Reviews in Oncology 2 (1989) 1
(in Acta Oncologica Vol. 28, Fasc. 1)

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EARLY BREAST CANCER

A review

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Abstract

The therapy of early breast cancer has been changing during the last decennium. It requires a multi-disciplinary approach and in each of these disciplines improvements have been implemented. The result is that treatment schedules can now be adapted to specific subgroups. In this review early breast cancer is defined as operable disease, using the critera set out by Haagensen. Emphasis is given to describing the new developments in prognostic criteria, since these form the basis for creating subgroups for specific treatment schedules. Distinction is made between the factors relating to growth rate and those relating to metastatic potential. Data on screening promises a beneficial effect of the implementation of screening in national health care programs. Important shifts are seen in treatment schedules; the place of postoperative radiotherapy after classic ablative treatment is being challenged, whereas it plays a major role in the new breast conserving therapy schedules. The data mentioned in the review suggest that a large proportion of 'operable' cases can be treated with breast conservation but details in the technique of breast conserving therapy are still under investigation. They form a major part of the coming prospective studies in breast cancer. Improvements in reconstruction techniques, creating better cosmetic results, make reconstruction more competitive with breast conserving therapy. The use of chemotherapy and endocrine manipulation in early breast cancer has now been clearly confirmed by the overview technique by the Peto-group, thanks to all efforts of individual trialists together.

Key words: Breast cancer, treatment early breast cancer, prognostic factors, breast conserving therapy, therapy options.

Many important changes in the treatment policy of breast cancer have been seen in recent years. The treatment of breast cancer requires a multidisciplinary approach and in all the areas of surgery, radiotherapy and medical treatment significant important improvements have been achieved over the last few years. Therapy schedules have been designed specifically for individual subgroups and their use tested in prospective trials has sometimes led to an improvement of the overall treatment results. This is certainly true for the quality of life aspects, but the effect on survival is more difficult to prove; pooling of data from several prospective studies with long follow-up is therefore necessary. In view of the abundant literature a review has to be selective. It is impossible to mention all important work, even when trying to restrict oneself to innovating aspects. Also simplification of the problems is unavoidable.

Definition of early breast cancer

There is no consensus in the definition of early breast cancer. It was decided to restrict this overview to operable patients with invasive cancer. Their disease is hoped to be localized in the breast and proximal lymph node regions. The 'locally advanced' cases, which may also have disease confined only to breast and regional area, are inoperable and preferably treated by primary radiotherapy often supplemented by hormonal therapy or chemotherapy. These patients are excluded from this overview.

The criteria for differentiating early (operable) breast cancer from the locally advanced cases have been defined carefully by Haagensen (1), the godfather of the breast carcinoma scientists. He also introduced internal mammary node and apex biopsies to separate the operable group from those who will benefit more from primary radiotherapy (2). The TNM system designed to divide the patients into different prognosis groups was not always workable in the sense of separating the operable patients from the locally advanced cases which need to be treated with different treatment techniques. The last adaptation of the TNM system (3) did achieve an improvement in this respect.

The proportion of breast cancer patients belonging to the group of early breast cancer and the composition of this group is changing with the years. Better techniques

for staging a patient mean that by more accurate exclusion of cases with clinically occult distant disease, the operable group seems to have a better prognosis than in the past. On the other hand this group will then be smaller. By the introduction of the screening programs a shift towards more early tumor types is seen.

We have to realize that there are grey areas between malignant and benign breast disease. The distinction of invasive cancer from lobular and ductal carcinoma in situ, and even from the different types of hyperplasia is not always clearly defined. This hampers the formation of a circumscribed group of patients with early breast cancer. The pathologists are now making a worldwide attempt to reach consensus in defining groups by means of objective and reproducible criteria.

The in situ ductal carcinoma (DCIS) is a specific entity, quite different from the group of early but invasive breast cancer. The treatment policy has been discussed in a recent EORTC workshop (4). Discussion of this subject is omitted from this review. Also the lobular carcinoma in situ will not be discussed, this being a condition where a wait-and-see policy is generally thought to be the most appropriate. Another complication is that the definition of tumors considered to be locally advanced is not the same in all centers.

Need for and pitfalls of prospective studies

With all the changes in the composition of the different groups we have to realize that randomized prospective studies are the only way of providing answers about the effectiveness of new treatment schedules in breast cancer. Comparison with historical controls is not acceptable. In addition, the fact that usually not one but several therapy details have been changed during the same period makes it impossible to get information on the impact of one particular treatment change in retrospective non-randomized studies. It is clear that historical controls are also unsuitable for studying the importance of specific therapies for specific subgroups of patients when such subgroups are defined by new techniques in tumor characterization.

Breast cancer, however, is a slowly growing malignancy. This implies that long follow-up periods are necessary before final conclusions can be drawn on the treatment of early breast cancer. Now that many cancers are detected by screening, the problem of lead time will be more pronounced making long-term follow-up even more necessary. This means that the answers will reach us far away in the future and in the meantime new developments in selection and therapy options may make the original questions irrelevant.

