Radiotherapy as part of a multidisciplinary treatment strategy in early breast cancer

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Introduction

Loco-regional radiotherapy after surgery for breast cancer has been used almost since the discovery of X-rays a century ago. The effects of post-operative radiotherapy have been evaluated in several randomised trials conducted during the past 50 years. These trials can be divided into two categories, namely category I where radical surgery has been compared with less extensive surgery plus radiotherapy, and category II where radical surgery has been compared with the same type of surgery plus radiotherapy [1–4] (Table 1). Thus, category I trials [2,3] are aimed to test whether radiotherapy could compensate for less extensive surgery with regard to local control and survival, and category II trials [1,3,4] are aimed to test whether more loco-regional therapy could improve local control and survival. In both types of trials, the baseline hypothesis is the Halsted concept.

Most trials conducted since the introduction of adjuvant systemic therapy in the 1970's have also included this treatment for the relevant risk groups irrespective of radiotherapy. Therefore, these more recent trials may, at the same time, answer the Halsted hypothesis, namely whether optimal loco-regional tumour control has an impact on survival in addition to adjuvant systemic therapy, and the systemic hypothesis which says that local control is not likely to affect long-term survival after breast cancer [5].

Table 1
Types of radiotherapy trials

Category I:
Radical surgery versus less extensive surgery plus radiotherapy
Category II:
Radical surgery versus same surgery plus radiotherapy
Adjuvant systemic therapy can be included in both categories

The general conclusion from these more recent trials is that maximal disease control, loco-regional as well as distant, has significant influence on the ultimate outcome. Therefore it is well established that the treatment of early breast cancer is a multidisciplinary approach consisting of loco-regional therapy (surgery ± radiotherapy and adjuvant systemic therapy).

The aim of the present paper is, within this frame, to focus on the indications for radiotherapy after surgery (breast-conserving surgery or mastectomy) and to focus on the mechanism — why loco-regional radiotherapy (RT) may have an effect — and the problems regarding radiation-related toxicity, relevant target, total dose, fractionation schedule, and timing of radiotherapy with surgery and systemic therapy.

Radiotherapy after breast-conserving surgery

Breast-conserving therapy (BCT) is now well established, and its use has increased during the past two decades. The evidence for this treatment mainly came from six clinical trials comparing mastectomy to BCT, (Morris et al. [6]). In these trials, which were conducted during the 1970's and 1980's, no statistically significant difference in survival between patients receiving these two forms of therapy were found. As a result, the National Institute of Health Consensus Conference on Breast Cancer recommended BCT followed by radiotherapy as the preferred treatment for the majority of women with stage I and II breast cancer in 1990 [7]. The meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [3] confirmed the results of these six randomised trials, which basically belong to category 1 studies comparing less extensive surgery plus radiotherapy with more extensive surgery. The dose level used for postoperative radiotherapy in these studies was 45–50 Gy in 22–25 fractions to the

residual breast with an additional boost of 10–25 Gy in 5–12 fractions to the tumour bed. Thus, the results generally confirmed that when comprehensive radiotherapy is used as a compensation for less surgery it could produce similar local control and overall survival as more extensive surgery. However, before the results of these trials were available, a major concern was whether BCT was likely to be as safe as mastectomy. This was mainly due to the results from two randomised trials conducted at Guys Hospital in London in the 1960's and carly 1970's [8]. In these two studies, BCT was also compared to radical mastectomy, but the treatment approach in the BCT arm differed substantially from that in the six more recent trials. The radical mastectomy group had an axillary clearance with subsequent axillary irradiation using what is now regarded as a low dose of RT. In contrast, the wide excision group had no axillary surgery followed by inadequate RT. As a consequence, the loco-regional relapse rate was very high in the wide excision group compared to the mastectomy group (50% versus 20%, respectively, at 25 years). The corresponding breast cancer mortality rates in patients treated by mastectomy compared to BCT were 38% versus 48% [8]. Thus, the results from these two studies is a clear documentation of the fact that obtaining optimal primary loco-regional tumour control has an impact on the ultimate survival, and therefore that BCT is only a safe treatment if the combined surgery plus RT treatment approach allows similar loco-regional tumour control as the best results from radical mastectomy.

