

carcinoma in situ, and 1.4% plus 6.1% of very small tumours, totalling 12% of early cancers. In the screening situation, however, the histology and size distribution is quite different. Among the screen-detected cancers of the first examination, 13% were of the intraductal type, which is comparable with the 2nd screening examination (based on 370 cases). The non-invasive and small invasive cancers up to 10 millimetres now amount to 39% and 42%, whereas in the clinical setting the latter was just 12%. Finally, the percentage of large tumours, i.e. more than 20 mm, declined from 50% outside screening to less than 20% in the screening programme.

In summary, the early outcomes of the Dutch screening programme are satisfying for several reasons. The invitation system is based on a 100 per cent covered population registry with high participation rates. The low referral rates, combined with high predictive values show that the number of false positive screening test results can be minimized. The data further show that the routine application of mammographic screening can attain high quality levels. This means that the 2-yearly screening programme for women aged 50 to 70 will yield the predicted 20% breast cancer mortality reduction.

Literature

1. Nab HW. Trends in incidence and prognosis in female breast cancer since 1955; registry-based studies in south-east Netherlands, dissertation Utrecht, Elinkwijk bv, 1995.
2. Visser O, Coebergh JWW, Schouten LJ, editors. Incidence of cancer in the Netherlands, 1991. Utrecht: SIG Health Care Information, 1994.

Ned Tijdschr Klin Chem 1995; 20: 285-288

Surgical management in operable breast cancer: DCIS, breast conservation and approach of the axilla; state of the art 1995

J. A. van DONGEN

In the past decade, there have been some important changes in the surgical approach of early breast cancer. Screening and adjuvant therapy have greatly contributed to the improvement of survival rates, and a shift towards earlier presentation by the screening efforts has resulted in a much more frequent feasibility of a breast-conserving approach. Several items in the technique and indication for breast conservation are still subject to discussion. The pre-invasive ductal carcinoma in situ (DCIS) is now a frequently diagnosed entity. Important research on DCIS is in progress.

Department of Surgery, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Amsterdam

Prof. Dr. J.A. van Dongen, Department of Surgery, The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), Plesmanlaan 125, 1066 CX Amsterdam.

3. Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the international workshop on screening for breast cancer. *J Natl Cancer Inst* 1993; 85: 1644-1656.
4. Landelijk Evaluatie Team voor Bevolkingsonderzoek naar Borstkanker. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland. Vol III. Rotterdam: Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit Rotterdam, 1994.
5. National Evaluation Team for Breast Cancer Screening (NETB). Nation-wide breast cancer screening in the Netherlands: support for breast-cancer mortality reduction. *Int J Cancer* 1995; 60: 777-780.

Summary

Breast cancer epidemiology and screening in the Netherlands. Verbeek ALM. Ned Tijdschr Klin Chem 1995; 20: 282-285.

Breast cancer is the most common cancer in Holland, with the highest incidence in women aged 50 to 70 years. Premenopausal cancer is related to the ovarian function, whereas postmenopausal cancer is related to exogenous factors. Screening trials including mammography, clinical breast examination and self-examination led to the set-up of specialized screening units and almost 90% of the women aged 50 to 70 years have meanwhile had their first invitation. From 1990 to 1992, 315,000 women were examined and breast cancer was found in 2100 women. The predictive value of the mammography was 50%, and 67% for the following biopsy. Screening significantly advances the diagnosis, while the prognosis for the early cancers forms a far bigger group in the screened population than in the group of clinically diagnosed breast cancer. It is predicted that 2-yearly screening of women between 50 and 70 years will reduce mortality by 20%.

Key-words: breast cancer, epidemiology, screening, mortality reduction, mammography, biopsy.

Treatment of the axilla is still a controversial subject with staging and treatment aspects; new techniques of selecting patients for surgery are now being studied. Some remarks on these important subjects will be given below.

DCIS

Improvements of mammography and the broad introduction of screening in countries with a high breast cancer incidence have raised the number of cases of in situ breast cancer to 15% of all detected breast cancers. Finding the right treatment for this disease is a major challenge in our daily medical practice. A good understanding of the biology is needed to find the optimal therapeutic measures; as for DCIS, there are still many uncertainties (1,2,3). It is difficult to estimate the risk of change to invasive disease, and also the time frame for this to happen is difficult to

predict. The growth rate of the non-invasive lesions is not known and the growth pattern is also a matter of discussion. The majority of DCIS is now thought to be unicentric, but multifocality, representing arborisation of the tumor, occurs very frequently. All these aspects might be different for different subgroups of DCIS. The traditional subdivision into comedo, solid, cribriform and micropapillary types is replaced by systems based upon variables such as the presence of necrosis and the architecture of the lesion. Also the use of biological determinants has been suggested. Modern subdivisions designed by the EORTC/DCIS pathology subcommittee (4) and those developed in Nottingham (3) and used by the Silverstein group (3) have in common that these systems should divide DCIS into categories with a clearly different biological behaviour.