Breast cancer is a frequent disease. Some answers might be solved in unicenter studies, but usually the expected differences are so small that very large numbers of patients are needed to show any superiority of one regimen over another; this even more so when we want to look into effects in subgroups of patients. The use of overview techniques, i.e. the collection of data from several centers, as introduced by Peto (5, 6) helps to solve such problems, but introduces in itself other difficulties, such as loss of homogeneity in the composition of the selected groups and in the therapy technique used. Large prospective multi-center studies are usually the best way to study therapeutic breast cancer problems.

Biology and denominators of biologic behavior

In the last decade the curability of breast cancer has frequently been a matter of discussion. Fisher and his group (7) challenged the classic cascade hypothesis, which indicates a step-by-step progression from local disease to nodal metastasis and finally distant spread, which made optimal loco-regional treatment imperative. The Fisher group propagates the idea of either generalized disease or not from the onset, nodal metastases being only indicators of distant spread. Local treatment would then have no or very little influence on the ultimate course of the disease and would serve as local control only. Their view, however, is probably too defeatist. A substantial number of breast cancer patients with nodal disease is alive and well after 15 years or more (8). Also, the reduction in breast cancer mortality reported from some screening programs clearly indicates that early treatment is beneficial. Better local control means more cure. Most breast cancer patients have an initial period without occult micrometastases. Loco-regional recurrence indicates a longer duration of tumor present in the body, with an increasing risk of producing metastases. The poorer prognosis in patients with local relapse after inadequate loco-regional treatment is difficult to demonstrate and it is clear that long-term follow-up in randomized studies of substantial size is necessary. Hayward et al. (9) was able to demonstrate such an effect and it is to be expected that in the long run the same will become clear in other studies (10).

The fate of the patient is not only determined by the metastatic potential but also by the growth rate, so the prognosis is a complex matter. Survival rate (always to be estimated in relation to a certain follow-up period) is not identical with cure rate. Patients with slow growing disseminated disease still can have a fairly long survival. This point is especially important in breast cancer, since very slow tumor growth is noticed rather frequently, with metastatic disease becoming apparent incidentally even after 15 years. It might be sensible to divide the prognostic factors into indicators of distant dissemination and indicators of growth rate. The use of prognostic factors, in particular those indicating the metastatic potential, is especially important since the adjuvant treatment given at the time of loco-regional therapy, with the aim of killing micrometastatic disease, is rather toxic. We want to be able to outline specific subgroups of patients with 'early' disease, whose tumors have an increased risk of being

already disseminated and for whom adjuvant therapy would seem to be more profitable than for the other groups.

Also the information gained from prognostic factors might be of use for the choice of the loco-regional treatment schedule. Mutilating treatment might be too high a price to pay for a small chance of cure.

Prognostic factors indicating cure rate. The best prognostic factor is the loco-regional stage of the disease, i.e. the size of the primary tumor and the nodal status (number and level of nodes with metastases). The TNM staging system is designed to separate as well as possible the groups with different ultimate prognosis. The reliability in this respect of the T and N components is far from perfect. Roughly 30% of the node negative, operated patients have a bad prognosis and even 36% of patients with more than 4 positive nodes are still alive and well after 10 years provided that also an apex biopsy is used for the selection of operable patients (11). Likewise prognosis is related to the size of the tumor, but—again—this is not a fully reliable indicator. We may improve predictability by adding other indicators of metastatic potential. Histological grading is usually considered to be the most useful, but most factors mentioned in grading may merely be items which indicate the growth rate. Probably only the degree of angio-invasion will reflect an increased capacity to disseminate.

The prognostic value of the level of steroid hormone receptors in breast cancer is controversial (12, 13). It has been frequently stated that when steroid hormone receptors are lacking the prognosis is poor. This may be true for the patients who receive endocrine therapy but a complete generalization of such a statement is not necessarily valid. The improvement of techniques demonstrating the receptor content (now using monoclonal antibodies, by which it has become possible to study material retrospectively) may be helpful in confirming whether or not steroid hormone receptors have a real prognostic value.

Prognostic factors which indicate mainly growth rate. These are indicators for a rapid or slow course of the disease if metastases are present; they do not predict the ultimate cure rate. Such factors are of another magnitude than those indicating metastatic potential, certainly when considering indications for additional (adjuvant) treatment. Nevertheless it is important for patient and doctor to know whether, if metastases do appear, this will be early or late. It is not unlikely that the epidermal-growth-factor-receptor (EGFR) (14), which was recently shown to correlate with early prognosis in breast cancer, belongs to this category.

'Grading' of a tumor probably utilizes factors mainly indicating growth rate but reproducible grading systems are hampered by the many inter-observer differences. The introduction of morphometry is an attempt to solve this (15): the grading is standardized and made reproducible, e.g. by using computer analyses of the histology images.

