Recent advances

Diagnosis and treatment of early breast cancer

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BMJ 1997;314:1736-9

When this review was commissioned, the topic seemed straightforward: early breast cancer. But I struggled, writing pages of unfocused and confusing material, darting back and forth between invasive and non-invasive disease. The problem stemmed from the fact that there is no universally accepted definition of what constitutes early breast cancer. Should an early lesion be defined by size, by the amount of invasion, by lymph node negativity, by clinical or histologic findings, by how long it has been growing? What was meant by early breast cancer 30 years ago, what is meant by early cancer today, and what will be meant by early cancer five to 10 years from now are all different. In addition, today's biologists, geneticists, and clinicians all define early breast cancer differently.

Defining early breast cancer

In 1971 Gallagher and Martin coined the term "minimal breast cancer."¹ It included ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) of any size as well as invasive breast carcinoma with a diameter of 5 mm or less. The object was to create a group of lesions with a nodal positivity rate of 5% or less and a survival probability of 90% or more at 10 years. Today, no one should consider grouping these three disparate lesions together. Lobular carcinoma in situ is a risk factor for the later development of invasive breast cancer; the risk is shared equally by both breasts, and most clinicians do not recommend any treatment.^{2,3} Ductal carcinoma in situ is a heterogeneous group of lesions so diverse and complicated, that a 70 chapter textbook has just been published entirely about it,⁴ and it should not be grouped with small invasive breast carcinomas.

Thirty years ago, early breast cancer was a palpable lesion, almost always invasive, with a diameter of 2 cm or less and without locally advanced signs such as skin oedema, ulceration, or attachment to the chest wall. Axillary lymph nodes were negative, and there were no signs of disseminated disease. The 10 year breast cancer specific survival rate was about 70% for such a lesion, and the average lesion had probably existed and been growing for six to eight years before its diagnosis.

Today, an early lesion is often non-palpable and smaller: 10 mm or less for an invasive cancer, and any size for a non-invasive lesion. Mammography has moved the time of diagnosis forward so that the average early lesion is now about three to six years old

Summary points

There is currently no universally accepted definition of early breast cancer

The best diagnostic tool is mammography, with fine needle aspiration or core biopsy used for definitive diagnosis

Most patients opt for breast conservation treatment: a wide initial excision directed by multiple hooked wires gives the best chance for complete excision first time with good cosmesis

Sentinel node biopsy is preferable to formal axillary dissection for initial treatment of the axilla

Aspirate bone marrow from both iliac crests to check for micrometastases

and a high percentage are non-invasive (ductal carcinoma in situ).

In the future a lesion will hopefully have to be below the threshold of all currently available diagnostic modalities. Early breast cancer will be neither palpable nor visible mammographically. Defining and understanding the molecular genetics of these tumours is likely to be the key to their discovery at a truly early stage.

Methods

Since it was difficult to define early breast cancer, I decided to focus on the diagnosis and treatment of small invasive breast cancer. For this discussion, small invasive breast cancer is defined as an invasive lesion with a diameter of 10 mm or less—in other words, T1a and T1b lesions according to the TNM (tumour, regional nodes, metastases) staging system.⁵ I selected the articles in this review for either their historical importance or their impact on current cancer treatment.

Diagnosing small invasive breast carcinomas

Although mammography has been the single most important factor in advancing the time of diagnosis,

physical examination by both patients (breast self examination) and doctors continues to be important in diagnosing breast cancer. Not all women are able or willing to obtain routine mammography; the age at which to begin screening mammography is hotly debated^{6,8}; the quality of mammography and the ability of individual radiologists vary greatly; and, no matter how good the films and the mammographer, a small percentage of breast cancers (5-15%) are simply not visualisable mammographically.

Physical examination—Most doctors cannot palpate a mass smaller than 8-10 mm during their routine examination, so nearly all T1a lesions (5 mm or less) will be found by mammography or incidentally within a pathology specimen removed for other reasons. Larger T1b lesions (6-10 mm) are more likely to be palpable, particularly if they are close to the skin and the breast is not too large. Most T1b lesions, however, are also likely to be non-palpable and diagnosed mammographically.

Mammography may reveal a small mass, generally irregular but sometimes regular, with or without microcalcifications. The lesion may also present radiographically as an architectural distortion, subtle asymmetry, or may be manifest solely as microcalcifications or increased focal vascularity.⁹

Biopsy is indicated when a mammographic abnormality with a reasonable suspicion of cancer is confirmed. Mammographically guided, fine needle aspiration is capable of detecting malignant cells, but, because fine needle aspiration generally does not remove sufficient tissue, there is no architecture and the presence of invasion usually cannot be confirmed. Because of this, stereotactic image guided core biopsy is probably a better diagnostic tool. If this is not available a wire or dye directed breast biopsy can be performed. I generally prefer core biopsy as a first step: if cancer is diagnosed definitive treatment can then usually be planned before entering the operating room, and if the biopsy is benign open surgical excision can generally be avoided.