Which patients are suitable for breast-conserving therapy?

Since the aim of breast-conserving therapy is to preserve the breast with both an optimal cosmetic result and optimal local tumour control, mainly T1 and small T2 tumours have been included in the trials where this treatment has been evaluated. In general, the outcome in terms of local control and survival is similar irrespective of tumour size, nodal status, histopathological grade and vascular invasion [9–13]. However, re-analysis of the European Organisation for Research and Treatment of Cancer (EORTC) and Danish Breast Cancer Cooperative Group (DBCG) breast conserving studies [12] have shown that young age (<35 years) carries a worse prognosis with respect to both local control and distant metastases in the BCT group compared to mastectomy. These results indicate that a high risk of local recurrences might be a source of distant spread in some of these young patients, and therefore that primary mastectomy should be the treatment of choice. But the adverse prognostic effect of young age also suggests that breast cancer in younger women is a biologically more aggressive disease, which might require more aggressive initial treatment in general [14–16].

In contrast, a detailed meta-analysis of the abovementioned six clinical trials has also shown an advantage for BCT over mastectomy in selected node-positive patients, which are the worst prognosis group, in terms of survival [6]. The explanation for this finding could be that although the BCT treatment did not intentionally include the regional lymph nodes with separate fields, the standard tangential fields, which are commonly used, incidentally treat a portion of the internal mammary nodes and lower axillary nodes in a majority of patients. In the mastectomy group, patients did not routinely receive any regional radiation. Support for this hypothesis comes from the fact that the survival benefit could only be demonstrated in the trials in which less than 50% of the node-positive patients (i.e., those that had BCT) were offered regional irradiation. In contrast, there was no difference in survival when node-positive patients routinely received loco-regional RT both in the BCT and the mastectomy groups. The adjuvant systemic therapy was equal irrespective of BCT or mastectomy and thus this observation indirectly supports the positive effect of postmastectomy RT in high-risk patients which is described below.

Is boost to the tumour bed needed?

It is standard practice to recommend RT to residual breast tissue after BCT. Furthermore, in most European countries, as well as in the US, it is also customary to give 'an additional boost' to the tumour bed area either by external irradiation (electron or photon) or by the use of interstitial brachytherapy. The rationale for adding the boost is based on the theory that a lower rate of local failures will be achieved if a higher dose of radiation is given to the part of the breast thought to have the greatest tumour burden [17,18]. Furthermore, such an increase in the dose to a limited area may not significantly increase the risk of local complications. Nonetheless, the final outcome in terms of local control and cosmesis is dependent on the balance between the surgical margins, the total dose and volume of the boost. The question of whether or not all patients need a boost after RT to the residual breast has been investigated in two large randomised trials. The first trial was conducted in Lyon, France, and included more than 1,000 patients with early breast cancer treated with lumpectomy,

axillary dissection, and tangential radiation therapy to the entire breast and then randomised to either no further treatment or treatment with an electron beam boost [19]. The surgical resection margin should be negative. The preliminary results have shown a 25% reduction in the actuarial local recurrence rate at 5 years from 4.5% in the no-boost arm to 3.6% in the boost arm. No difference in overall survival could be found. On the basis of these results, the Lyon group seemed to advocate the use of an electron beam boost also in patients with negative margins. The second randomised study is the EORTC boost trial (Protocol 22881 and 10882) [20]. This study includes 5,318 patients treated with BCT, RT to the residual breast and who were randomised to no boost versus 15–16 Gy boost. Preliminary results from the complete resection group have shown that there is an overall significant difference in local control of 6.8% versus 4.3% at five years in the no boost and boost arms, respectively [20]. No difference was observed so far in the overall survival rates. A more detailed analysis of this very large study has revealed that the boost has a major impact on the local control rate especially in young patients (<40 years) where the overall local failure rate is rather high, whereas there was only a marginal or no difference in the local control rate at 5 years when comparing the boost and no boost in women above 50 years of age. These results indicate that boost is needed in young patients, and especially in patients younger than 40 years of age. The results also indicate that patients above 50 years of age who had complete resection may only obtain a marginal benefit from a boost. The decision about whether or not to give a boost should also take into account the results from the cosmetic outcome and cost-effectiveness. The influence of the boost on the cosmetic outcome has been evaluated in the EORTC boost trial [21] and the conclusion is that a boost dose of 16 Gy has a negative, but limited, impact on the cosmetic outcome. Furthermore, the average cost-effectiveness ratio from the boost treatment is calculated to be well above the commonly cited threshold for cost-effective care and thereby outweigh the marginal benefit [22]. However, long-term follow-up (10–20) years of these favourable patient groups will reveal further information concerning the ultimate local control rate, as well as the ultimate survival in relation to receiving a boost or not.

