Clinical Assessment of Axillary Lymph Nodes and Tumor Size in Breast Cancer Compared with Histopathological Examination: A Population-Based Analysis of 2,537 Women.

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Abstract

Background

Clinical assessment of axillary lymph nodes status and tumour size are important factors in the management of patients with breast cancer. The first aim of this study was to determine the accuracy of axillary lymph node status in relation to the presence of metastases as revealed by histopathological examination. The second aim was to compare the tumour size as assessed by physical examination, with the size obtained by histopathological examination.

Method

This study was based on a consecutive series of 2537 patients diagnosed with breast cancer in Malmö, Sweden, between 1987 and 2002. These patients had available information in the South Swedish Breast Cancer Group registry, corresponding to 97%. The axillary lymph nodes status was compared with the results of the histopathological examination for the presence of metastases. Tumour size by physical examination was compared with the tumour size after histopathological examination.

Results

There were 674 women with axillary lymph nodes metastases according to histological examination, only 206 of these cases had palpable lymph nodes at clinical examination. The sensitivity was 30% and the specificity 93%. There were 812 tumours measured to be larger than 20 mm according to histopathlogical examination, but only 665 of these tumours were considered larger than 20 mm by clinical examination. This corresponded to a sensitivity of 81% and a specificity of 80%.

Conclusion

We conclude that the possibility of axillary metastases estimated by clinical examination is subjected to a large proportion of false-positive and false-negative results. Similarly, tumour

size estimated by clinical examination is subject to under- and over estimation in comparison to histopathological examination.

Key Words: Breast cancer, Axillary lymph nodes status, Tumour size, Histopathological examination.

Introduction

Clinical assessment of axillary lymph nodes status is an important factor in planning of the surgical strategy in patients with breast cancer (1, 2, 3, 4). The likelihood of axillary lymph node metastases as determined by clinical examination before histological examination remains difficult to predict (3, 5, 6, 7). Clinically palpable axillary lymph nodes are widely considered as a contraindication to the sentinel lymph node procedure (2, 6), as a consequence, a number of patients without regional disease are undergoing axillary dissection with subsequent potential complications (8).

Pre-operative assessment of tumour size in breast cancer is also an important key factor in deciding the appropriate treatment according to current guidelines for the management of breast cancer (9). Tumour size may be estimated using different modalities before surgery, but clinical assessment by palpation remains the first and easiest way to estimate tumour size. There may be a considerable difference between the estimated tumour sizes pre-operatively and after histological examination (1, 10, 11).

This study was based on a consecutive series of 2537 patients diagnosed with breast cancer in Malmö, Sweden, between 1987 and 2002.

The aim of the present study was to determine the accuracy of clinically assessed axillary lymph node status in relation to the presence of metastases as revealed by histopathological examination post-operatively. An additional aim was to compare the pre-operative tumour size as assessed by physical examination, with the size obtained by histopathlogical examination.

Materials and methods

Patient registry

The South Swedish Breast Cancer Group (SSBCG), which was established in1977, has issued guidelines for treatment of patients with breast cancer (12). SSBCG set up a clinical registry in 1981, which continued until 2003. In Malmö since 1977, each patient with breast cancer is reviewed and discussed at a weekly breast cancer conference at which there are representatives from the departments of oncology, radiology, surgery, plastic surgery and pathology.

Decision about the management, i.e. extent of surgery and the use of adjuvant therapy, primarily depends on tumour size, lymph node status, hormone receptor status, age and menopausal status. All this information was entered into the register run by the SSBCG.

Data about the axillary lymph node status by physical examination was collected together with the results obtained by histopathological examination of these lymph nodes. Information was also collected on tumour size according to the physical examination prior to the surgery and after the histopathological examination, TNM, type of surgery and adjuvant treatment.

All information was already available at a computerised database at The South Sweden Regional Tumour Registry.