The 10 year survival rate for patients with non-palpable invasive breast cancer of diameter 10 mm or less is over 85%, a rate substantially better (by 15-40%) than for patients palpable breast cancer.¹⁰⁻¹³ Some of this advantage (though certainly not all), which is due to lead time bias,¹⁴ will disappear over longer periods of follow up (10-20 years).

Treatment

The past 20-30 years have seen dramatic changes in the treatment of breast cancer, the most important of which has been a shift toward breast conservation, initially motivated by retrospective data, the Women's Movement, and the media, and later supported by prospective randomised trials.^{15 16}

As survival data for infiltrating lesions has accumulated during the past decade, it has been clearly shown that survival after breast conservation treatment—excision of the tumour, dissection of the axillary nodes, and radiotherapy—is equivalent to that after mastectomy for properly selected patients. Furthermore, 12 year data from the national surgical adjuvant breast project (NSABP) protocol B-06 have revealed equivalent survival rates for mastectomy and for lumpectomy with or without radiotherapy.¹⁶ In this study lumpec-

tomy patients who did not receive radiotherapy had a significantly higher risk of recurrence of local breast cancer, but there was no increase in mortality, suggesting that local recurrence in the breast is a marker of poor prognosis but not a cause of distant disease.¹⁷ On the other hand, experimental data in laboratory animals clearly shows that metastases can metastasise.¹⁸

If this is true in humans (and why should it not be?) then local invasive recurrences have the potential to cause systemic disease which may not have been present when the primary lesion was originally diagnosed and treated. This is particularly worrying when ductal carcinoma in situ recurs locally with invasive breast cancer. Local recurrence and metastasis, however, are quite different. Metastases have shown that they have the biological ability to spread to other organs and establish growth. Local recurrences in the breast are, in most cases, continued growth of residual, previously unresected, disease and have not necessarily shown any metastatic potential.

As data confirming the survival equivalence of mastectomy and breast conservation treatment continue to accumulate, the diminished role of mastectomy will decrease even further. The need for radiotherapy in every case of breast conservation will also be questioned, as Veronesi and associates have done for patients over the age of 55.¹⁹ Schnitt et al, however, continue to maintain that radiotherapy is required for all patients with invasive breast cancer, no matter how small or histologically favourable their lesions.²⁰ The differences in these two studies may be explained by the much larger volume of tissue resected by Veronesi et al.

Axillary lymph node dissection

For most of this century, dissection of the axillary lymph nodes was considered both therapeutic and prognostic. In 1985 the results of the national surgical adjuvant breast project protocol B-04 were published.²¹ This trial compared radical mastectomy with total mastectomy (with and without radiotherapy) and revealed no survival difference whether or not the axilla was treated. This study converted our perception of axillary lymph node dissection from a procedure that was thought to be both therapeutic and prognostic to one that was only prognostic, although this position is not accepted by all.²²⁻²⁴

If axillary lymph node dissection is viewed as simply another test that yields prognostic information on which to base decisions about adjuvant chemotherapy, then it will be unnecessary in many patients since the decision to give adjuvant chemotherapy will already have been made based on factors determined during the pathological examination of the primary tumour.²⁵⁻²⁸ For example, most medical oncologists will give adjuvant chemotherapy for tumours larger than 2 cm, some for tumours larger than 1 cm. Most will give chemotherapy for tumours with poor prognostic factors, such as high S phase fraction, aneuploidy, and negativity for hormone receptors. For patients with clinically negative axillary nodes and with tumour markers that already suggest the need for adjuvant chemotherapy, axillary dissection adds little useful information. It does not change the recommendation for chemotherapy, and it may cause some morbidity (short hospitalisation, arm swelling, pain, etc).

Fig 1 Axillary node positivity by tumour category and palpability for 1554 patients. Differences in nodal positivity between palpable and non-palpable T1b, T1c, and T2 lesions were significant (all $P < 0.002$). The 35% difference between T3 lesions were not significant ($P = 0.06$) because there were too few non-palpable T3 lesions ($n = 7$). (Reprinted with permission from Silverstein et al²⁶)

Supporters of routine axillary dissection point out that extensive axillary involvement often brings with it a recommendation for high dose chemotherapy with autologous stem cell or bone marrow transplant and perhaps axillary radiation. These recommendations could not be made without an axillary dissection. Extensive axillary involvement, however, is unlikely in patients with clinically negative axillae. The axillary nodes are affected in less than 10% of all cases of T1a and non-palpable T1b breast cancer (fig 1), and routine dissection for these patients must be questioned.