What is the optimal dose and fractionation?

The standard dose and fractionation for radiotherapy after BCT is 45–50 Gy delivered in 2 Gy daily fractions. This dose level is sufficient to control 80–90% of subclinical disease [17] and to secure minimal normal tissue damage.

As mentioned above, there is an increasing need for RT resources due to the increased number of women with early breast cancer who need RT. Therefore, it would be attractive if the number of fractions (and overall treatment time) could be decreased. In Canada and the UK such fractionation schedules have been used traditionally for many years. To determine if such a shorter fractionation schedule (42.5 Gy/16 fractions in 22 days) was equally effective with the conventionally 50 Gy/25 fractions in 35 days, a randomised trial was performed in Canada [23]. The preliminary results showed no differences either in local recurrences, survival or cosmetic outcome, but the numbers of events and the observation time is still limited. It is important to notice that the trial only included patients with limited breast size, no postoperative complications, no regional irradiation and no adjuvant chemotherapy. However, the long-term results have to be evaluated together with the long-term cardiac morbidity before a final evaluation is made. In this context, it is of concern that a separate study in Canada has shown an increased cardiac mortality in patients with left-sided tumours treated with dose per fractions >2.5 Gy, whereas this was not found in similar patients treated with a conventional dose per fraction schedule [24].

Is radiotherapy needed in all patients?

Due to screening in several countries, an increased number of women will be diagnosed with breast cancer in very early stages which means that more and more women are suitable for BCT. In some countries, the utilisation rate of BCT has changed from around 25% to 60–70% of all cases. Considering that RT is a standard requirement after BCT these figures illustrate the increased need for RT resources. Therefore, it would be relevant to evaluate whether these very early screening-detected stages of breast cancer treated with BCT really need post-operative RT. There are now data from seven randomised trials comparing BCT plus axillary dissection with the same surgery plus RT [4]. Overall, the results from these studies have shown a significant and substantial improvement in local control in irradiated patients compared to non-irradiated. On average, the local recurrence rate has been reduced from 23% to 7% at 10-years by the use of RT and it has not yet been possible to define a subgroup where the local tumour control could not be improved by the addition of irradiation in the form of post-operative RT. There

was no difference in overall survival at 10 years. Until now, the general belief has been that local recurrences in residual breast could be salvaged by later mastectomy and that such recurrences would not have impact on the ultimate survival. However, the results from longer follow-up of one of the trials have shown a statistically significant increase in the number of distant metastasis in non-irradiated patients [25] indicating that long-term survival may be affected if the primary local therapy was inadequate.

One third of breast cancer cases occur in women above 70 years of age. In general, the course of disease and the outcome of treatment in elderly women does not differ from that in younger women [26]. The indication for RT after BCT in elderly women with early stage disease also treated with tamoxifen has been evaluated in two recent randomised trials [27,28]. The preliminary results indicate that RT in addition to tamoxifen definitively improves local control. The question on whether this benefit is worthwhile considering the life expectancy and other medical problems in these elderly patients, can not be answered until longer follow-up of the trials become available.

