow up care provided by general practitioners was as
effective as that delivered by hospital based specialists in
terms of quality of life and time to detection of distant
metastases. They found that women detect most recurrences
as interval events and present to the general practitioner,
irrespective of continuing hospital follow up.29 However,
there were only 26 events in 296 patients over the 18 month
follow up, so the statistical power is limited. A survey
forming part of this study showed that 69% of general
practitioners in England consider that they have the skills
necessary to conduct routine follow up. A similar survey of
Australian general practitioners would be helpful.

There is no evidence as to what constitutes optimal follow up;
analyses of hospital outpatient clinics have been
proposed to address the various requirements of follow up,25 17 19
including monitoring treatment related toxicity,
diagnosing and managing psychological problems, and
collecting long term data. In countries such as Australia
with a strong primary care base, one alternative is to give
responsibility for routine follow up to the general practitioner
(specially in rural areas), with the option to reinitiate
specialist hospital care if problems develop. General practi-
tioners in the UK have expressed a willingness to undertake
this responsibility.24 However, this option may require further
general practitioner education to improve follow up in
primary care.

The current incidence of breast cancer is high. Early
detection of primary cancers and the strict use of adjuvant
therapy not only result in longer survival but also lengthen
the disease-free interval, thus increasing the number of
patients requiring follow up.

In this retrospective analysis and review of current
evidence, a regular follow up schedule did not appear to
offer an obvious advantage in the detection of recurrence
after potentially curative treatment. Adequate quantification
of late toxicity effects and of the value of psychological
support cannot be ascertained from this study.

Any new approach to follow up must fulfill various
requirements, including monitoring treatment related toxici-
ty, diagnosing and managing psychological problems, and
collecting long term data. From international research it
appears that given adequate preparation both patients and
general practitioners may be happy with early discharge, and
this will not compromise surveillance for recurrence.

To change the follow up protocol for the management of
primary breast cancer in Australia the following questions
need to be considered:

<table>
<thead>
<tr>
<th>Table 4</th>
<th>First indicators of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator</td>
<td>No (%) of patients (n = 42)</td>
</tr>
<tr>
<td>Symptoms or finding of abnormality on self</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Follow up examination</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Routine mammogram</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Unknown or not in file</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Recurrence by visit type and presence or absence of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of recurrence</td>
<td>Scheduled visits</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>2</td>
</tr>
<tr>
<td>Metastatic</td>
<td>2</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>0</td>
</tr>
</tbody>
</table>

Information was not available for four patients.
- Can breast cancer follow up be adequately provided in the community?
- Are there any special categories of women who may benefit from hospital based follow up?
- What does evidence indicate should be the components of long term follow up, if any?
- What are the effects on long term outcomes such as mortality and morbidity of follow up by a specialist compared with follow up in primary care in Australia?
- Will Australian women accept follow up by the general practitioner?
- What are Australian general practitioners’ views on follow up of cancer patients?
- What are the psychological effects of follow up?

REFERENCES