The use of cell kinetic parameters has likewise been introduced to indicate prognosis (13). This again is mainly related to the speed of growth. Some groups have used the labelling index to identify, in the group of node negative patients, a subpopulation which would profit from adjuvant therapy (16). If the high labelling index specifically indicates a more rapid growth rate of occult metastases and not the metastatic potential, the advantage of adjuvant therapy in the high labelling index cases would show only in the first years whereas in the low labelling index cases it would be expected at a later date. From such a point of view the selection of patients for adjuvant therapy based on their labelling index might need reappraisal from studies with long follow-up. Also the more recently described prognostic features, such as the level of cyclic AMP binding protein in breast cancer tissue, could be an expression of growth rate, since it appears not to be related to standard prognostic factors such as node status. The influence on survival and recurrence rate have indeed only been investigated in short-range follow-up studies so far (17). However, growth rate and metastatic potential may be interrelated. Tubiana concluded from his material based on long-term studies (follow-up periods of more than 15 years) that the cases with a low labelling index do keep a lower probability of relapse, over very long intervals (18). On the other hand information is coming from screening programs that interval cancers do not have a worse prognosis if compared with screening-detected cancers of the same size, where it is to be expected that the growth rate is higher in interval cancers (19).

The same uncertainty exists about the interpretation of the prognostic importance of probes derived from molecular biology. The presence or amplification of specific oncogenes might be associated with prognosis. The group of Slamon & McGuire (20) suggests a relationship with survival. Data of the Amsterdam group (21), however, where the development of monoclonal antibodies against neu-oncogene has enabled the study of patient series retrospectively, did not show a significant relationship with prognosis in stage II breast cancer when data were corrected for tumor size, etc. Moreover, they found a very high percentage of cases staining with monoclonal antibodies against the neu-oncogene in the comedo type of DCIS, by definition a non-metastasizing tumor condition. The Amsterdam group believes that the oncogene expression is mainly related to growth rate.

Other prognostic factors. Adequate therapy is a major prognostic factor. Patients who are not treated at all will die from the disease and in the majority this will be within 5 years after detection of the tumor, the mean survival time being 30–40 months (22, 23).

It is not unrealistic to postulate that there are also patient-related prognostic factors, such as age (24) and lymphoreticulo endothelial response (25) but the literature is controversial. It is obvious that other previous or concomitant diseases will influence prognosis—also due to

their influence on the choice of therapy for the breast cancer.

Several other factors have been suggested to be important for prognosis, but have not been proved. The use of flow cytometry, giving information on the ploidy of cells has been disappointing (13); also endocrine characterization of patients appears not to be of practical value. The same is true for the search for specific enzyme patterns, which might also indicate tumor growth rate.

It is unclear whether certain risk factors for developing breast cancer also indicate a risk situation for subsequent rapid tumor growth or high metastatic potential. Do, for instance, patients from breast cancer families have more malignant tumors? The methodology for investigating such questions is frequently very complex and solid answers are not to be expected.

The sensitivity of the tumor to chemotherapy and/or endocrine manipulation can—in itself—also be considered as a prognostic factor influencing certainly survival time. With our presently available methods these therapeutic manipulations never influence the final cure rate in cases with overt metastases. When used in adjuvant setting the option is also to improve the ultimate cure rate. Demonstrating and measuring the sensitivity to chemotherapy and/or endocrine manipulation is not easy and certainly never absolute. The steroid receptor studies have provided the clinician with relevant and reliable tools. Such factors, when not used for selection of patients for adjuvant therapy, might in the light of time as yet be considered to have certain prognostic importance.

Screening for breast cancer

The rationale for screening in breast cancer is the better treatment result when the tumor is detected at an early stage. The aim of many ongoing studies is to confirm this postulate (26, 27). Screening for breast cancer is generally done using mammograms. This diagnostic method is particularly effective for the older age group, where the frequency of breast cancer is highest, since in these patients the imaging properties are enhanced due to regression of dense glandular structures over the years.

Technical improvements have reduced the radiation dose of mammograms to a very low level, with a virtually negligible toxicity (late risk) (28). The sensitivity and specificity of the mammography depend largely on the quality of the mammograms. This means that within screening programs quality control projects are very important. It is clear that adherence of the population to screening programs has a direct relationship with the effectiveness of screening.

Some studies show an amazingly high reduction of mortality. Already 7 years after the start of the randomized Swedish two-county-study a reduction of breast cancer mortality of 30% has been registered (29). The late results of the HIP study (30), which was performed with in modern standards suboptimal mammography, continue to show a reduction in breast cancer mortality for the screened population. It is interesting that in this late analysis there also appears to be a reduction for the age group under 50. In the HIP study physical examination was also included and this might have contributed to the benefit for the group under the age of 50. The impact of physical examination in screening programs is now being studied in Canada (31). This study will specifically provide information on the benefit of the combination of mammography, physical examination and breast self-examination. A program to evaluate the effect of stimulating self-examination is being studied in a randomized setting in Moscow and Leningrad (32) and several other programs are underway in many countries to confirm the favourable screening results and to address open questions. In Holland two large screening studies were initiated more than 10 years ago, using a case control approach (33, 34). They show an important reduction in mortality from breast cancer in women over the age of 50. It should be realized that such data indicate a benefit for women who are screened but do not give complete information on the effect of screening programs since this also depends on the response rate (adherence rate) of the group of women invited to participate. From the Dutch studies it is clear that the attendance rate can be disappointing despite extensive promotion of activities by the organizing groups. It may, however, be expected that when the benefit of screening becomes more obvious and more widely known, the compliance of the women invited will be higher. Some points are still unsolved in the search for optimal screening systems: for example, should women under 50 also be screened and what is the optimal interval between screening rounds (35)? There is a tendency to shorter intervals for the younger age groups. In view of the very promising reduction in breast cancer mortality seen in several countries so far, breast cancer screening programs are now being initiated by governments and cancer societies worldwide.