Should post-operative irradiation include the whole breast or only tumour bed?

Along with the studies of whether or not RT is needed in BCT there is also other attempts to save RT resources and the inconvenience of treatment. Currently, a new approach, consisting of one large fraction of external RT given peri-operatively to the tumour bed is under evaluation. The method and protocol design was presented at the 2001 St. Gallen conference. Although this approach seem to be attractive both with regard to convenience to the patients and the economic resources involved, the method should be regarded as experimental until further evidence concerning selection criteria, tumour control and morbidity has been demonstrated.

Radiotherapy after mastectomy

There are few topics in oncology which have generated so much controversy over the years as postmastectomy RT. The role of postmastectomy RT for women with early breast cancer was evaluated in some of the earliest prospective randomised trials of category II [1,3]. Altogether more than 15,000 patients have been included in such trials during the past 50 years and overall the results have shown that postmastectomy irradiation substantially reduces the risk of loco-regional recurrences at a 20-year follow-up from 30% to 10% [4]. However, the impact of this reduction on the risks of distant failure and ultimately death due to cancer has been controversial. Repeated meta-analyses of all the studies addressing this question has not shown benefit in terms of long-term survival (10 and 20 years) either in node-negative nor in node-positive patients. However, it appears in a detailed analysis of cause of death in irradiated patients compared to non-irradiated that there is in fact a significant reduction in death from breast cancer in irradiated patients compared to non-irradiated [29]. Unfortunately, the benefit in terms of a reduction of breast cancer death is counterbalanced by an excess death from other causes, mainly cardiovascular disease in the irradiated patients. These results together with the optimism due to the positive results of adjuvant systemic therapy, which occurred in the late 1970's and early 1980's, led to almost complete abandonment of the use of postmastectomy irradiation [30]. However, this treatment received renewed interest with the publication of two randomised trials from Denmark and British Columbia in 1997 [31,41]. In both these trials, the role of RT in premenopausal patients who also received adjuvant chemotherapy was addressed. Both trials demonstrated a substantial reduction in loco-regional recurrences in irradiated patients compared to non-irradiated (reduction from 35% to 8%) and a significant improvement in long-term survival with an absolute benefit of about 10% at 10 years in both studies. Thus, the magnitude of improvement in overall survival was in the same order as the general improvement in long-term survival from adjuvant systemic therapy [33]. These results have definitely supported the general principle that attaining maximal initial loco-regional tumour control is necessary to achieve the highest possible ultimate survival rate also in the presence of adjuvant systemic therapy. Therefore, within the past few years there has been much activity to try to confirm this indication for the use of postmastectomy irradiation in the current multidisciplinary treatment strategy for early breast cancer.

New trials with combined systemic therapy and radiotherapy

Besides the recent publication of the Canadian study and the Danish DBCG 82b trial, there are now data available from another large Danish trial (DBCG 82c) and from 15 other smaller studies, where the main question has been to evaluate the role of postmastectomy irradiation, restricted to high-risk

patients who were also receiving adjuvant systemic therapy [32,34,35]. These studies were all included in the recent meta-analysis, but specific analysis on the outcome of RT in this particular subgroup was not done by the EBCTC group [4,36]. Such analysis has, however, been performed by Whelan et al. on the basis of the available published data, and this analysis included more than 6000 patients randomised to receive or not to receive loco-regional RT in conjunction with the same systemic therapy in both groups [34]. These patients were all treated during the 1970's and 1980's with rather contemporary RT and mainly patients with a high risk of loco-regional recurrence (node-positive and/or large tumours) were included. The results showed substantial benefits in irradiated patients with decreases in the annual risk of loco-regional failures by 75%, of total recurrence by 31%, and overall mortality by 17%. These results are in fact in agreement with the general results from the meta-analysis, although the magnitude of the effects, when all the patients included, are on average much less. The reason for that is that the meta-analysis has included studies with large numbers of patients at low risk for loco-regional recurrence (node-negative and small tumours) [37–39]. Furthermore, the meta-analysis also included very old studies of patients treated with radiation techniques and radiation doses and fractionations which nowadays are considered inappropriate. Especially in these older studies, an excess cardiac mortality has been observed, whereas this has not been observed so far in the two large Danish trials or in the Canadian study, where the observation time has passed 15 years without any indication of excess cardiac mortality or morbidity [40,41].