The therapy poses specific ethical problems. Complete removal of the lesion yields a 100% cure rate. Total mastectomy should cure all patients with DCIS. The problem is that it is difficult to recommend mastectomy for non-invasive lesions while at the same time offering breast-conserving therapy for invasive cancers. All data suggest, however, that with less than total mastectomy, the local recurrence rate ranges between 10 and 60% (depending on follow-up time and technique) (5). Half the number of recurrences is invasive and a number of these patients will die of the disease. The addition of radiotherapy reduces the local recurrence rate, but a considerable number of recurrences is still seen. All discussions focus on the definition of a "safe margin": a technically difficult definition for surgeons and pathologists. When very wide margins are certain, the addition of radiotherapy might not be necessary.

A major question is whether the new subclassifications are indeed helpful in identifying the groups with a high risk of progression or in finding groups for which the addition of radiotherapy is not helpful. We need to be very cautious; after a long-term follow-up, "early" results might change.

Breast-conserving therapy

Breast-conserving therapy (BCT) is considered to be a valuable alternative for mastectomy in a large proportion of operable breast cancer patients. The quality of life is improved and the survival rate is not impaired, provided that optimal techniques are used and proper patient selection is carried out. The standard BCT includes wide lumpectomy, axillary clearance and RT to the breast with a boost at the excision area. The results of BCT were compared with those after mastectomy in a number of randomized trials.

Also within the EORTC (European Organisation on the Research and Treatment of Cancer) a prospective randomized trial was performed, comparing mastectomy with BCT. This study also focused on larger tumors (T2; size 2-5 cm). The prospective trials and retrospective studies yielded data which are helpful in answering the large number of questions that are still open in relation to breast-conserving technique and patient selection.

Surgical technique cannot be discussed without

taking patient selection into consideration. This also means that some aspects of patient selection have to be addressed when the technique is described, and vice versa.

There are different opinions about surgical technique details. For lumpectomy, semicircular incisions appear to give the best cosmetic effect, apart from the medial and lateral regions where horizontal incisions are preferable. Cosmesis is improved by using separated incisions for lumpectomy and axillary clearance. En bloc resection is only indicated in cases with tumor localization high in the upper-outer quadrant. In these cases we advocate very wide breast tissue margins to minimize the risk of implantation in the operative field, which might occur when margins are involved. If margins are involved, there is a need to extend radiotherapy to all the areas of implantation risk (in en bloc cases also the axilla), even if secondarily wider breast resections are performed.

Patients with larger tumors and with more advanced nodal status have poor prognosis and this is not so much influenced by local therapy. In patients with poor prognosis, mutilation should be avoided if possible, so BCT should be considered for these patients. Several approaches have been designed to make breast-conserving therapy possible for patients with larger tumors. However, it should be borne in mind that the EORTC study revealed that large size and node positivity are risk factors for local recurrence, especially in the BCT arm (6). Also in this group, local recurrence might change a curable situation to an incurable one in some cases. The The Milano group has advocated an approach in which pre-operative chemotherapy reduces the size of larger tumors, so that a more limited excision is considered to be possible. The effect of this neo-adjuvant chemotherapy on the primary tumor was impressive (7), but longer follow-up should be observed for a final judgement on the value of these breast-conserving treatment approaches for larger tumors. These techniques should be considered as experiments and can only be used in trial setting. For standard care, patients with tumors, in which a local excision with an attempted margin of 1 cm of healthy tissue would not lead to a cosmetically acceptable result, should be treated with mastectomy.

In some (small) subsets of patients (tumor < 1 cm; specific pathologic subtype) exclusive surgery without radiotherapy might be a safe procedure. However, so far, the trials studying such options have not yielded promising results.

Local recurrence means failure of breast conservation; the breast has yet to be removed. Survival might be impaired by the longer tumor exposure; the impact of local control on survival is difficult to prove. The survival curves in the large NSABP study (8) in which one of the study arms was formed by patients treated without radiotherapy, hence with a high proportion of recurrences, still fail to show such a negative effect on ultimate survival for the group as a whole, but the survival rate in a subgroup of smaller tumors with tumor negative nodes was clearly influenced (9). Local recurrences are also observed

after mastectomy, hence only the extra (specific) risk by breastconservation is important in the discussion on contra-indications for BCT. Salvage treatment of recurrence is curative only in a minority of cases and the EORTC study (6) comparing mastectomy with breast conservation showed that survival after treatment of local recurrence was equally bad in both study arms. A higher local recurrence risk after BCT has now reached statistical significance in this trial. This will ultimately be translated to some effect on survival. A comparative analysis of the failures in both study arms will help us in finding specific subgroups in which there is less local recurrence when mastectomy is chosen instead of breast conservation. Creation of a risk score should be helpful to identify patients for whom ablative treatment should be preferred to BCT. In a multi-variate analysis of the data of all patients treated for breast conservation at The Netherlands Cancer Institute, age, completeness of excision and vascular invasion were the major independent prognosticators for breast recurrence (10). In a uni-variate analysis, Extensive Intraductal Component (EIC) was also an important factor; EIC is usually large-sized and complete excision is rarely possible.