Sentinel node biopsy

Sentinel node biopsy may be an answer to the current debate about treating the axilla. The sentinel node (or nodes) is the node that is most likely to drain the primary tumour. It can be found with a vital blue dye or radioactive tracer, or a combination of both. The main studies of sentinel nodes reported to date confirm a near perfect correlation with the node status of the dissected axilla.²⁹⁻³¹ In other words, the status of the sentinel node accurately predicts the status of the axilla in almost all cases. Sentinel node biopsy is a simple outpatient procedure once the technique has been mastered. If the sentinel node is negative, no further axillary surgery is indicated. If the sentinel node is positive, some physicians will elect to complete the axillary dissection; others may not.

However, this new technology introduces yet another therapeutic dilemma to the complex process of selecting treatment for breast cancer—micrometastases (metastases with diameter ≤ 2 mm) and how to deal with them. With normal histopathological processing with haematoxylin and eosin stain, a certain percentage of axillary dissections are found to contain metastases, depending on numerous tumour factors such as tumour size, nuclear grade, presence of lymphatic or vascular invasion, and tumour palpability. If pathologists are specifically told: "This is the sentinel node. Please give it special attention," the nodal positivity rises

by about 5-10%.²⁹ If the sentinel node is then processed immunohistochemically for cytokeratin, nodal positivity rises by yet another 5-10%.²⁹⁻³³ If more sensitive techniques are used, such as polymerase chain reaction to a variety of tumour antigens, an even higher rate of nodal positivity can be expected.^{34 35}

Are these tumour cells a marker of systemic metastatic disease or are these "affected" lymph nodes simply doing their job of eliminating a few circulating cancer cells with little metastatic potential? We are not sure of the prognostic meaning of a few positive cells detected by immunohistochemistry or polymerase chain reaction.

My current practice

Just about all patients with small invasive breast carcinomas are candidates for breast conservation treatment, and, if they choose, all of their treatment can be on an outpatient basis. With this in mind, I manage patients with suspicious lesions in the following manner. Fine needle aspiration or core biopsy is performed to confirm that malignant cells are present. I then counsel the patient regarding the pros and cons of mastectomy versus breast conservation treatment. If the patient chooses breast conservation (and most do), I plan a wide initial excision, generally using multiple hooked wires to guide the resection. During this operation I perform a sentinel node biopsy and aspirate bone marrow from both iliac crests to check for micrometastases.³⁶ The patient generally goes home 1-2 hours after this procedure has been completed.

I strongly believe that the initial excision of the tumour is the best time to achieve two opposing goals: wide margins and good cosmesis. As a surgical oncologist, I want the widest possible rim of normal breast tissue surrounding the lesion. From a cosmetic point of view, however, I want to remove the smallest amount of tissue possible. An excision biopsy directed and bracketed by multiple wires gives me the best chance of achieving both goals the first time that I enter the operating room (fig 2). When I fail to get clear margins the first time, re-excision generally diminishes the cosmetic result. After my initial excision, I mark the biopsy site with metallic clips. This aids the radiation oncologist in focusing a boost if one is required. It also aids the radiologist in long term mammographic follow up.

Fig 2 Craniocaudal mammogram taken after insertion of four bracketing wires around an area of architectural distortion and microcalcifications (same patient as in fig 3)

Fig 3 Reconstructed breast after skin-sparing mastectomy and autologous (TRAM flap) reconstruction. The island of skin that has been replaced is circular and exactly the same size as the nipple-areolar complex that has been removed (top). All other skin is breast skin that has not been removed. The size and shape of both breasts are similar. The nipple-areolar complex is reconstructed and tattooed to match the opposite breast (bottom)

If the patient chooses mastectomy, I always discuss immediate reconstruction with her. Small invasive cancers can be safely treated with skin-sparing mastectomy and immediate reconstruction with autologous tissue.³⁷ This type of procedure generally yields an excellent cosmetic result (fig 3).

The future

Our current approach to breast cancer is morphological rather than aetiological; in other words, phenotypic rather than genotypic. It is almost certain that important genetic changes precede morphological evidence of malignant transformation. We must learn how to recognise these genetic changes, then how to exploit them, and, ultimately, how to prevent them. As technology improves and the time of diagnosis is advanced, the definition of early breast cancer will continue to evolve.

Funding: None.

Conflict of interest: None.

- Gallagher HS, Martin JE. An orientation to the concept of minimal breast cancer. *Cancer* 1971;28:1505-7.
- Fisher ER, Constantino J, Fisher B, Palekar AS, Paik SM, Suarez CM, et al. Pathologic findings from the national surgical adjuvant breast project (NSABP) protocol B-17: five year observations concerning lobular carcinoma in situ. *Cancer* 1996;78:1403-16.
- Swain S. Lobular carcinoma in situ. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:595-610.
- Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997.
- Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ. Breast. In: *Handbook for staging of cancer*. Philadelphia: JB Lippincott, 1993:161-7.
- Smart CR, Hendrick RE, Rutledge JH, Smith RA. Benefit of mammography screening in women ages 40 to 49 years. Current evidence from randomized controlled trials. *Cancer* 1995;75:1619-26.

