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Position Paper
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The curative role of radiotherapy in the treatment of operable breast cancer

J. Kurtz* for the EUSOMA Working Party

Radiation Oncology Division, Hopitaux universitaires de Genève, CH-1211 Geneva 14, Switzerland

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1. Introduction

The last quarter of the twentieth century has brought about sweeping changes in the loco-regional treatment of breast cancer. Randomised trials have consistently established that survival rates after conservation surgery and breast irradiation are equivalent to those observed after modified radical mastectomy [1]. Moreover, during the same period the use of mammography in asymptomatic women has led to a relative increase in small tumours, ideally suitable for breast conservation. As a consequence, the use of conservation surgery has risen progressively during the 1980s and 1990s, with a corresponding increase in the importance of breast irradiation. In addition, recent meta-analyses of randomised trials have established that breast cancer mortality can be significantly reduced by loco-regional radiotherapy (RT), and that the increased intercurrent mortality observed in older trials was caused by an excess in cardiovascular deaths, presumably avoidable, associated with the earlier techniques [2,3]. Newer trials of post-mastectomy radiotherapy (PMRT) have demonstrated a clear survival improvement, without excess cardiac morbidity, leading to an increased confidence in the use of adjuvant loco-regional RT [4,5].

The extent of the swing to conservative surgery varies amongst geographical regions, depending, at least in part, on the availability of radiotherapy services. With the increasing diffusion of medical technology throughout Europe, this factor will probably assume a decreasing importance for the choice of primary breast cancer therapy. In urban areas with a high socio-economic standard, it is likely that mastectomy will come to be practised in a dwindling minority of patients. According to the Geneva Tumour Registry, the proportion of all curative breast operations that were conservative rose from 3% before 1985, to 51% in 1990, then to 67% since 1998 (*Registre genevois des tumeurs*, unpublished data, 2000). As a consequence, patients currently requiring mastectomy are likely to have larger tumours and positive lymph nodes, and will frequently be considered for PMRT. In such a setting, a substantial majority of primary breast cancer patients will therefore receive RT as part of their initial treatment. These changes come at a time when the prevalence of breast cancer is increasing significantly due, at least partly, to the ageing of the European population. For Geneva, an increase of more than 50% in the number of new breast cancer cases is projected for the period between 2000 and 2010 (*Registre genevois des tumeurs*, unpublished data, 1998). The demand for radiotherapy services required to treat breast cancer patients may thus be expected to increase substantially. Accordingly, the European Society of Mastology (EUSOMA) believes that a position paper regarding the use of RT in breast cancer is timely and useful.

This document discusses the indications for adjuvant RT in operable breast cancer (clinical stages T0-3, N0-1, M0), the technical principles for its proper execution, and where possible, notions of its optimal co-ordination with other treatment modalities. As the breast cancer literature is vast, analysis was necessarily restricted to data having a high likelihood of being reliable, making every effort to draw conclusions likely to be pertinent to

* Corresponding author. Tel.: +41-22-382-7101; fax: +41-22-382-7117.

E-mail address: john.kurtz@hcuge.ch (J. Kurtz).

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RT as it is currently practised, and taking into account technical developments in the field. The participants strove to provide a framework for a European consensus, hoping to encourage greater uniformity in the indications for radiotherapy. Although guidelines for quality control in loco-regional treatment were addressed in a previous EUSOMA position paper [6], the current document will also highlight the concepts pertinent to quality assurance of RT in breast cancer treatment. This document therefore proposes relevant quality objectives and outcome measures and the standard RT data set (Appendix) included in the Quality Target (QT) Audit system approved by EUSOMA.

2. General conclusions from trial overviews

Through 1990 more than 40 unconfounded trials were carried out, in which more than 20 000 breast cancer patients were randomised to receive surgical treatment (with or without systemic therapy) versus the same treatment plus adjuvant RT [2]. Much of what is known regarding the benefits and hazards associated with adjuvant RT stems from analyses of these individual trials, or from overviews of multiple trials. Only a small number of more recent trials include patients treated with breast conservation, so that most long-term data (particularly regarding late treatment complications) come from older trials of adjuvant PMRT. For this reason, post-mastectomy loco-regional RT and breast irradiation following conservation surgery will be discussed separately in the following sections.

