Eur J Cancer Clin Oncol, Vol. 19, No. 12, pp. 1741–1747, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00
Pergamon Press Ltd.

Breast Conserving Therapy in Operable Breast Cancer; a Review

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INTRODUCTION

SURGERY has been long judged to be the only way of treating breast cancer successfully. The Halsted operation and its variations have saved the life of many patients, and the ensuing mutilation was thought to be the price which had to be paid for cure. Recurrence of the disease, however, has caused in many patients feelings of grief, and frustration towards the operation. Even in patients who have been cured mutilation often leads to serious distress. For this reason, possibilities to reach optimal local results, together with conservation of the breast, are welcomed with great enthusiasm. Refinements in radiotherapy have now caused combinations of limited surgery and radiotherapy to be considered by many as real alternatives to breast ablation, at least in certain subgroups.

However, the literature on this topic is still confusing and controversial and it is difficult to draw conclusions. A variety of statements appearing in a large number of editorials and other publications illustrate different points of view on the possibility of breast-conservation. Medical opinion has undergone a major shift in the last 10 yr [1–3]. The Strassbourg meeting in 1972, devoted to breast conserving therapy [4], was attended mainly by radiotherapists. Most of them restricted the selection for breast conserving therapy to the elderly or to those who refused ablative therapy. Only a few surgeons participated in this meeting, some of them only to warn against the dangers of such a change in policy. Vera Peters, [5], only a few years later, spoke of cutting the Gordian knot and, recently, at the first meeting of the European Society of Surgical Oncology a complete session was devoted to this problem [6], concluding that breast-conserving therapy is probably a safe procedure in many cases of operable disease.

We are facing an impressive change in ideas on the subject and the warnings, though multiple, are waived away by many. Yet the conclusion that the breast need not be removed is insufficiently backed by data and we have to realize that for most groups of operable patients the therapy is still experimental and in need of further trials.

DIFFICULTIES IN LITERATURE INTERPRETATION

Interpretation of the literature data is difficult for many reasons:

Selection

The mingling of different groups of patients in the reported series (different stages; even mixing operable and inoperable cases) is a major point of concern. In the few series where specially outlined groups are described, selection still frequently creates serious biases. Many authors say that they favor breast conservation only in sharply delineated 'pushing type' tumors. If results of breast conserving therapy are to be compared with mastectomies performed in the same clinic during the same period, serious selection must play a role.

Randomized prospective studies are needed, but even in randomized studies the interpretation of conclusions might be difficult.

One of the exclusion criteria used in many trials on breast conservation is a rather large tumor in a rather small breast. This certainly leads to a concentration of relatively small tumors in a T_2 patient group. If such randomized prospective studies do prove that some stage II patients [including patients with T_2 tumors (2–5 cm)] are also doing well with breast-conserving therapy, we should still keep in mind that this conclusion may not necessarily be valid for all stage II patients.

Stratification is therefore needed in the interpretation of the results of many trials. Also, patient groups should be large.

Necessity of confirmation

A few comparisons have shown that repeated series of the same patient groups with the same trial setting and the same questions to be answered did not produce equal results. Only when trial results at different times and in different clinics are confirmed can conclusions be accepted. This confirmation is frequently lacking.

Different staging systems used

The use of different staging systems is confusing. The groups of stage I and II patients account for different populations when older systems are compared with the last WHO TNM system.

Short follow-up

A serious pitfall is the fact that in many reported data long-term follow-up is lacking. Breast cancer is a slowly growing tumor, so in all breast cancer studies long-term follow-up is mandatory. This is certainly true for studies on the primary treatment of 'early' breast cancer. The long-term follow-up is even more essential in breast-conserving therapy because of the risk of new tumor formation in the retained breast tissue, a hazard that does not exist when no breast tissue is left. Apart from the 'normal' risk of tumor formation in breast tissue, a possible extra risk in breast tissue surrounding a carcinoma is frequently postulated. Radiotherapy may influence this point. Hopefully this risk will be diminished, but many hint at the risk of tumor induction by radiotherapy. Dosage seems to be a crucial point.