Which patients need radiotherapy after mastectomy?

Despite the evidence of the positive effect of postmastectomy RT, several practical questions face us in the clinic on a day to day basis. These questions include (a) the identification of subgroups of node-positive patients who may not obtain a net benefit from loco-regional irradiation, (b) the potential risks associated with the use of radiotherapy in combination with newer chemotherapeutic agents (e.g., anthracyclines, taxanes, and herceptin) and (c) the efficacy of irradiation of the individual anatomical region (i.e., breast/chest wall, various nodal areas) [42,43].

There has been many debates concerning the question of whether patients with small tumours and few positive nodes would benefit from loco-regional irradiation in addition to adjuvant systemic therapy. In contrast, there has been a general acceptance that patients with large tumours and many positive nodes benefit from postmastectomy irradiation [42]. In this regard, it would be helpful to consider the hypothesis of the tumour pathogenesis that underlies the therapeutic concepts.

It is well known that the primary tumour size is a significant prognostic parameter for the final outcome. Koscielny and Tubiana have mathematically illustrated the relationship between the tumour volume and the ultimate probability of developing distant metastases [39,44–46]. This model, which has been derived from results of long-term follow-up of breast cancer patients not treated with adjuvant therapy, clearly reveals that the likelihood of ultimately developing distant metastases is especially pronounced in patients with large tumours (2 cm) and many positive lymph nodes (>3). In this group, the majority of patients will finally develop distant spread of disease without systemic therapy.

Radiotherapy is a loco-regional treatment, which can eradicate only local and regional deposits of disease and thereby inhibit subsequent fatal metastases [47]. Therefore, from this model one would expect that RT would be most effective in patients who do not have occult distant disease at the time of diagnosis and in those patients who have their distant micrometastases controlled by adjuvant systemic therapy. The results from the Danish and Canadian studies are in fact in agreement with this hypothesis. The percentage reduction in loco-regional failure is in fact greater in patients with 1–3 nodes than in patients with 4 nodes or more [31,32,41,48]. However, there are only data from a few studies [49] where the risk of loco-regional failure in clinical relevant subgroups has been evaluated, and the extent of primary surgery, mainly in the axilla, as well as the aggressiveness of the systemic adjuvant therapy may be competing factors influencing the indication for loco-regional RT, especially in patients with small tumours and few positive nodes.

Current consensus for postmastectomy radiotherapy

On the basis of recent lack of data and the above considerations, the current consensus about the indication for postmastectomy irradiation is that such treatment should be recommended to patients with 4 or more nodes and patients with T3 and T4 tumours. Furthermore, it is the recommended that clinical trials are initiated examining the indication for RT in patients with small tumours and 1–3 positive nodes [43,59]. The EBCTCG overviews, as well as individual randomised trials, have shown that all patient

subgroups seem to benefit to a similar degree from systemic therapy when proportional reductions in recurrence are considered, and that absolute differences in outcome are substantially greater for patients at higher risk than for those at lower risk. The same principle likely holds true for postmastectomy RT concerning reduction in loco-regional recurrences and all recurrences. However, with the Koscielny and Tubiana model in mind, the ultimate survival benefit from postmastectomy RT may prove to be more pronounced in patients in earlier stages and less extensive disease due to the much larger likelihood of developing distant metastases in patients with large tumours, which will ultimately exceed a possible benefit of improvement in loco-regional tumour control unless more effective systemic therapy changes the course of the disease. Thus, the controversy about the indication for RT in patients with small tumours and 1–3 positive nodes still exists.