Study population

All cases with breast cancer diagnosed in Malmö, or registered as residents in Malmö, between 1961 and 2004 were retrieved from The Regional Tumour Registry during the autumn of 2005.

Excluding cases with unknown civil registration number (6), multiple cases in the same individual (1921), benign lesions (26), cases diagnosed before the establishment of the clinical registry at the SSBCG in 1981 (3326), and following end of data collection into the SSBCG registry, 31 Dec 2003 (245), left 4557 cases. Out of them, 202 were not registered as residents in Malmö, 481 had been treated outside Malmö and 28 were found at autopsy. An additional 41 cases had a mismatch between date of diagnosis in The Regional Tumour Registry and the SSBCG registry of more than 180 days. This left 3805 cases. Routines for collection of information in to the SSBCG registry had changed slightly over time, with many missing cases in the beginning of the period and during the last year the SSBCG registry was run. The final cohort consisted of cases diagnosed between 1 Jan 1987 and 31 Dec 2002, in all 2629 individuals. Out of these 2629 women, 2537 individuals had available information in the SSBCG registry, corresponding to 97%.

Statistical methods

Axillary lymph node status by physical examination was regarded as positive in case of palpable lymph nodes, and as negative in case of non-palpable lymph nodes. The axillary status was compared with the results of the histological examination for the presence of metastases. Axillary lymph nodes with metastases were regarded as positive, and those without metastases as negative.

The patients were divided into two groups according to tumour size, those with tumours smaller than 20 mm and those with tumours larger than 20 mm. This choice was made according to the TNM classification (13, 14). Tumour size by physical examination pre-operatively was compared with the size of the tumour after histological examination.

A “positive test” for axillary lymph node status was palpable lymph nodes and for tumour size it was a tumour perceived as larger than 20 mm. Sensitivity, specificity, positive

predicative value (PPV), negative predicative value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and 95% confidence intervals (CI) were calculated. Confidence intervals for the estimated parameters were computed by a general method (based on constant chi-square boundaries) (15).

Comparisons were made in two different periods: 1987-1994 and 1995-2002. Patients were further divided into three age groups. One group assumed to be mainly pre-menopausal with age <50 years, a second group to be mostly post-menopausal with an age of 50-70 years, i.e. women invited to the mammography screening programme, and a third group with postmenopausal women aged >70 years.

Results

There were 674 women with axillary lymph nodes metastases according to histological examination, only 206 of these cases had palpable lymph nodes at clinical examination, and the sensitivity was 30%, the specificity 93%, the PPV 76%, and the NPV 67%, table 1. Sensitivity was low and specificity was high in all age groups. The +LR was 5.1 and -LR was 0.73. No large differences were noticed in relation to different time periods, table 1.

According to histopathlogical examination, there were 812 tumours measured to be larger than 20 mm, but only 665 of these tumours were considered larger than 20 mm by clinical examination. This corresponded to a sensitivity of 81%, a specificity of 80%, a PPV of 72.0%, and a NPV of 87%. Sensitivity related to the pre-operative diagnosis of tumours larger than 20 mm was considerably higher for women older than 70 years, while this group had a lower specificity concerning the detection of tumours larger than 20 mm. The +LR was 4.2 and the -LR was 0.22. All results were similar in relation to different time periods, table 2.

Discussion

Among women with palpable lymph nodes, 24 % had no lymph node metastases, and in women with no palpable lymph nodes 32 % had lymph node metastases according to the histopathlogical examination. This suggests large difficulties in the clinical estimation of the axillary lymph nodes status.

Patients with clinically suspicious axillary nodes comprise a variety of findings. Normal lymph nodes vary widely in size, consistency, and fat content (3, 16). Lymphadenopathy is an element of many non-malignant diseases and reactive adenopathy may not be distinguishable from metastasis (16).

