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1. Introduction

Radical mastectomy was the first effective procedure in breast cancer. More extensive surgery does not improve long-term survival and less aggressive local treatment gives identical long-term survival to radical mastectomy. Modified radical mastectomy, and even more conservative procedures such as lumpectomy are now widely used.

Postoperative radiotherapy is another important local treatment. It is always performed after breast conservative surgery and frequently after mastectomy. The aim of postoperative radiotherapy is to reduce locoregional recurrences, therefore reducing mortality.

With technical progress, major postradiotherapy complications are less frequent, however its indications must be limited to patients for whom benefit is proved

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and consistent. As extensive surgery has no effect on the prevention of distant metastases, control of distant metastases by extending local treatment such as radiotherapy is doubtful.

Systemic adjuvant treatment (chemotherapy or hormonal therapy) reduces distant metastases and improves long-term survival. It has also been proved to reduce local recurrence.

2. Impact of postoperative radiotherapy on mortality

Many trials on postoperative radiotherapy in early breast cancer have been published. Nevertheless, there is no consistent proof of a significant mortality reduction, thus suggesting only a small reduction, if any, exists. As randomised trials of radiotherapy for early breast cancer may not have been extensive enough to reliably detect differences in long-term survival, the Early Breast Cancer Trialists' Collaborative Group performed a systematic overview on the results of such trials. It collected information on each woman randomly assigned to treatment in any trial concerning postoperative radiotherapy, that began before 1985. Data on mortality were available in 36 trials comparing radiotherapy with surgery with the same type of surgery alone. A total of 17 273 women were available for analysis on mortality [1]. Overall mortality was 40.3% with radiotherapy and 41.4% without, corresponding to a non-significant reduction of 2.6±2.5%. The mortality reduction that could be produced by radiotherapy appeared slightly larger after mastectomy with axillary sampling (14±7) or after breast conservative therapy (12±9) than after mastectomy alone (3±4) or after mastectomy with axillary clearance (−3±4). Nevertheless, there was no evidence that radiotherapy helped in certain surgical subgroups and not in others. The radiotherapy target was the breast in all trials with lumpectomy, and the chest wall in 32 out of 36 trials with mastectomy. The axillary or supraclavicular fossa were targets in most trials. The internal mammary chain was irradiated in three out of five trials with mastectomy alone, in three out of four trials with mastectomy plus axillary sampling and in 24 out of 27 trials with mastectomy plus axillary clearance. Radiotherapy did not include the internal mammary chain in the conservative procedure trials.

Data on causes of death were available for 13 627 women in 28 trials, 7.7% of women died of non-breast cancer-related deaths in the radiotherapy groups whilst 5.7% died of non-breast cancer-related deaths in the non-radiotherapy groups. In contrast, 34.1% of women assigned to radiotherapy died of breast cancer, compared with 36.9% of the controls ($P = 0.03$).

This overview on more than 15 000 patients shows a reduction in breast cancer-related deaths. Nevertheless, an overall or subgroup reduction in mortality could not be demonstrated.

Two recently published trials have updated the results on postoperative radiotherapy. In British Columbia, 318 premenopausal women with node-positive breast cancer were randomly assigned, after radical mastectomy, to receive chemotherapy plus radiotherapy or chemotherapy alone [2]. Radiotherapy targets included the chest wall and regional lymph nodes. Chemotherapy was cyclophosphamide, methotrexate, 5-fluorouracil (CMF). After 15 years of follow-up, women who received chemotherapy plus radiotherapy had a 29% reduction in mortality from breast cancer ($P = 0.05$), but no significant reduction in overall mortality.

The Danish trial included 1708 women who had undergone mastectomy [3]. They were randomised to receive eight courses of CMF plus irradiation of the chest wall and regional lymph nodes, or nine courses of CMF alone. This trial included premenopausal women. 1571 patients had positive axillary lymph nodes. With a median follow-up of 114 months, the estimated 10-year overall survival was 54% in the radiotherapy and CMF group compared with 45% in the CMF alone group ($P < 0.001$). A multivariate analysis using the Cox model does not find any interaction between radiotherapy and prognostic factors (tumour size, number of positive nodes, grade, age) and confirms the mortality reduction with radiotherapy: relative risk 0.71 ($P < 0.001$). This is the first trial demonstrating a mortality reduction due to postoperative radiotherapy in early breast cancer. Methods and results of this trial are perfectly reliable, however, the local recurrence rate is very high in both groups and particularly in the CMF alone group.

One must note that the only trial showing a beneficial effect of radiotherapy on survival was for patients having received CMF chemotherapy without anthracyclines.

A recent meta-analysis demonstrated that chemotherapy with anthracyclines is more effective than chemotherapy without anthracyclines. Use of anthracyclines as adjuvant treatment in breast cancer has become standard practice in many countries. This new approach raises new questions. Will more efficient chemotherapy not reduce the relevance of irradiation therapy?

What will be the long-term toxicity resulting from the association of radiotherapy and anthracycline-containing chemotherapy, particularly on the heart? The association of internal mammary chain irradiation with anthracycline chemotherapy presents a risk of cardiac complications on a long-term basis. The dose to the heart can be reduced by electrons, nevertheless, only trials demonstrating the innocuousness of this association will enable it to be accepted as standard. In the meantime, it is preferable to avoid overtreating patients with associations which have a potentially cumulative toxicity and whose additional beneficial effects are not proven.

3. Impact of radiotherapy on local and regional recurrence

Prevention of local recurrences varies after radical or conservative treatment.