Loco-regional failure after mastectomy in patients treated with systemic therapy

Breast cancer management, including systemic therapy, has changed since the trials from the 1970's and 1980's. Much more extensive use of screening mammography has resulted in a greater proportion of smaller tumours and less axillary nodal involvement. In addition, the use of adjuvant systemic therapy, both chemotherapy and endocrine therapy, has increased to the point at which it is now the usual treatment for patients with invasive breast cancer, even in patients with small tumours and with no involvement of the axillary nodes [43]. Also, chemotherapy regimens have become more effective, and longer duration tamoxifen has proved to be more effective than tamoxifen treatment for only 1–2 years as was the standard in the past. The extent of surgery, especially axillary dissection, may also influence the risk of loco-regional recurrences [43,50]. Therefore, it is not possible to predict the general value of the two Danish trials, as well as the other trials conducted 15–20 years ago, in today's clinical situation. We do not know to what extent the positive effect of RT results from compensation for suboptimal surgery and/or suboptimal systemic therapy. Also, we do know to what extent the positive effect of radiotherapy results from a true additional contribution to the loco-regional tumour eradication that cannot be obtained by further surgery and/or more effective systemic therapy.

Therefore, an obvious question is what do we know about the loco-regional recurrence rate with the current extent of surgery and the current use of effective systemic therapy? Concerning the extent of surgery, there are only few studies, which can give information about loco-regional failure rates in relation to more or less aggressive surgery. However, there are a few studies comparing radical mastectomy with modified radical mastectomy indicating higher loco-regional failure rates in patients initially treated with modified radical mastectomy. Also, from the two Danish studies it appears that the number of nodes removed is related to the rate of axillary recurrences, which were rather high due to the limited axillary dissection in most patients. Similar findings have been shown in an analysis of the Eastern Co-operative Oncology Group (ECOG) trial [50]. However, the risk of chest wall recurrences as well as supraclavicular, infraclavicular or internal mammary node recurrences is not affected by further axillary dissection and therefore it is not likely that more aggressive surgery as the only loco-regional treatment will sufficiently reduce the loco-regional failures even in the presence of a systemic therapy. The effect of different systemic therapies on the loco-regional failure rate has not been well studied. There seems to be only a little variation between the different chemotherapy regimens used today. For example cyclophosphamide, methotrexate, 5-fluorouracil (CMF)-based and doxorubicin-based regimens were approximately equally effective with regard to loco-regional failure [51,52]. Even in studies using high-dose programmes there seems to be a high risk of loco-regional recurrence after surgery and systemic therapy alone [53]. Concerning the effect of adjuvant tamoxifen alone or in addition to chemotherapy there is only sparse information. Tamoxifen given in addition to chemotherapy or as an adjuvant alone seems to reduce the loco-regional failure rate modestly in parallel with the general reduction in recurrences from systemic therapy [54,55]. The conclusion about the loco-regional failure rate in the context of the current extent of surgery and the current use of systemic therapy is that local tumour control remains a significant problem in high-risk patients and therefore such patients could be candidates for post-operative irradiation.

What is the optimal timing of RT and systemic therapy?

The evidence concerning the optimal sequencing of chemotherapy and RT is sparse. The interval between surgery and the start of RT may affect mainly the risk of loco-regional recurrences, whereas a delay in beginning chemotherapy, in order to give RT first, may reduce the effect on distant failures [56–58].

A trial addressing this particular question from the Joint Centre for Radiation Therapy, Boston [57] has shown that node-positive patients randomised to receive chemotherapy before RT had a better outcome in terms of freedom from distant failures and overall survival than patients treated with RT before chemotherapy. This could not be found in node-negative patients.