The choice of the optimal primary therapy

The essential option of local treatment is to realize local control, which is essential for the quality of life. Local control should be maximal since, as was stated earlier in this review, local relapse impairs the survival and cure rate. Therapy might be tailored for different tumor presentations (e.g. different tumor stages).

The classic Halsted approach (removal of breast and axilla en bloc, including the muscles between breast and regional area) is now considered to be an overtreatment of many patients.

Changes in the therapy plan are now becoming possible by means of a better and more precise staging, a better insight into the biologic behavior and by better possibilities to predict prognosis. Such improvements in knowl-

edge could lead to the delineation of subgroups of breast cancer patients where less extensive treatment is equally effective as the standard radical mastectomy. Less extensive treatment might mean treating only the breast or even only part of the breast. Also alternatives for complete surgical treatment of breast and lymph node area have emerged, for example a combination of limited surgery and aggressive radiation, resulting in less mutilation.

The area to be included in the primary treatment, the breast

Unexpected extension of the tumor in the breast and multicentricity/multifocality have been considered arguments to include the whole breast in the routine treatment of breast cancer. This viewpoint can be, and has been, challenged (10, 19, 36).

The argument of multifocality/multicentricity for performing a complete mastectomy on the side of the reference lesion would only be reasonable if multifocality is a predominantly unilateral disease. However, such a concept is not based on data. Many pathology studies have even underlined that there is an equal risk of microfoci of tumor in the other breast. Also the interpretation of the clinical importance of such microfoci in both breasts is difficult; many are in situ lesions of which we do not know the biological behavior. The younger the patients the longer the time at risk for developing a second tumor in the remaining breast tissue. However, even in young patients this risk for the other breast is usually accepted and only few centers consider 'preventive' measures.

Tumor extensions (seen in some pathological sections as multiple foci) form strong arguments for not relying on treating only a small part of the breast. The important work of the Nijmegen group (37) shows that only outside a zone of 4 cm around the reference tumor is the risk of such 'extensions' negligible; in other words, treatment of tumor including a 4 cm zone may be sufficient. This finding was independant of the size of the tumor. Possibly the histology is of influence. Those tumors with an extensive ductal carcinoma in situ component might have more extensive arborization. From such data we might conclude that for the majority of cases very wide excisions (with at least a 4 cm margin) are as effective as removing the whole of the breast.

Many older series have already shown a considerable risk for breast recurrence after local excision alone, even when free margins were histologically confirmed, but in these studies certainly no 4 cm margin was used. This risk was very convincingly shown in a NSABP study where the importance of the subsequent radiotherapy was investigated in a randomized setting (36).

Randomized studies to study the safety of the very wide excisions alone (feasible only in very small tumors because of the cosmetic implications) have now been initiated in Milan (10) and Sweden (19).

The area included in the local treatment: axilla

Staging in cancer has been improved largely by better imaging techniques, but detection of tumor positive lymph nodes in the axilla is still imperfect. Palpable lymph nodes may simply be reactive lymph nodes, whereas on the other hand impalpable nodes can harbour tumor foci. Attempts have been made by lymphography and, more recently, by scanning with labelled monoclonal antibodies against tumor antigens, to detect occult nodal disease. Contrast lymphography was not a reliable tool in the clinic and the other methods are still in an experimental stage, having so far low specificity and sensitivity.

This means that we have to deal with the traditional 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 cure rate. Delayed treatment, when metastatic disease becomes evident, should then be equally effective. Also a number of patients already have signs of distant spread when the nodes become palpable. This problem of knowing the best approach for the N0 situation has been the subject of a randomized NSABP study (38), which seemed to indicate that a wait-and-see (delayed treatment) policy would be 'safe'. These conclusions have been challenged by Harris (39) who states that from a methodological point of view the NSABP conclusions were not possible. He calculated that in 5 to 10% patients with 'early disease' cure is attained thanks to 'effective axillary treatment'. For this group one should consider to what extent delay of treatment would impair prognosis. The gain will certainly not be of great magnitude, thus requiring very large studies. The fact that delay will never actually improve prognosis can 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. Since axillary clearance also provides us with staging information to be used in the selection of patients for adjuvant therapy, it is generally considered to be an important routine part of primary treatment, even by the NSABP group.