Absence of information on local results

Complete information on the local recurrence rate and local recurrence-free interval is withheld in many reports and no uniformity exists in describing this important, if not essential, point. Differentation between tumor recurrence and new tumor formation, reoccurrence, is difficult. For practical reasons they are usually mentioned together. The longer the observation the higher the recurrence rate. The mean tumor-free interval period lengthens when series report longer follow-up. Statements such as "most recurrences are observed within a 3-yr period" may be valid for mastectomy series, but it is misleading to use them in studies where breast conservation is the option. We have to note that even in studies with long-term follow-up a good insight into the local results is frequently not provided. In many series local recurrence is not mentioned when it emerges together with distant metastases.

Variety in technique used

Another point of concern is that a great variety of techniques of breast conservation have been used and frequently the therapy used in a reported patient series was not consistent. This is a serious shortcoming and may give a wrong idea of the possibilities of refined therapy modifications.

Difficulty in quality of life interpretation

Assessing the quality of life is difficult as is the evaluation of the cosmetic results. These basic aspects in determining the value of breast conservation are rarely reported in a reliable and reproducible way. Slogans such as "the cosmetic result was good in 80%" or "patients were happy in more than three-quarters of the cases" are not really informative.

Demonstrating that the oncologic prognosis in patients treated with conservation of the breast is equal to the prognosis after ablative procedures does not necessarily mean that breast-conserving therapy will always be a preferred therapy.

IMPORTANT PATIENT SERIES

The history of breast conservation in operable breast cancer began in 1924 with the work of Keynes [7, 8].

He was—*avant la lettre*—giving high-dosage radiotherapy after excision of the breast tumor. He treated the breast and àxilla, the main difference with modern schedules being the use of internal irradiation. The use of radium for these patients had also been advocated at that time by Hirsch [9] and Pfahler [10]. Keynes was probably aware of the fact that the external radiotherapy with their machines was insufficient. He was a great advocate of the use in his surgical clinic of interstitial radiotherapy. Only a few groups followed his ideas: the Maisin (Belgium) [11] and Mustakallio (Finland) [12] groups. The Mustakallio group mainly used external radiotherapy. In the '30s they were the only group to systematically treat their operable breast cancer patients with conservation of the breast.

In the early '60s French centres again focused their attention on breast-conserving therapy. The group of Calle [13] continued the tradition introduced by Baclesse *et al.* at the Fondation Curie [14, 15]. This group, and also Pierquin *et al.* from Créteil [16] and the Spitalier–Amalric group in Marseilles [17, 18], can now report on large series with reasonably long-term follow-up.

The findings of Vera Peters (Canada), first reported in 1967 [19], are important because of the great number of patients, the long follow-up and

the use of matched controls in the result interpretation.

A first prospective clinical trial was started as early as 1960 at the breast unit of Atkins and Hayward in London. This work was largely inspired and continued by Hayward [20–23].

Also, more recent prospective trials, a relatively small one at the Gustave-Roussy Institute [24] and a very important study at Milano with a large number of patients [25], provide important data, but for stage I patients only.

In the U.S.A. and Europe now other trials are in progress which include stage II patients, but no data are available as yet from these studies [26–28].

Most of the other publications with data on breast-conserving therapy cannot be used to draw valid conclusions on therapy effectiveness because of selection, short-term follow-up, incompleteness of data or other shortcomings. Many, however, provide us with information on details of the problems.

CONCLUSIONS FROM AVAILABLE DATA

Results in relation to patient selection

All studies with maximal radiotherapy given to the entire breast suggest good results for stage I patients (UICC TNM system; tumor 0–2 cm, no suspicious nodes. The stage I patient group is a small but growing subgroup of operable breast cancer patients.) This is clearly shown by survival rates expressed as 5- and 10-yr results and even by a few centres as 20-yr survival. Some non-randomized studies even suggest a slightly better 10-yr survival rate than results of large surgical series. The randomized studies which use high-dosage radiotherapy have also shown good results in this stage I group to date [24, 25]. We have to realize that the number of local recurrences increases when the observation period is extended. This is clearly demonstrated by the data from Marseilles [18, 29, 30]. Many of the re(oc)currences appear very late. Even when secondary tumors are treated early and would have a normal cure rate, which is by no means sure, e.g. because of the altered lymph drainage [31], there will still be an incurable subgroup. So the patients after breast-conserving therapy are fundamentally at a disadvantage when compared with those who cannot develop such a new tumor. To estimate the factual importance of this point and the impact for patient selection, studies with very extensive follow-up are needed. Up to now, even in most series with very long follow-up, the point of the local recurrence is not recognized as a serious factor influencing survival. So happily, the negative effect is probably diluted. It should be realized, however, that this is a point of concern, especially for the younger patients with their many years at risk, whereas at the same time we should also be aware of the fact that breast conservation is probably important for precisely that patient group.