Clinically positive axillary lymph nodes are usually considered as a sign of regional metastases while their absence is regarded as a good prognostic factor (17). However, several previous studies have shown that clinical examination of axillary lymph nodes and estimation of suspicious metastases by palpation is an inaccurate way of assessment even when the examination is performed by an experienced surgeon (2, 18). C Lanng et al showed in a study involving 301 patients that even if the examination was performed by a specialist breast surgeon, the examination had little value. When the surgeons considered the axilla to be normal, they were wrong in 44% of cases (6). Other studies has reported similar results, e.g. Voogd et al who showed in a population-based study involving 5123 patients that 34% of patients who were known to have non-palpable lymph nodes before surgery had positive lymph nodes at pathological examination after axillary dissection (18).

Tumour size by palpation had a high specificity concerning the detection of tumours larger than 20 mm in pre-menopausal women, while it had a low specificity in post-menopausal women where overestimation of tumour size at palpation was most common.

Tumour size estimated by physical examination was used in this analysis although the palpated tumour size is usually used in decision making along with radiological size. This is

particularly the case when dealing with tumours larger than 40 mm where neoadjuvant therapy might be the primary choice of treatment (12). In addition the estimated tumour size is an important factor per-operatively in cases of partial mastectomy and breast conservative surgery in order to achieve sufficient macroscopic marginal.

There are different ways to estimate tumour size, physical examination, mammography and ultra sonography are common methods, and many studies have indicated that measurement by ultrasonography is the most accurate way (9, 19, 20, 21), e.g. Hieken TJ et.al. who showed in a study including 180 patients with invasive breast cancer that ultrasonography is more accurate than mammography in assessing breast cancer size (20). Moreover, Shoma A et.al showed in a study involving 162 patients that it was common to overestimate the tumour size during clinical examination (19).

Overestimation of the tumour size may be due to several reasons. Local bleeding and increased inflammatory reaction/oedema after biopsy could result in an overestimation. In addition, the physical palpation includes not only the tumour but also the surrounding tissue and the skin which in turn might increases the estimated tumour size (3, 10).

Another explanation could be that breast specimens undergo shrinkage after histological fixation, e.g. Docquier PL et.al. (21) and Yaep BH et al. (22) suggested that breast specimens undergo shrinkage after histological fixation, losing more than a third of their original closest free margin, whilst the tumour itself does not shrink substantially.

The strengths of the present study include the size of the sample, more than 2500 patients with breast cancer. The patient cohort was a population-based consecutive series and there was no selection, in terms of tumour stage or other reasons, to or from Malmö University Hospital. Validity of the diagnosis was probably very high as cases were identified from two sources, The Regional Cancer Registry and the clinical registry run by the SSBCG. The histopathological assessment was performed at one department of a limited number of

pathologists, several of them working in the department for decades. Similarly, all pre-operative examinations were performed in the same surgical department.

Our study shows that estimation of suspicious regional metastases by clinical examination is very difficult, and finding palpable lymph nodes during clinical examination in patients with breast cancer does not necessarily mean regional metastases of breast cancer. This is of great importance as palpable lymph nodes are widely considered as contraindication for performing the sentinel node procedure (2, 6), which may save these patients from an unnecessary axillary lymph node dissection (23). On the other hand the absence of palpable lymph nodes in the axilla does not exclude metastases. There are different ways of assessing the axillary lymph node status prior to surgery; i.e. physical examination, radiological examination (ultrasonography, mammography, CT, Pet-CT, and MRI) and needle biopsies. The present study indicates the need for such additional examinations in order to improve accuracy of the pre-operative assessment of axillary lymph node status.

The result of our study also indicate that whenever the pre-operative tumour size at physical examination is used as decision-making value in choosing the appropriate management of patients with breast cancer, there is a clear risk of over- and underestimation of tumour size, and additional measurement by help of other modalities must be taken in consideration.

We conclude that the possibility of axillary metastases estimated by clinical examination is subjected to a large proportion of false-positive and false-negative results. Similarly, tumour size estimated by clinical examination is subject to a considerable misclassification with both under- and over estimation in comparison to histopathological results.

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