When the staging information becomes less important for therapy planning, discussion will be renewed. To outline subgroups where early treatment will be specifically beneficial, should then be an important, albeit very complicated, task.

It is now generally accepted that after complete axillary clearance, postoperative radiotherapy directed at the axilla and periclavicular region (McWhirter field) is only very rarely indicated. Routine postoperative irradiation of the axilla creates serious morbidity (arm edema) in a high percentage of cases.

Primary radiotherapy without surgery of the axilla in N0 cases is advocated by some groups. This is only reasonable if the toxicity of axillary irradiation is less than that after axillary clearance. So far no randomized studies

have been published which compare these toxicity aspects.

The area to be included in the primary treatment: the parasternal nodes

If treatment of the axillary nodes is considered important not only for staging purposes but also for disease control, then the same should apply for the parasternal nodes.

The fact that some long-term survivors are seen in the patient group where tumor positive parasternal nodes have been removed, suggests that for a subgroup of breast cancer patients indeed treatment of this area adds to survival and cure. Since, however, it has not been possible to illustrate this clearly in randomized studies, the number of patients profiting will be small. Only one randomized study has addressed this question and within that study the conclusions and interpretation of the data seem to be difficult and controversial. In the first report a distinct advantage following the extended operation was reported for the subgroup of patients with tumor located in the central or medial part of the breast with proven positive axillary nodes (40). This was recently confirmed by the long-term follow-up of patients in one of the participating centers (41) but challenged by the other main participant of this trial (42). It is generally postulated that radiotherapy alone directed to the parasternal area can produce the same effect as surgery. Despite the fact that there are no data to substantiate such a statement, it does not seem to be advisable to perform extensive operations with increased morbidity to achieve an unproven, certainly only small, increase of the possible positive effect. Therefore radiotherapy is generally preferred to surgery of the retrosternal area.

One of the pitfalls of radiotherapy is that the target area is difficult to delineate. Lymphoscintigraphy has shown that standard parasternal fields indeed do not cover the nodal area at risk in 30% of the cases (41) and the possibility of adjusting the parasternal field is one of the major advantages of the lymphoscintigraphic technique. Fletcher frequently emphasizes that many of the data which are used to deny a profitable effect come from groups where the radiotherapy was performed inadequately; he is a proponent of this adjuvant radiotherapy.

In a Norwegian study (43) a beneficial effect was seen even using parasternal irradiation without scintigraphy to outline the target volume.

Specific subgroups, for which the extra treatment of the parasternal area might be considered, are the medially and centrally localized tumors and all patients with positive axillary nodes (irrespective of the localization of the tumor in the breast). Other groups select their patients for parasternal treatments only based on the size of the tumor in the breast.

Recently Cuzick et al. (44) concluded from overview studies that adjuvant radiotherapy after breast surgery (including parasternal irradiation) might not only be ineffective but also harmful, as a result of radiation toxicity to the heart. The discussion about the indication for and optimal technique of the parasternal irradiation (c.q. parasternal dissection) has certainly not come to an end.

Therapy choice; ablative therapy or breast conservation: a dilemma

Until recently the standard treatment of stage I and operable stage II–III breast cancer has remained ablative, despite pioneer work on breast conserving therapy as early as in the 1920s (45). Increasing pressure by several, mainly French, groups culminated in a conference on breast conservation in Strasbourg in 1970 (46).

The mutilation aspect of the loss of the breast has been investigated many times and it is clearly shown that ablative therapy causes considerable impairment of the quality of life (47). It is therefore essential that the selection of patients for amputation should be done with great care.

As an example, for some time already patients with a high risk for recurrent disease have not undergone amputation because primary radiotherapy was considered to provide a good alternative before the inevitable development of distant disease. The result in this group encouraged the development of the breast conserving approach, whereby part of the surgery was replaced by aggressive radiotherapy. Breast conservation should lead to an important improvement of the quality of life (48).

Breast conserving therapy in operable cases became more widely accepted as a result of the convincing data collected in randomized studies. The Milan data (49) showed clearly that, in patients with small tumors and without palpable nodes, survival after wide quadrantectomy and axillary clearance, followed by radiotherapy to the breast, was equal to survival after amputation. The recent NSABP data (36) and the data from the EORTC study (50) suggest that also for larger tumors the results are equivalent to those of mastectomy. Since breast conserving therapy always involves lumpectomy and the size of the lump will affect cosmesis, one important consideration beforehand is the size of the tumor in relation to the size of the breast.

Ablative treatment: variations in technique

Following the principles set out by Moore (51), an operation to ensure maximal local control was designed both in the USA (52) and in Germany (53) as early as at the end of the 19th century. Since then this operation, the radical mastectomy (removal of breast, pectoral muscles and axilla en-bloc) has been the treatment of choice for operable, early breast cancer.