The Overview by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) provides the most statistically solid evidence of the existence of treatment effects [2], whose precise magnitude is necessarily obscured by the inclusion of trials in which different types of RT were administered in association with various types of surgery. Nevertheless, a certain number of general conclusions can be drawn from the Overview:

(a) Adjuvant RT (as a generic term) *reduced the annual odds of local recurrence* by a factor of 3. With techniques using daily fractions of approximately 2 Gy [2], this effect appears to be somewhat larger (approximately a *factor of 4*).
(b) A clear cause–effect relationship was demonstrated between the observed reduction in loco-regional failure (LRF) and decreased mortality due to breast cancer. The 68% reduction in the annual odds of LRF resulted in a 13% reduction in the annual odds of death from breast cancer observed after the second year. *Amongst Overview patients, the observed 20% absolute reduction in LRF was associated with an absolute improvement of 5% in long-term breast cancer-specific survival* [2]. Thus, for every 100 patients irradiated, 20 LRFs were prevented and five deaths from breast cancer were avoided, indicating that a 4-to-1 ratio exists between the local control benefit and survival benefit associated with RT.
(c) However, this survival benefit was largely offset by an *increase in mortality due to causes other than breast cancer observed in the irradiated patients* [2,3]. This negative effect, due principally to cardiovascular causes, was seen most clearly in studies started prior to 1975, with techniques that are no longer in use today. The deleterious effect of RT on intercurrent mortality in more recent trials was not statistically significant, which may indicate either that the more modern techniques are safer, or that the follow-up of these trials is not yet sufficiently long to demonstrate the effect. It is thus likely that the net overall survival benefit associated with RT is somewhat less than that indicated in (b) above.

Considering the heterogeneity of Overview trials, the workshop participants expressed concern regarding the pertinence of certain Overview results to current treatment practices, which in most cases favour a combination of surgical, pharmacological and radiotherapeutic treatments, and which emphasise the importance of meticulous care in the planning and execution of RT. It is considered likely that an overview restricted to newer trials in which RT was combined with systemic therapy provides more reliable estimates of the benefits provided by contemporary loco-regional RT [7], at least in the short- and medium-term (through 10 years or more). Regarding the excess non-breast-cancer mortality observed long-term in irradiated Overview patients, newer trials are encouraging, but follow-up from these studies is not sufficient to allow definitive conclusions to be drawn. Extending the long-term follow-up in subsequent Overviews of these trials will be of substantial importance.

3. Multidisciplinary aspects

The use of RT should be viewed as part of a multidisciplinary team approach to the management of breast cancer patients. The advantages of a dedicated breast unit have been discussed in a previous EUSOMA document [8]. The radiation oncologist must be a full member of the team and ideally should participate in the elaboration of the overall treatment strategy for each patient. This is particularly important in the selection of patients for breast-conserving approaches. Only by adhering to appropriate surgical quality criteria [6] can RT be implemented in an optimally effective fashion. RT should not be viewed as a measure to compensate for

inadequate or poorly-conceived surgical treatment. By the same token, multidisciplinary co-operation requires that full attention be paid to optimising both loco-regional and systemic therapies. In patients requiring chemotherapy outside of a research protocol setting, RT should not be unduly delayed by use of highly protracted non-standard schedules. The issues of treatment delays and sequencing are discussed below.

Quality objective	Outcome measure
• To ensure appropriate RT indications.	• The radiation oncologist must be a full member of a multidisciplinary team.
• To ensure appropriate integration of RT with surgical and systemic treatments.	• All patients are to be discussed in a multidisciplinary context. • The radiation oncologist should establish close multidisciplinary links and co-ordinate follow-up with surgery and medical oncology units.

4. General comments regarding RT technique

Although the technical recommendations presented in this paper intend to reflect 'best contemporary practice', in reality such practices are heterogeneous, both regarding equipment, definition of treatment volumes, doses and fractionation [9]. It is generally accepted that breast cancer RT should be primarily carried out using megavoltage photons (cobalt-60 gamma rays or 4–8 MV X-rays from a linear accelerator). For more complex treatment plans (internal mammary nodes, small-volume 'boost' therapy) megavoltage electrons are required. In addition, there may be a role for brachytherapy in selected boost treatments. Modern treatment planning techniques are obligatory, including radiation beam simulation and computer-aided dose calculations. The use of Computerised Tomography (CT)-scanning in treatment planning is sure to grow in importance in coming years [10,11], particularly in cases where maximal protection of normal tissues (e.g. heart and lungs) is especially important (e.g. in association with potentially cardiotoxic chemotherapy).