The measurement in the psychological benefit of breast-saving procedures remains a difficult point [32], but in general a positive effect is postulated.

Even in the group of stage I patients most centres advise the use of some exclusion criteria to increase the safety of the new therapy: e.g. multicentricity and impossibility of close follow-up [1–3, 33].

For all situations other than the hitherto-described selected stage patients, breast-conserving therapy should still be considered to be experimental and data from further trials have to be obtained before introducing this therapy as a standard.

Techniques of breast-conserving therapy

The therapy schedule followed in most clinics is a fairly aggressive one, and this also has its drawbacks. In general, an excision of the tumor is followed by axillary dissection. The entire breast is irradiated with a booster on the field of the tumor excision, and sometimes the axillary operative field is also irradiated after the operation [1–3]. In some centres the axillary region is irradiated instead of a surgical approach.

Lumpectomy. Lumpectomy is thought to be necessary to reduce tumor load before radiotherapy in order to diminish the risk of local recurrence of tumor growth. Keynes was already aware of this point [7, 8]. Nevertheless, in many series, especially those of the radiotherapists, patients are included where no excision preceded the irradiation. Careful consideration of the follow-up data of differently treated patients shows the better results gained by prior excision. Some French data [13, 16–18] and those of the Hellman group in Boston [34] are very informative in this respect.

Cosmesis, of course, is the point against local excision, especially where large tumors are involved. On the other hand, from the argument of reducing tumor load, lumpectomy should not be left out especially in those cases. The margin of normal breast tissue surrounding the tumor which should be excised with the palpable mass is a matter of discussion [35]. It is difficult to draw conclusions on this point from the literature. It seems that the given radiotherapy is effective in destroying non-palpable disease, so a small margin of normal-looking tissue might be sufficient [34, 36]. Undoubtedly the safest way is to adhere to a large margin, as is advocated by the

Milan group [25]. But the cosmetic result is impaired after excisions with wide margins, especially in the bigger tumors [37]. This was clearly shown in the evaluation of the Guy's trials. [20, 21].

If the tumor is situated near the axilla, an *en bloc* procedure of tumorectomy and axillary dissection is performed. Especially when no routine irradiation of the axillary region follows, the danger of possible tumor contamination of the complete operative field including the axilla should be kept in mind. It would be wise here to take a safer, wider margin around the tumor. Curiously, this aspect of implantation risk is only mentioned very rarely in the literature, and perhaps it is not often recognized. I believe that in these *en bloc* cases wide tumorectomies are necessary. This, however, appreciably worsens the already rather poor cosmetical results in the *en bloc* excision group.

Axillary dissection. The axillary dissection is thought necessary for staging purposes in order to define exactly those groups in need of adjuvant therapy. This argument for a surgical approach to the axilla might be less strong if other means of predicting the prognosis are found or if arguments for adjuvant therapy become less solid. Surgery of the axilla is also considered to be an important part of the treatment, especially in cases with palpable nodes. The Guy's trial clearly shows that doses of about 3000 rads are insufficient to eradicate non-operated palpable metastatic disease in the axilla [20, 21, 23]. Also, the French series, using high-dose radiotherapy directed to the axilla, show that salvage surgery is sometimes needed when at first presentation the nodes are thought to contain tumor [13, 16, 18, 38]. From most of the French data one gets the impression that they prefer patients without palpable nodes [13, 16]. The number of patients in their series with suspicious nodes is lower than in a normal breast cancer population of T_1 and T_2 patients.