With the improvement of the breast reconstruction technique, ablative treatment with direct (or delayed) reconstruction might become competitive with BCT. Especially the transposition of the muscles of the abdominal wall (TRAM flap) gives very good results, because no internal prosthesis is required.

The axilla

The lymph node status is still considered to be of major importance in the cure rate prediction of breast carcinoma patients. Removal of the axilla is thus not only a therapeutic operation but also a staging event. Pre-operative detection of tumor-positive lymph nodes in the axilla is imperfect. Palpable lymph nodes may simply be reactive lymph nodes, whereas impalpable nodes can harbour tumor foci. Attempts to detect occult nodal disease have been made by lymphography and, more recently, by scanning with labeled monoclonal antibodies against tumor antigens. Contrast lymphography was not a reliable tool in the clinic and the other methods are still in an experimental stage, so far with a low specificity and sensitivity. This means that we have to deal with the traditionally incorrect clinical interpretation of the axilla in 30% of the cases.

Some groups state that early treatment of the clinically free axilla has no impact on the cure rate. Delayed treatment, when metastatic disease becomes evident, should then be equally effective. The fact that delay will never actually improve prognosis should, however, be considered as a fundamental argument for early dissection. Moreover, tumor outgrowth in the untreated axilla might be locally inoperable, leading to serious impairment of the quality of life.

The introduction of a sentinel node biopsy might be helpful so that patients can be selected more precisely for axillary clearances. The use of sentinel node

biopsy for selecting patients for treatment of the regional lymph nodes was described for melanoma by Morton and co-workers in 1992 (11). The value of this technique is currently being investigated in several centers. The Netherlands Cancer Institute has now gained experience with more than 50 patients, mainly with melanoma. Experiences with the first 30 patients were published by Nieweg et al (12). The hypothesis is that dissemination first occurs in the lymph node situated at the other end of the lymphatic vessel draining the primary tumor. This node is called sentinel node or first echelon node. Spread of tumor cells to other nodes occurs from the sentinel node as a secondary source or from the primary lesion when the sentinel echelon node is occluded by extensive tumor growth. With this technique, metastatic tumor cells are found in clinically normal nodes in approximately 20% of melanoma patients. In less than 1% of the cases, metastatic tumor cells are found in other nodes, when the sentinel node is tumor-free. At our Institute, unsuspected metastases were found in 12% of patients for whom this new approach had been used.

A research project was started by Nieweg at The Netherlands Cancer Institute with the object of testing the possible suitability of this procedure for selecting patients with breast cancer for axillary clearance. Now, axillary node dissection forms an integral part of the surgical treatment for breast cancer. Lymph node dissection is thought to be of value for staging and regional tumor control, and in some patients with metastatic nodes, the axillary clearance may bring about a cure. The hypothesis to be tested is that dissemination in breast cancer patients also occurs first in the lymph node on the direct drainage pathway from the primary tumor and that only after this first step other regional nodes become involved. If the hypothesis proves to be correct, the first echelon lymph node will play a pivotal role in lymphatic dissemination.

The objectives of the study are to investigate:

- whether this first echelon axillary lymph node can be identified and
- whether the presence or absence of tumor cells in this first echelon node is indeed indicative of the presence or absence of tumor cells in the remainder of the axilla.

Patients who are scheduled for modified radical mastectomy are eligible for this study. Following injection of patent blue dye in the tumor at the beginning of the operation, mastectomy is performed in the usual manner. The specimen is dissected after the completion of surgery. The blue stained lymphatic channel coming out of the tumor will be sought and dissected until it enters the first blue stained lymph node. This node will be excised from the specimen and examined separately. In a subsequent study, Nieweg and his group will investigate the sentinel node during operation. The additional use of lymphoscintigraphy and a small gamma ray counter for intra-operative use will be helpful to localize the node that we are looking for. Still, standard mastectomy will follow. The sentinel node exploration area will be

included in the specimen. In both parts of the study, the results of the histological examination of the sentinel node and the remainder of the axillary nodes will be compared.

If this technique proves to be suitable for finding this strategic node and if the aforementioned hypothesis proves to be correct, then axillary lymph node dissection can be reserved for patients with metastatic tumor in the first echelon lymph node. Then 60% of breast cancer patients will be spared a useless surgical procedure. With such an approach, the same information for staging and the same local regional control as in current practice will be obtained. Initial experience has confirmed the feasibility of such an approach; it was possible to find a sentinel node in all tested breast cancer cases.