Although adherence to particular treatment prescription practices has a limited scientific basis, more uniformity would facilitate comparisons among centres. Some effort has thus been made to standardise treatment volume definitions [12], but the clinical value of these formalisms has yet to be demonstrated. Dose prescription practices remain highly empirical. Within the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Co-operative Group, the application of 50 Gy in 25 2-Gy fractions has been adopted as the standard prescription for adjuvant radiotherapy of large volumes (breast, chest wall, nodal areas) [13]. Boost doses to smaller volumes at higher risk usually consist of 10–20 Gy fractionated external beam, or using brachytherapy, when appropriate. The treatment of gross residual disease is not the subject of this paper. Dose prescriptions differing markedly from those outlined above are uncommon. Putatively equivalent schedules are advocated by some investigators, and comparative trials are underway in the United Kingdom and Canada [14].

Quality objective	Outcome measures
• To ensure optimal RT quality	• CT-scans should be available for volume definition ($\geqslant 3$ scans) • Target volume should be checked by radiation beam simulation • Dose calculation should be computer-aided • Standard RT fractionation should be used • Patients should be included in randomised clinical trials

5. Impact of delaying RT and sequencing of RT and chemotherapy

As the effectiveness of adjuvant therapy diminishes with increasing numbers of clonogenic cancer cells, it is oncologically sound practice to begin such treatment as soon after surgery as is practicable. In patients not receiving chemotherapy, it is recommended that RT should start within 8 weeks [6]. When both chemotherapy and RT are to be given, the following sequences are possible: RT followed by chemotherapy, chemotherapy followed by RT, concurrent radio-chemotherapy, and RT 'sandwiched' between courses of chemotherapy. As there are few prospective trials regarding these issues, the question of optimal sequencing of adjuvant RT and chemotherapy remains unresolved, leading to considerable variations in current practices.

Sequential schedules inevitably result in delays in the administration of one treatment modality. Although trials of pre-operative versus postoperative chemotherapy

suggest that beginning treatment with chemotherapy is not prejudicial to survival [15], there is no conclusive evidence that delaying chemotherapy is detrimental. Nonetheless, there is a current tendency to favour early administration of chemotherapy, when indicated. However, it is unclear whether or not delaying RT until after completion of chemotherapy decreases loco-regional control, and the survival consequences are unknown. Retrospective studies on the impact of delaying RT yielded conflicting results. In patients who received no chemotherapy, some studies showed that delaying RT up to 8 weeks after surgery did not increase local recurrence [16]. However, the specific impact of delaying RT in patients with risk factors for local recurrence has not been studied.

Of the few randomised trials addressing the issue of sequencing, one small study of 244 patients who received 12 weeks of chemotherapy and RT showed no differences in outcome (survival, local recurrences and distant metastases) whether one or the other treatment modality was given first after breast-conserving surgery [17]. In an overview of trials of RT after mastectomy in patients who received chemotherapy, a survival benefit was found in patients commencing their RT before 6 months after surgery [7]. Since newer adjuvant programmes tend to call for increasing numbers of chemotherapy cycles, potentially detrimental delays of more than 6 months in starting RT may become frequent. Alternative approaches to treatment sequencing should therefore be investigated.

Early initiation of each treatment modality after surgery can be facilitated both by using alternating 'sandwich' schedules, or by the simultaneous administration of RT and chemotherapy, and may be beneficial regarding both loco-regional control and survival. Although the effectiveness of RT could be enhanced by concomitant chemotherapy, toxicity might also be increased. For this reason, the concomitant administration of anthracyclines and RT is not recommended [18]. Various phase I-II trials are ongoing to test the toxicity of various combinations, and a phase III trial is underway in the United Kingdom. Two phase III trials comparing concomitant and sequential adjuvant therapies have been conducted in France, each including more than 600 patients. Results from these trials are not yet available. There are no randomised data published regarding the sequencing of tamoxifen and RT, which may be administered together or sequentially.