The supposed profit achieved by diminishing tumor load before giving radiotherapy also makes axillary dissection a logical procedure. The risk of lymph edema of the arm, which is probably increased when compared to results of radiotherapy alone, is the main point against axillary dissection. This lymph edema risk is considerable if surgery is followed by radiotherapy. Not only arm edema is a problem in these patients but also breast edema, which occurs rather frequently after axillary dissection [39]. Cosmesis and some practical points would be reasons to prefer radiotherapy to surgery of the axilla.

In the weighing of pros and cons, a tendency towards a surgical approach of the axilla still emerges and in most recent publications this switch towards axillary dissection is clear, especially in the cases with palpable nodes.

For the select group of T_1N_0 cases a different point of view is taking shape. The reported data strongly suggest that in the stage I patients without suspicious nodes radiotherapy is effective. Only a few cases in this group have tumor-positive nodes, and then with mostly only a minor tumor volume.

The eventual bad side-effects of high dose radiotherapy such as fibrosis should be weighed against the disadvantages of surgery. It is a great pity that as yet no trials are in progress to investigate the possibilities of breast conservation with axillary radiotherapy instead of axillary dissection in the N_0 cases.

It might be even a point for discussion to omit axillary treatment in these selected T_1N_0 cases, with delayed axillary dissection if nodes become palpable. No such studies in combination with breast conservation are in progress.

Radiotherapy directed to the breast. Radiotherapy following the lumpectomy is generally thought to be an essential part of therapy. Not only tumor left behind after lumpectomy [33, 40], but also multicentricity [33] and intramammary spread [41] may cause a great number of local recurrences if no radiotherapy follows local excision [29, 40]. Yet an NSABP study is in progress in which local excision without radiotherapy is one of the options [26, 27]. Such a study might be considered dangerous and for many unacceptable. The results, however, will be very interesting. Long-term evaluation is necessary.

High dosages are thought to be necessary to kill even minimal tumor load [42–44]. Baclesse was one of the first to focus attention on the dose–effect relationship [14]. However, radiation sequelae such as fibrosis, leading to shrinkage of the breast tissue and the risk of radiation necrosis, do limit the dose [44, 45]. Therefore the idea of booster therapy using sophisticated techniques directed to the area of most risk was originated. Hellman's group clearly demonstrated that increasing the dose by using internal boosters led to a diminished local recurrence rate while still producing fair cosmetic results [34].

The data of Calle *et al.* show us the major problem created by the difficulty in differentiation between fibrosis and recurrence. Secondary surgery was thought necessary for a considerable number of patients, but in histology many of these patients proved to be free from active tumor [13]. So many reasons make preventing fibrosis an important aim of the chosen therapy schedule.

The difficult point of tumor induction by

radiotherapy is still unsolved [46]. There are strong suggestions that a low dose is more dangerous than a high dose [40, 47]. This might explain the high number of late local re(oc)currences in the older series which used low-dose radiotherapy [48–51]. Also, the Marseilles findings suggest that the highest frequency of recurrences is found in subgroups with lower radiation dose. However, in this large Marseilles series, with very long follow-up, the number of recurrences also seems to be higher than the frequency of tumor formation in the opposite breast in patients with high-dose radiotherapy [18, 29].

CONCLUSION

The available data give a strong suggestion that for the small group of stage I breast cancer patients breast conservation is a safe procedure, but even in this group some selection is indicated. Long-term observation of the patient groups under study is needed to show that in the long run this option is also valid. The ongoing studies have a great responsibility to investigate this aspect. The technique of breast cancer treatment with preservation of the breast is complicated, and intensive cooperation between radiotherapist and surgeon is fundamental. Variations in effective therapy techniques suggest that tailoring breast-conserving therapy for different tumor conditions might improve results.

Many important points in the field of breast-conserving therapy appear to be still unsolved. Further studies are necessary, e.g. to study the relation of radiosensitivity with special histologic subtypes or with special growth patterns. More information on the effect of radiotherapy on normal breast tissue, *a fortiori* to 'premalignant' breast tissue, is urgently needed.

We must hope that future studies will also show that an often-quoted argument put forward by Keynes to start breast-conserving therapy will be a reality: in his 1937 publication he postulated that patients would come earlier to be treated for their breast cancer if breast conservation was an alternative to mutilation [8]. If that were the case, then, indeed, these new therapy lines may provide a double benefit.

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