Literature

1. Dongen JA van, Fentiman IS, Harris JR, et al. In situ breast cancer: the EORTC consensus meeting. *Lancet* 1989; 2: 25-27.
2. Dongen JA van, Holland R, Peterse JL, et al. Ductal carcinoma in situ of the breast: second EORTC consensus meeting. *Eur J cancer* 1992; 28A: 626-629.
3. Recht A, Dongen JA van, Fentiman IS, et al. Third meeting of the DCIS working party of the EORTC, Venezia 28 Feb. 1994 - Conference report. *Eur J Cancer*, in press 1994.
4. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. *Seminars in Diagnostic Pathology* 1994; 11: 167-180.
5. Dongen JA van, Peterse JL. Ductal carcinoma in situ of the breast. *Oncology & Haematology* 1995; 2: 8-11.
6. Dongen JA van, Bartelink H, Fentiman IS et al. Factors influencing local relapse and survival and results of salvage treatment after Breast-conserving therapy in operable breast cancer: EORTC trial 10801, Breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer* 1992; 28A: 801-805.

Ned Tijdschr Klin Chem 1995; 20: 288-293

High dose chemotherapy in breast cancer reviewed

J. W. BAARS¹, S. RODENHUIS¹, E. van der WALL^{1,2} and J. H. SCHORNAGEL¹

Breast cancer develops in approximately 10% of women in Western Europe and the United States of America (1-4). Of those who contract the disease, one out of three to four will die (1-4).

Despite modern treatment techniques (3,4), the mortality rate has remained essentially unchanged in the last 50 years.

Department of Medical Oncology¹, Antoni van Leeuwenhoek Ziekenhuis, the Netherlands Cancer Institute, Amsterdam and Academic Hospital of the Free University, Department of Medical Oncology², Amsterdam

Address correspondence to: J.W. Baars, Department of Medical Oncology, the Netherlands Cancer Institute, Antoni van Leeuwenhoek Ziekenhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.

7. Bonadonna G, Veronesi U, Brambilla C, et al. Primary chemotherapy for resectable breast cancer. *Rec Res Cancer* 1993; 127: 113.
8. Fischer B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumor recurrence after lumpectomy. *Lancet* 1991; 338: 327.
9. Stablein, et al. A reanalysis of NSABP protocol B06. Report Emmes Corporation. March 30, 1994, table 10, p 14.
10. Borger J, Kemperman HJWPM, Hart AAM et al. Risk factors in breast conservation therapy. *J Clin Oncol* 1994; 12: 653.
11. Morton DL, Wen DR, Wong JH et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127: 392-399.
12. Nieweg OE, Baidjnath Panday RKL, Muller S et al. Lymphoscintigraphy, lymphatic mapping and sentinel node biopsy in melanoma patients using a single dose of ^{99m}Tc-colloid. *Eur J Surg Oncol* 1994; 20: 332-333.

Summary

Surgical management in operable breast cancer: DCIS, breast conservation and approach of the axilla; state of the art 1995. Dongen JA van. Ned Tijdschr Klin Chem 1995; 20: 285-288.

Ductal carcinoma in situ (DCIS), breast conservation and the approach of the axilla are major controversial aspects in breast cancer surgery. DCIS discussions focus on new useful subclassifications and possibility of breast conservation. Research has given better insight in biology of DCIS.

Breast conserving therapy (BCT) gives equal survival rates if compared with mastectomy. The slightly elevated local recurrence risk is not yet translated into worse survival. Riskfactors for the excess local recurrence risk by BCT are being identified. Experiments are ongoing to test different BCT techniques for the very small and for the larger breastcancers. Removal of the axilla has important staging aspects and is therapeutic for patients with positive nodes. A research project is initiated to study if a "sentinel node biopsy" can be used as reliable guidelines to select patients without palpable nodes for axillary clearance.

Key-words: breast cancer, carcinoma in situ, breast conservations, axillary clearance, sentinel lymph nodes.

It is well known that the probability of survival at 10 years after diagnosis correlates with the number of involved axillary nodes at the time of mastectomy (1,2,5). Following local regional treatment with surgery, women with 1-3 axillary lymph node metastases have a 10 year relapse rate of 65%-70%. The outlook for women with 4 or more lymph node metastases is even worse, with a 10 year relapse rate of 84%-86% (6). A meta-analysis conducted by The Early Breast Cancer Trialists Collaborative Group (EBCTC) confirmed the data of randomised trials that the disease-free and overall survival of premenopausal stage II (axillary lymph node metastases) breast cancer patients can be improved by adjuvant chemotherapy (7). Although the benefit of adjuvant chemotherapy could be observed in all nodal categories, the final