Qualty objective	Outcome measures
• To optimise therapeutic benefit from RT	• Patients not taking adjuvant chemotherapy should start RT as soon as possible after last surgery, at the latest within 8 weeks (minimum target: $\geqslant 90\%$)
	• Patients taking adjuvant chemotherapy should start RT within 4 weeks after the last cycle (minimum target: $\geqslant 90\%$)
	• As a measure of timeliness of adjuvant therapy as a whole, in patients taking chemotherapy RT should start within 6 months of last surgery (minimum target: $\geqslant 90\%$)
	• Interruptions of treatment should be avoided: no more than 1 week difference between actual and planned end of treatment (minimum target: $\geqslant 95\%$)
	• Concomitant delivery of RT and anthracyclines should be avoided (target 100%)

6. Breast irradiation following conservation surgery

6.1. Technique of whole-breast irradiation

Breast irradiation [9,19] is carried out using opposed tangential photon beams (4–8 MV X-rays or telecobalt), angled with respect to the chest wall to minimise lung exposure. Beam dimensions are chosen to encompass the entire breast with adequate margins. Use of conventional or CT simulation is required. Computer-assisted dose optimisation, at least based on a central-axis contour, is desirable. Compensating devices (e.g. wedge filters) and lung density corrections are recommended, where appropriate. The importance of careful treatment planning, particularly to minimise potential cardiopulmonary toxicity, is highlighted in Section 6.3. The issue of tumour-bed 'boost' irradiation is discussed in Section 6.4.

6.2. Benefits from breast irradiation

Breast irradiation is the accepted standard of care after breast-conserving surgery for invasive cancer. The subject of breast irradiation has recently been reviewed and debated [20]. Randomised trials show that breast irradiation reduces the relative risk of ipsilateral breast tumour recurrence (IBTR) by approximately 75%, i.e. 4-fold (Table 1), regardless of the type of breast-conserving operation (i.e. lumpectomy, quadrantectomy or segmental resection). On the average, breast irradiation yields an absolute improvement in overall survival of 3% at 10 years; no unfavourable effect of RT on non-breast cancer mortality has thus far been identified in these patients (EBCTCG 2000 Overview, unpublished). Since RT protects patients from the negative consequences of

Table 1
Crude rate of local breast recurrence in randomised conservation trials

	IBTR (%)			
	mfu (months)	without RT (RT−)	with RT (RT+)	HR
NSABP B-06 [23] (lumpectomy)	125	200/572 (35%)	51/568 (9%)	4.1
Scottish Cancer Trials [22] (lumpectomy)	68	72/294 (24%)	17/291 (6%)	4.2
Uppsala-Orebro [24] (segment excision)	106	44/197 (22%)	13/184 (7%)	3.1
Ontario [21] (lumpectomy)	91	148/421 (35%)	47/416 (11%)	4.0
Milan 3 [25] (quadrantectomy)	109	59/273 (22%)	16/294 (5%)	4.50

mfu, median follow-up; RT−, conservative surgery alone; RT+, with breast irradiation; IBTR, ipsilateral breast tumour recurrence; HR, hazard ratio; NSABP, National Surgical Adjuvant Breast and Bowel Project.

cancer recurrence in the operated breast, including breast loss [21,22] and uncontrolled local cancer growth [22], breast irradiation has achieved a very high level of acceptance. Nonetheless, the absolute benefit derived by certain subgroups of low-risk patients is presumed to be small.