An excellent book on the history of breast cancer treatment was published by De Moulin on the occasion of the 3rd EORTC Breast Cancer Conference in 1983 (54). In this broad historical overview one of the chapters was dedicated to the development of modern surgery, indicat-

ing that many more names besides that of Halsted should be linked to the classic radical approach to breast cancer. There have been several variations of the radical mastectomy suggested in the past in an attempt to achieve better local control or less mutilation, but they have not been shown to affect survival. The superradical approach in which the parasternal and sometimes also the supraclavicular nodes were removed, did not lead to a significant improvement (42).

On the other hand steps towards more limited surgery, leaving in situ the pectoralis major muscle (55) or both pectoral muscles (56), did not seem to impair the cure rate, albeit that no reliable randomized studies are available to confirm this. The aim of such operations was to improve the quality of life and indeed there is some cosmetic improvement by leaving the pectoral muscles intact. Also the operation provides some advantages for secondary reconstructive procedures. However, it must be remembered that these advantages are small and the loss of the breast still remains the major mutilative factor. In addition, problems of paresthesia caused by the resection of the intercostobrachial nerves, as well as the phantom breast phenomenon, are no less than for other types of mastectomies (57). Measuring the quality of life after the different procedures is a complex affair, since the tools required for objective estimation are not always easy to handle.

Several publications on local recurrence hint at a slight increase in chestwall recurrences in the group of patients treated with the more limited mastectomies. Therefore many hospitals advocate a rather tailored therapy and advise resection of the muscles in cases considered to have elevated risk of local recurrence. Of course, in cases where there is a suspicion of tumor fixation to the muscles, resection of at least the sternal part of the pectoralis major muscle is imperative. Also it is stated in standard works on breast cancer treatment that there is some evidence that tumors occurring in the deeper third of the breast within 1 cm of the pectoral fascia and any tumors larger than 4 cm, might advantageously be treated by a Halsted mastectomy (58).

Many institutions even advocate adding routine radiotherapy to Patey (55) and Madden (56) operations to reduce the risk of local recurrence.

Breast conserving therapy: refining the indication; Variations in technique

Literature on the topic of breast conserving therapy is becoming less confusing and controversial. In recent workshops (10, 59) the still open questions were identified and research to answer some of such subjects is ongoing in several centers and groups.

The interpretation of the data remains difficult for many reasons. In retrospective studies the selection of patients and the mingling of different prognostic groups (stages; operability) are important points of concern. Often the follow-up is too short and the proffered data incomplete. The use of different staging systems can be confusing. In older systems stage I and stage II account for different populations than when using the TNM system; even the TNM system has recently been changed. Thus, only randomized prospective studies with long follow-up can give conclusive answers (48).

The history of breast conservation in operable breast cancer began in 1924 with the work of Keynes (45). He used high-dose radiotherapy on the breast and axilla after excision of the breast tumor. The main difference with modern schedules is that he used only brachytherapy, even for the regional fields. Keynes was probably aware of the fact that external radiotherapy with the machines of his time was inferior to the use of radium. Only a few followed his ideas: Baclesse in Paris (60) and Mustakallio in Finland (61). The Mustakallio group was in the 1930s the only group to treat their operable breast cancer patients routinely with conservation of the breast. In the early 1960s French centers again focused their attention on breast conserving therapy and in 1972 Gros organized in Strasbourg the first big meeting devoted almost exclusively to breast conserving therapy (46). The group of Calle continued the tradition introduced by Baclesse et al. at the Foundation Curie (62). This group and also Pierquin & Marin from Creteil (63) and the Spitalier-Amalric group in Marseille (64, 65) have now reported large series of patients with long-term follow-up. The findings of Peters (66), first reported in 1967, are important because of the large number of patients, the long follow-up and the use of matched controls. More recently the Boston group (67) has been highly active in disseminating data from a large group of patients treated with breast conservation.

The first prospective clinical randomized study was started as early as in 1960 at the breast unit of Atkins and Hayward in London (9, 68). More recent prospective trials, a rather small one at the Gustave-Roussy Institute (69, 70) and a now classic study in Milan with a large number of patients (49), provide important data. It includes long follow-up, but for stage I patients only. Results show the efficacy of the breast conserving therapy.

The NSABP group (36) and the EORTC (50), both including T2 patients, closed their trials to intake some years ago. The NSABP, B-06-trial is of great importance since it shows the necessity of adding radiotherapy after lumpectomy, even when patients with a radical excision are excluded. In the study 3 treatment-arms were compared: total mastectomy and axillary clearance, segmental mastectomy and axillary clearance with external radiotherapy, and segmental mastectomy with axillary clearance without radiotherapy to the breast. In the study-arm of limited surgery without radiotherapy a 6-year breast recurrence rate of over 30% was seen, as against only 8% in the group where radiotherapy was added.

In the EORTC trial in which 904 patients were accrued, 85% of the cases had T2 tumors. In this study high-dose radiotherapy was given to all patients in the breast conservation arm and this included a high booster dose of 25 Gy via iridium implants. The dose of the external radiotherapy was 50 Gy in 5 weeks. In the EORTC trial the lumpectomy was intended to be macroscopically complete but a considerable number of patients were found to have microscopic incomplete excisions. So far no differences have been seen in survival between the breast conservation arm (with radiotherapy) and the control (mastectomy) arm, in either of the recently reported trials.