Another option in integrating chemotherapy and RT is the sandwich approach, where one or more cycles of chemotherapy are given before RT, then chemotherapy is stopped and RT is given, and finally the remaining cycles of chemotherapy are continued. In the British Columbia and the Danish DBCG 82b trials this approach resulted in a reduced risk of distant failures and improved survival rates in the combined-modality arms despite the interruption of the chemotherapy programme. Similar beneficial results from the use of such sandwich approaches are also observed in other smaller studies, as referred to in the American Society of Clinical Oncologists (ASCO) guidelines for postmastectomy RT [59]. No consensus could be achieved, however, with regard to whether it was better to use a sandwich approach or deliver all of the chemotherapy before RT (as commonly done in most European and North American centres). There was consensus, that doxorubicin or epirubicin should not be administered concurrently with RT, due to unacceptable acute and late toxicity (see later). The theoretical considerations of the possible mechanism for the survival effect of the RT, described above, outlines the use of systemic therapy before RT. This is because only in patients without systemic disease or those that are cured for distant micrometastases by the adjuvant systemic therapy, residual loco-regional tumour deposits could be a nidus for a secondary dissemination, that otherwise, would not have happened.

Radiation-related morbidity

The target area for post-operative irradiation to the breast/chest wall and/or regional lymph nodes includes many delicate and critical structures such as brachial plexus, lung, heart, ribs, shoulder joint, and blood and lymph vessels. It is of utmost importance to recognise radiation effects of such tissues and there should be a balance between the risk of failure caused by inadequate treatment and the risk of unacceptable normal tissue injury caused by the treatment. Radiation-induced normal tissue injury is usually categorised into acute and late effects. Acute radiation damage occurs during or shortly after the course of irradiation and is often related to the injury of rapidly proliferating tissues such as the epithelium. The symptoms are usually transient, and with appropriate symptomatic treatment, acute effects are rarely dose-limiting. Late radiation damage occurs after a latency of months to years. The effects are usually irreversible and may be progressive, leading to considerable morbidity and in rare circumstances mortality. Several studies on radiation-induced morbidity in relation to radiotherapy in breast cancer have revealed a broad range of treatment-related complications as indicated in Table 2. Some of the morbidity endpoints cause only minor symptoms, for example telangiectasia which is important only in terms of the cosmetic outcome whereas complications such as oedema, impairment of shoulder movement, and brachial plexopathy can cause serious and irreversible disability for the patient. One of the most serious concerns in adjuvant radiotherapy is the potential association with radiation-induced heart disease. As mentioned above, the EBCTCG meta-analysis has demonstrated considerable excess of cardiac death in the irradiated compared with the non-irradiated patients [4].

Table 2
Important radiation-related morbidity

Arm oedema
Impairment of shoulder movement
Brachial plexus damage
Telangiectasia
Breast appearance
Subcutaneous fibrosis
Rib fractures
Pneumonitis and lung fibrosis
Ischaemic heart disease
Treatment-induced malignancies

Interaction with surgery

The radiation-related morbidity is influenced by a number of factors, for example interaction with surgery, interaction with chemotherapy, dose and fractionation, and RT volume. The complications in relation to extent of surgery and post-operative irradiation are especially frequent with the combination of axillary dissection followed by post-operative RT which includes the axilla. Several studies have shown that the frequency of lymph oedema and impairment of shoulder movement is increased by the addition of RT. When full axillary irradiation is carried out after lymph node dissection the frequency may be as high as 40–50% [60–62], whereas the overall risk for lymph oedema after surgery alone or RT

alone is much less. The frequency also varies with the extent of surgery and the size of the fraction dose [63]. The use of large fractions >2.5–3.0 Gy generally increases the late normal tissue injuries. As mentioned in relation to BCT, the use of large-dose fractions could cause impaired cosmetic outcome as well as increased risk of cardiac toxicity [24]. Thus, if any critical structures are included in the target, large dose fractions should be avoided since all clinical and experimental radiobiological studies have confirmed that any potential late complication will develop with a significantly higher risk in the large dose fraction group compared to standard dose fractions [64].