6.3. Complications of breast irradiation

The acute side-effects (fatigue, local inflammation and breast oedema) resolve rapidly in most patients. In patients whose RT does not include lymph nodal areas, symptomatic pulmonary reactions are uncommon, and resolve without treatment [9]. The central lung distance (CLD), defined at simulation by the distance from the deep field edge to the thoracic wall in the central axis plane [26], is often used as a surrogate for the lung volume encompassed by tangential beams. Keeping the CLD <3 cm may be a useful treatment planning guideline for limiting pulmonary exposure in tangential breast treatment. After breast-conserving surgery, breast and chest wall pain are more frequent in irradiated than in non-irradiated patients, but this difference disappears after 6–18 months [27]. Rib fractures, sometimes asymptomatic, are observed in 1–2% of patients [9]. Tangential RT has not been shown to contribute significantly to arm or shoulder symptoms after axillary dissection [28], despite incidental irradiation of the lower axilla. In the majority of patients, breast irradiation has a relatively minor influence on the long-term cosmetic result, which is a direct consequence of surgery [29,30]. However, in a minority of patients, radiation-induced fibrosis and skin changes, particularly related to boost treatment, can markedly effect cosmesis. This may relate to inhomogeneities in RT dose, especially in patients with large breasts [31]. RT does not appear to have a substantial untoward influence on patients' long-term satisfaction with the state of their conserved breast, or on their quality of life [27].

Serious long-term complications, mostly anecdotal, have only rarely been attributed to tangential breast RT. Although contra-lateral breast cancers and other second malignancies might be expected to be more frequent in irradiated patients, no significant increase has been observed after local breast irradiation [9,32]. Nonetheless, techniques should be favoured, particularly in younger patients, that limit the scattered radiation dose to the opposite breast [33]. Sarcomas appearing in the breast or the chest wall are considered radiation induced [9], but fortunately they are rare, concerning less than 0.5% of irradiated patients. The incidence of acute leukaemia seems increased in patients receiving chemotherapy in addition to breast irradiation [9].

Although RT of the left breast sometimes encompasses a portion of the left ventricle, no increase in cardiac morbidity or mortality has been clearly associated with techniques that do not include lymph nodal areas [34]. A population-based cohort study, based predominantly on patients treated with 2.5 Gy fractions using cobalt machines, showed a higher incidence of cardiac-related mortality in patients older than 60 years of age irradiated after conservation surgery for left-sided compared with right-sided breast cancers [35]. Moreover, there may be an increase in cardiac events in patients receiving anthracycline-containing regimens in association with left-breast irradiation [18,36]. As the potential for cardiac toxicity clearly exists, care should be taken in treatment planning of left breast cancer to limit the dose to the heart [11,37,38] (e.g. by appropriate choice of beam parameters and the use of shielding blocks), provided that the adequate irradiation of the involved breast quadrant is not compromised. The degree of cardiac exposure using tangential beams

can also be influenced by positioning techniques [39,40]. The maximum heart distance (MHD) intersected by the tangential beam appears to correlate well with the risk of late cardiac mortality [11]. Mathematical models based on clinical data suggest that treatment techniques limiting the MHD to less than 1 cm should be associated with $<0.5\%$ excess cardiac deaths [11].

Quality objective	Outcome measures
• To avoid cardiopulmonary complications	• Irradiated lung volume should be minimised: Central Lung Distance <3 cm (minimum target: $\geqslant 95\%$) • Heart exposure should be minimised: Maximum Heart Distance <1 cm (minimum target: $\geqslant 90\%$)

6.4. The 'boost' to the tumour bed

Since IBTRs are most often observed within the vicinity of the index lesion, a localised radiation boost to the tumour bed is frequently recommended, using either external beams or brachytherapy. Randomised trials have demonstrated that boost irradiation significantly improves local control compared with whole-breast irradiation alone [41,42].

After 50 Gy whole-breast irradiation, adding a boost of 16 Gy decreases local recurrence rates by a factor of almost 2 [41]. The absolute benefit from boost treatment is particularly marked in young patients, and is indicated for all patients less than 50 years of age. In older patients, omission of boost irradiation may be considered in the absence of risk factors for local recurrence.

On the negative side, boost treatment has been shown to significantly reduce the proportion of favourable long-term cosmetic results observed [43]. Telangiectasias can result from an excessive dose delivered to vessels that are located in the first 5 mm beneath the epidermis [44], and dose- and volume-dependent fibrosis [45] can lead to breast retraction and deformity. Optimisation of boost delivery is thus of importance. The surgeon can contribute to the accuracy of boost therapy by placing the skin incision directly over the tumour and by the use of radio-opaque clips. Choice of boost technique is likely to depend largely upon the personal preference and training of the radiation oncologist involved and upon the local infrastructure. For deeply-seated tumours, interstitial brachytherapy allows smaller volumes to be treated and lower skin doses delivered compared with standard external electron beam boost [46].