The therapy schedule now followed in most clinics is a fairly aggressive one. In general, excision of the tumor is followed by axillary dissection. The entire breast is irradiated, with a booster dose on the field of the tumor excision; usually the axillary operative field is not irradiated after the operation. In some centers the axillary region is irradiated instead of surgical clearance.

In all trials and unrandomized series the number of local recurrences (breast recurrences and rare axilla recurrences) increases when the observation period is extended. The true local recurrences are seen mainly initially, those appearing later after breast conservation generally being considered as new tumors. Veronesi's data (71) suggest that the frequency of these new tumors is comparable with the incidence of new tumor formation in the opposite breast, increasing with the years, but incidence in the irradiated breast starts a couple of years later than that of tumors in the other breast. From such findings it seems that also the premalignant and the malignant structures are influenced (but not killed) by the radiotherapy given. It is important to assess more precisely the magnitude of this risk for patients who have been treated conservatively, since this risk is non-existent after mastectomy. For this, studies with very long follow-up are needed. Up to now the point of local recurrence is not recognized as a serious factor influencing survival (72); any negative effect certainly is strongly diluted.

A major point in this discussion is the possible curability of the new tumors. Their detection might be late, being hampered by fibrosis, thereby diminishing the effect of salvage mastectomy. Also, the altered lymph stream after the previous breast conserving operation might impair prognosis. Despite the fact that a negative effect of second tumors has not actually been demonstrated in the survival curves of large studies, a local recurrence certainly has an impact on the individual patient. Methods are needed to identify patients specifically prone to local recurrence in order to treat them either with extra radiotherapy or to carry out surgical ablation in the first place. Choosing an extra high booster dose creates a dilemma since the chance of fibrosis is increased, whereby detection of a local recurrence is hampered.

From several studies it now appears that the patients with an extensive intraductal component (EIC) in and around the infiltrating tumor are the patients with a high risk of breast recurrence (73–75).

Since young age and a positive family history of breast cancer are also contributory risk factors to developing new tumors in the breast, it is certainly clear that young patients and those with a family history as well as an extensive DCIS component, are at very high risk of breast recurrence. The risk of recurrence in the cases with extensive DCIS component will probably diminish if it is possible to perform a re-excision with histologically confirmed tumor-free margins. In cases with irradically excised extensive DCIS component re-excision should always be advised and if this would create an unacceptable cosmetic result it might be better to perform ablation of the breast, certainly for young patients with a family history of breast cancer. Some centers (73) suggest that also in the group with an incompletely excised DCIS component, an extra high booster dose given to a large volume might be effective in preventing recurrence. The side effects of the radiotherapy in combination with the excision produce, often even with only moderate boost dosages, a cosmetically bad effect which becomes still worse in the course of time. The most recent Milan trial addresses the question of the effects of quadrantectomy without radiotherapy. Such an approach for small tumors might create excessively wide margins so that the true local recurrence rate is negligible. The normal suppleness of the breast tissue is then not disturbed by radiotherapy; this improves the cosmetic results and the possibilities for reliable follow-up by breast palpation. In the former Milan study, which was only recently closed, lumpectomy and radiotherapy including a high boost, was compared to quandrantectomy and radiotherapy with low or no boost. The impact of the size of the excision on cosmesis will be the issue of this study, since it is to be expected that the survival and local recurrence rate of both arms will be the same.

Reconstruction of the breast after mastectomy: restoration of symmetry after breast conserving therapy

Although ablative treatment is now performed much less frequently, it is still necessary for certain indications. In the more extensive, but still operable, tumor situations even radical mastectomies, with resection of the pectoral muscles, will be the treatment of choice. For many mastectomy patients breast reconstruction should be considered, now that the techniques for reconstruction have improved considerably. One problem which arises is that in this group of more advanced tumors there is a substantial proportion of local recurrences after the ablation. In order to combat this risk, postoperative radiotherapy is given. Both these aspects have an impact on the reconstructive procedures, not only in indication, but also in relation to the timing and technique.

Since local recurrences generally present within 2

years, most authors advocate a 2-year observation period before starting reconstruction. When, however, the recurrence risk is considered to be low, the patient could benefit from early reconstruction. Even simultaneous (immediate) reconstruction is advised by several authors (76, 77) in cases of ablative treatment for early disease (e.g. patients with DCIS, too extensive for breast conservation).

The restoration of the symmetry in volume is certainly more important than reconstruction of the nipple. Many patients do not even follow through with the reconstruction of the nipple-areolar complex. For them, the fact that the use of an external prosthesis is no longer necessary, is the most important point in the improvement of the quality of life.

Several new techniques have been developed for breast reconstruction (78) and also the use of tissue expanders adds to the results. The tissue expander is used to gradually make the submusculo-fascial pocket wide enough to place a permanent silicon breast implant of sufficient size to restore the symmetry.