Interaction with hormone- and chemotherapy

With the increased use of adjuvant chemotherapy the interaction with such treatment and radiation becomes a daily clinical problem in the decision about the optimal timing of chemotherapy and RT, both with respect to optimal general disease control and with respect to acute and late complications resulting from the combination of these treatments. It is well known that simultaneous chemotherapy and RT increase the acute and late skin reactions significantly. This is especially pronounced by combination of methotrexate and anthracyclines together with RT whereas cyclophosphamide alone produces only minor interaction phenomena in the skin [65]. There is also evidence to show that late complications, such as lymph oedema, subcutaneous fibrosis, impairment of shoulder movement, brachial plexopathy, and lung fibrosis are especially increased by concurrent chemotherapy and RT [66]. The combination of anthracycline-containing chemotherapy and RT must be very carefully monitored. Doxorubicin is a cardiotoxin, which primarily affects the myocardium. The risk of congestive heart failure with doxorubicin is well known. RT of the heart either concurrently or sequentially with doxorubicin appears to increase the risk of developing cardiac damage [67]. This risk has been studied mostly in patients with lymphoma, but there are reports in breast cancer patients as well. In particular, one study has reported a three-fold to four-fold increased risk of cardiac events among breast cancer patients who received a high total cumulative dose of doxorubicin and subsequent left-sided breast and/or chest wall and nodal RT compared to irradiated patients with right-sided cancer or non-irradiated patients [68]. When lower cumulative doses were used no increased cardiac events could be observed, irrespective of the radiation fields. Thus, these data strongly indicate careful evaluation of the relevant target to be included. Although the lower internal mammary nodes are localised close to the anterior part of the heart on the left side it should be seriously emphasised *that the heart is not the target*. The use of newer drugs such as taxanes and herceptin will apparently further stress the need for an awareness of this problem.

Also, RT to patients who do not receive cardiotoxic drugs or any drugs at all carries a potential risk of cardiac complications, especially ischaemic heart disease occurring 10–15 years after the radiation therapy. Reports from the Canadian Register, the Swedish Registry, and the overview analysis have clearly demonstrated the association between postoperative irradiation and the risk of death caused by cardiac toxicity [24,69–71]. This complication is most pronounced in left-sided breast carcinomas where the treatment with tangent fields often includes the anterior part of the heart and thereby the left anterior descending coronary artery [24,72]. The Stockholm group was one of the first to quantify the volume of heart irradiated and the dose received and to relate this to cardiac damage. In patients treated with tangential fields for left-sided tumours and including internal mammary nodes a three-fold increased risk of cardiac death was found compared to untreated controls [73,74]. A subsequent review of early stages breast cancer patients from Stockholm treated between 1976 and 1987 with lumpectomy with tangential fields without inclusion of internal mammary nodes showed no increased risk of acute myocardical infarction with a median follow-up at 9 years [75]. Also, an analysis of the two Danish trials [40] showed no increased risk of cardiac morbidity or mortality with a 12-year follow-up for the entire group or in left-sided tumours. In these patients, the treatment technique was especially designed both to assure inclusion of the internal mammary nodes situated in the four upper intercostal spaces and to avoid unnecessary irradiation of the underlying lung and heart. The internal mammary nodes as well as the chest wall were irradiated through anterior electron fields where the electron energy was chosen from individual measurements of the chest wall thickness. Thus, the conclusion is that long-term cardiac mortality due to RT can be avoided by the use of proper treatment planning and radiation technique [76].

Conclusion

The general conclusion is that loco-regional tumour control has an important impact on survival in early breast cancer and that there is a clear evidence that

residual, inadequately treated loco-regional disease can be the nidus of subsequent dissemination. Thus, the message about RT is that adjuvant RT is an important part of the multidisciplinary treatment of early breast cancer. The indications for RT are to improve loco-regional control in patients who have a high risk of developing loco-regional recurrence after surgery, and also, to improve survival in patients who have a high risk of residual tumour after surgery and who do not yet have disseminated disease. However, the effort to find an optimal balance among the treatment modalities must be continued. There are many problems still to be solved, such as, the definition of the optimal extent of the target of RT, in relation to the risk the individual patient has for remaining loco-regional tumour deposits. Furthermore, the optimal timing of surgery, RT and systemic treatment to obtain maximal effect from the therapies and to avoid unfavourable effects still has to be evaluated.

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