3.1. Conservative treatment

When dealing with small-sized tumours, conservative treatment is appropriate. Without postoperative radiotherapy, recurrences are frequent. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 trial [4], 210 out of 570 (37%) patients treated by lumpectomy without radiotherapy presented with local recurrence, giving a risk of local recurrence at 12 years of 35%. In this trial radiotherapy resulted in a marked decrease in local recurrence. Only 62 out of 567 (11%) patients treated by lumpectomy with radiotherapy presented with local recurrence, giving a risk of local recurrence at 12 years of 10%. This important reduction in local recurrence after conservative treatment was demonstrated in several trials [5,6].

Tumour size is one of the main prognostic factors for local recurrence. Some patients have a very low recurrence risk, these patients will have very little benefit from radiotherapy treatment. Better knowledge about the risk factors for local recurrence may help in clinical decision making, leading to a selective rather than a routine use of radiotherapy of the breast after breast conservative surgery. Nevertheless, up to now, such a low-risk population has not been identified [7].

3.2. Radical treatment

Analysis of loco-regional failure after mastectomy has shown the chest wall to be the most common site of recurrence. The chest wall is concerned in 57–83% of loco-regional recurrences and is the unique failure site in 44 to 67% of breast cancer recurrences [8,9]. The axillary recurrence rate after axillary dissection is low (1–3%) and is more frequent when a greater number of nodes are positive.

The incidence of lymph node metastases of the internal mammary chain in primary breast cancer, with central or medial tumour locations, ranges from 10% in axillary node-negative patients to approximately 50% in node-positive patients [10].

The clinical detection of internal mammary recurrences is difficult and must be done by computer tomography (CT) scan making the internal mammary nodes recurrence rate difficult to determine. Furthermore, clinical recurrences in internal mammary nodes or in the axilla are the only site of recurrence in 5–10%.

Thus, postoperative radiotherapy can reduce chest wall recurrences [1] as far as axillary recurrences are concerned, at least in node-positive patients [11]. However, prevention of internal mammary chain recurrence is more difficult to assess [12].

4. Discussion

According to the meta-analysis, postoperative radiotherapy in breast cancer does not give any significant increase in overall survival. Only one trial tends to demonstrate the contrary, but the evidence is insufficient to be convincing. We can, therefore, consider that, from this point of view, it is of no benefit. Its indication is limited to the reduction of local recurrences. After conservative treatment without radiotherapy, the risk of local relapse is approximately 30%. Irradiation of the whole breast allows a reduction in this risk to approximately 10%. Up to now, the indication for postoperative irradiation is formal in the case of conservative treatment. However, with the introduction of screening, the detected tumours are smaller. Some of these cancers present a very low risk of local relapse and it is important to identify them to avoid unnecessary irradiation in patients presenting such tumours. After mastectomy, the risk of recurrence mainly concerns the chest wall. This risk is linked to lymph node involvement, to tumour size and to the quality of surgery (excision limits). In low-risk patients, irradiation does not offer sufficient benefit. Therefore, irradiation is only justified in patients presenting extensive lymph node invasion ($N+ \geqslant 4$) or for large tumours (T3, T4) or when the excision is insufficient. Isolated lymph node relapses are far less common than relapses on the chest wall. The risk factors for lymph node relapse are, first and foremost, risk factors for relapse on the chest wall. Unless specific risk factors provide evidence of a population for which lymph node risk is independent from local risk, the indication for lymph node preventive irradiation also involves population already at risk of chest wall relapse. In these cases, the volume to be irradiated needs to be discussed, since all patients at risk of lymph node relapse are also at risk of local relapse. Irradiation of the chest wall after mastectomy should systematically be proposed. Should we associate it with axillary lymph node or internal mammary irradiation? Systematic irradiation of lymph node chains has not yet been validated. No studies have yet demonstrated the superiority of lymph node plus chest wall irradiation compared with irradiation of the chest wall alone, even if limited to the reduction of lymph node recurrence. If one accepts that irradiation has a preventive role on dissemination, then the preventive role of irradiation of the chest wall is sufficient. The relevance of preventive radiotherapy depends on the level of risk. Thus, the lymph node areas are of less interest than the chest wall. No studies have been carried out concerning the role of internal mammary irradiation on survival or on lymph

node recurrence. Furthermore, radiotherapy is not devoid of risks or side-effects and should therefore be reserved for forms presenting an important risk of recurrence, in other words, forms which already present an important risk of relapse on the chest wall.

5. Conclusion

Radiotherapy is widely used in breast cancer treatment. Nevertheless, data on its long-term benefit are missing and some of its indications are not universally agreed upon.

Like an evidence-based medicine, radiotherapy should be used in cases where a beneficial effect has been proved. Targets and doses should be chosen according to data from randomised trials or sufficient proof of benefit leading to a consensus. Thus, if postoperative radiotherapy in conservative procedures is indicated, boost usefulness needs to be confirmed. In the same way, axillary nodes and internal mammary chain irradiation must be justified by long-term results before these techniques are widely used. Chest wall radiotherapy has been proved to reduce local recurrences without benefit on overall survival. Chest wall irradiation must be limited to high-risk patients.

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Arbiter

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Irradiation for breast cancer treatment has a very prominent place whatever the specific aim of this treatment: to cure the patient locally (without any further recurrence in the conserved breast or in the chest wall) or generally (without any distant recurrence). Three tumour types are focused on in current practice:

- Small tumours are those which can be treated by first-line conserving surgery (provided they are unicentric and without any widespread ductal carcinoma *in situ* (DCIS)). We have to divide them between two subgroups of low and high risk of local and/or distant recurrences. Irradiation of the breast and of nodal areas does not have the same impact on local risk of recurrence and of death in these two subgroups.

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