- Tabar L, Fagerberg G, Hsiu-Hsi C, Duffy SW, Smart C, Gad A, et al. Efficacy of breast cancer screening by age. *Cancer* 1995;75:2507-17.
- National Institutes of Health consensus development statement. Breast cancer screening for women ages 40-49. 1997 Jan 21-23. URL: http://odp.od.nih.gov/consensus/statements/cdc/103/103/_stmt.htm.
- Gamagami P. New early signs in breast cancer. In: *Atlas of mammography*. Boston, MA: Blackwell Science, 1996:179, 203.
- Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM. Breast cancer treatment and natural history: new insights from the results of screening. *Lancet* 1992;339:412-4.
- Silverstein MJ, Gamagami P, Masetti R, Legmann MD, Craig PH, Gierson ED. Results from a multidisciplinary breast center: analysis of disease discovered. *Surg Oncol Clin North Am* 1997;6(2):301-14.
- Rosen PP, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol* 1989;7:355-66.
- Rosen PP, Groshen S, Kinne DW, Norton L. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. *J Clin Oncol* 1993;11:2090-100.
- Kopans DB, Halperin E, Hulka CA. Statistical power in breast cancer screening trials and mortality reductions among women 40-49 with particular emphasis on the national breast screening study of Canada. *Cancer* 1994;74:1196-203.
- Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection and radiation therapy in patients with small cancers of the breast. *N Engl J Med* 1981;305:6-11.
- Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995;333:1456-61.
- Fisher B, Anderson S, Fisher E, Redmond C, Wickerham L, Wolmark N, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet* 1991;338:327-31.
- Hart IR, Fidler IJ. Role of organ selectivity in the determination of metastatic patterns of B16 melanoma. *Cancer Res* 1980;40:2281-7.
- Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993;328:1587-91.
- Schnitt SJ, Hayman J, Gelman R, Eberlein T, Love SM, Mayzel K, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer* 1996;77:10941-100.
- Fisher B, Redmond C, Fisher E, Bauer M, Wolmark N, Wickerham L, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985;312:674-81.
- Hellman S. Natural history of small breast cancers. *J Clin Oncol* 1994;12:2229-34.
- Gardner B, Feldman J. Are positive axillary nodes in breast cancer markers for incurable disease? *Ann Surg* 1993;218:270-8.
- Harris J, Osteen RT. Patients with early breast cancer benefit from effective axillary treatment. *Breast Cancer Res Treat* 1985;5:17-21.
- Silverstein MJ, Gierson ED, Waisman JR, Senofsky GM, Colburn WJ, Gamagami P. Axillary lymph node dissection for T1a breast carcinoma: is it indicated? *Cancer* 1994;73:664-7.
- Silverstein MJ, Waisman JR, Gamagami P, Gierson ED, Gamagami P. Predicting axillary node positivity in patients with invasive carcinoma of the breast by using a combination of tumor size and palpability. *J Am Coll Surg* 1995;180:700-4.
- Barth A, Craig PH, Silverstein MJ. Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. *Cancer* 1997;79:1918-22.
- Cady B. The need to reexamine axillary lymph node dissection in invasive breast cancer. *Cancer* 1994;73:505-8.
- Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394-401.
- Alex JC, Krag DN. The gamma-probe-guided resection of radiolabelled primary lymph nodes. *Surg Oncol Clin North Am* 1996;5:33-41.
- Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818-22.
- Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391-8.
- Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993;2:335-40.
- Noguchi S, Aihara T, Motomura K, Inaji H, Imaoka S, Koyama H. Detection of breast cancer micrometastases in axillary lymph nodes by means of reverse transcriptase-polymerase chain reaction. Comparison between MUC1 mRNA and keratin 19 mRNA amplification. *Am J Pathol* 1996;148:649-56.
- Bostick P, Sarantou T, Huynh K, Conrad A, Chawla S, Giuliano A, et al. A multiple marker RT-PCR assay for detection of occult metastasis in frozen section of sentinel nodes from breast cancer patients [abstract]. *Proc Am Soc Clin Oncol* 1997;16:153a.
- Diel IJ, Kaufmann M, Costa SD, Holle R, von Minckwitz G, Solomayer EF, et al. Micrometastatic breast cancer cell in bone marrow at primary surgery: prognostic value in comparison with nodal status. *J Natl Cancer Inst* 1996;88:1652-64.
- Singletary SE. Skin-sparing mastectomy with immediate breast reconstruction: is it safe? *Breast Dis Yearbook Q* 1995;6(3):259-60.