When insufficient skin surplus is obtained despite the use of tissue expanders, more complex reconstructions using distant flaps are necessary. With the latissimus dorsi musculo-cutaneous flap (79) an extensive skin island, supported with muscles, can be transpositioned to the scar of the mastectomy. This is of great help in patients in whom partial resection of the pectoralis major muscle has been performed. The latissimus dorsi musculo-cutaneous flap is generally considered to be one of the most reliable and safe flaps in reconstructive surgery.

The TRAM flap (80) (transverse rectus abdominis musculo-cutaneous flap) can be used when the blood supply of the musculus latissimus dorsi has been impaired, or when the muscles have wasted because of denervation. The additional advantage of the TRAM flap is the fact that in many cases the quantitiy of tissue brought to the thorax is so large that no internal implant is necessary. The operation, however, has a high complication rate (difficulties in blood supply, abdominal wall problems, etc.) and requires great skill of the surgeon in remodelling the breast.

In cases where intensive radiotherapy treatment has been given, the use of omental flaps should be considered, since the greater omentum is thought to have specific properties, which induce vitality in marginal oxygenized, fibrotic tissue. The most important field of indication for using the greater omentum is radionecrosis or localized tumor recurrence necessitating full thickness thoracic wall resections (81).

Reduction of the other breast may be of great help in creating symmetry.

All the described procedures, but especially the reduction of the other breast, may also help in restoring symmetry after breast conserving therapy (e.g. in the case of a wide lumpectomy or tissue shrinkage due to radiation fibrosis). Even primary use of latissimus dorsi flaps can be considered after breast conserving therapy for larger tumor masses.

Adjuvant therapy

As we mentioned earlier in this review still more than half of the 'operable' patients ultimately die of disseminated disease. In this patient group micrometastatic lesions must already be present at the moment of the primary treatment.

When the success of chemotherapy and endocrine manipulation on overt metastatic disease became evident, the step towards adjuvant treatment at the time of the first operation became logical, since it aims at killing micrometastases and thus at improving the ultimate cure rate. Even if the cure rate could not be improved, a benefical effect could be achieved by prolonging the disease-free period and/or prolonging life. Toxicity of the adjuvant treatment should be carefully assessed, since a considerable proportion of the patients will in fact not need it, having already been cured without the adjuvant therapy. In addition, prior adjuvant therapy might adversely affect the response rate to subsequent chemotherapy at a later date (82). Also cost and benefit analyses are important and efforts should be made towards identifying the patient groups where the profit of adjuvant therapy will be the greatest. However, the subject of finding prognosticators specifically for the metastatic potential is a very complex one, as was mentioned earlier in this overview.

The patient selection problem becomes somewhat less important when the adjuvant therapy is non-toxic.

In the field of adjuvant therapy a number of very carefully performed prospective randomized studies have been carried out, but frequently with confusing conclusions (83). The Bonadonna group (84) was the first to show a clear, albeit small, cure benefit for some subgroups of patients upon the use of adjuvant chemotherapy. In addition the Nato trial, coordinated by Baum in the UK (85) as well as other studies, strongly suggested an important effect of adjuvant antiestrogenic (tamoxifen) treatment in postmenopausal patients. This was confirmed by a very carefully set-up Scottish trial, coordinated by H. Stewart (86).

Many groups such as those in Milan (84), in Denmark (87), the Fisher group (88), and the Ludwig group (89) have systematically carried out studies to identify the best patient selection criteria and dose schedules. Many contradictory results have emerged from these studies. In 'neo'-adjuvant chemotherapy the medical treatment precedes the local treatment (90, 91). A delay in local treatment might be harmful in the non-responding cases. On the other hand it is an advantage to know the effectiveness of chemotherapy in certain cases where it is necessary to decide whether to continue the adjuvant treatment after the local therapy. So far no randomized studies have addressed the neo-adjuvant approach.

Peto has the great merit of having introduced the over-

view technique to provide us with more solidly based conclusions. He succeeded in bringing all trialists of the world together and managed to combine data of all trial patients in a scientifically acceptable way. The Peto overview results have been presented at several recent meetings and the conclusions were recently published (92). They show a significant increase in 5-year survival from 64% to 73% by combination chemotherapy in premenopausal patients. For postmenopausal patients an increase in 5-year survival from 68% to 73% was seen for adjuvant anti-estrogenic therapy. A decrease in tumor recurrence after chemotherapy and by tamoxifen in the other age groups is mentioned in the discussion part of this article. This will be expanded in a monograph to be published by the trialists group.

Of course there are still many open questions and some of them cannot be addressed or cannot yet be addressed by the overview technique. To answer such problems as the impact of timing the therapy, of total dose, dose intensity and therapy duration, of the effect of adjuvant therapy in node-negative patients, and of the need for long duration of tamoxifen in postmenopausal patients, still more studies are needed. Fortunately the group of breast cancer trialists will continue their effort in pooling results.

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