6.5. *Breast irradiation for ductal carcinoma* in situ *(DCIS)*

Since the introduction of screening mammography, there has been an enormous increase in the detection of DCIS. For this relatively 'new' disease, the principles of optimal breast conservation technique have not yet been as well established as for invasive cancers. Two prospective trials, randomising patients after complete excision of the lesion to receive 50 Gy breast irradiation versus no further treatment, both show an approximately 2-fold reduction in the risk of local recurrence [47,48]. No impact of RT on the (excellent) survival rates is observed to date. Both trials show a recurrence rate of approximately 10% at 5 years, of which half are invasive cancers. In the available trials of breast irradiation for DCIS, no boost was used, and the potential role of a localised boost remains to be studied. As the effect of RT on local recurrence may be less marked in DCIS than in invasive disease, the 'standard' dose of 50 Gy might not be sufficient to provide optimal benefit.

DCIS is usually a non-palpable, ill-defined lesion, whose extent is often larger than that suspected mammographically, making a truly complete surgical excision difficult to achieve. The width of the tumour-free margin is generally believed to be the most important risk factor for recurrence [49]. Some retrospective studies observed a low recurrence risk when DCIS was excised with a margin exceeding 10 mm [49], suggesting that it might be safe to omit RT in this subgroup of patients. The prospective trials, however, do not confirm this. While the multivariate analysis of the EORTC trial showed margin status to be the strongest factor associated with the risk of recurrence, the group of patients who had negative re-excisions seemed to benefit most from RT, with very low recurrence rates in this group [47]. This suggests that RT is most effective with a low residual tumour load. Many uncontrolled studies claim to have identified subgroups of patients with DCIS that can be adequately treated with 'complete' local excision alone. However, the randomised trials indicate that RT reduces local recurrence in all subgroups of patients with DCIS. Therefore, until conclusive randomised evidence allows definition of subgroups in whom RT can be safely omitted, RT should remain part of the standard breast-conserving procedure for all patients with DCIS, as is the case for invasive cancer.

Even more than in invasive cancer, breast-conserving surgery for DCIS requires a careful multidisciplinary approach. Radiologist, surgeon and pathologist should collaborate closely to excise all microcalcifications, in view of achieving wide, microscopically complete excision of the malignant lesion. In this regard, in addition to specimen radiography, it is recommended that a post operative mammogram should be performed in all cases prior to beginning RT.

Quality objective	Outcome measures
• To diminish the incidence of local recurrence after conservative surgery for invasive cancer	• Whole-breast irradiation is to be considered the standard of care (minimum target: $\geqslant 95\%$) • Boost to the tumour bed should be administered in patients < 50 years of age (minimum target: $\geqslant 95\%$) • The surgeon should perform the skin incision directly over the tumour and/or leave radiopaque clips in the tumour bed
Quality objective	Outcome measure
• To diminish the incidence of local recurrence after conservative surgery for DCIS	• Whole-breast irradiation is to be considered the standard of care (minimum target: $\geqslant 90\%$)

7. Loco-regional RT after total mastectomy and axillary surgery

7.1. Estimating the benefits from post-mastectomy radiotherapy (PMRT)

In a historical context, loco-regional irradiation after modified radical mastectomy refers to radiotherapy involving the ipsilateral chest wall, as well as the ipsilateral axillary, supra- and infra-clavicular, and internal mammary lymph node chains. Such a comprehensive approach was used in almost all PMRT trials [2]. As indicated above, recent trial overviews establish conclusively that loco-regional RT following ablative surgery not only improves tumour control within the irradiated volume, but also improves overall survival in appropriate high-risk patients. However, due to the heterogeneity of both surgical and radiotherapeutic techniques within the analysed trials, it is difficult to apply these results to contemporary practice. 'Radical' surgical techniques vary considerably among centres, regarding both the breast and axillary nodes. Classical techniques of 'modified radical mastectomy' have given way to total mastectomy, with or without removal of the pectoral fascia, and skin-sparing approaches have been introduced. Complete axillary clearance is less often practised, with increased use of level 1–2 dissections, axillary sampling and sentinel-node biopsy.

Moreover, patients at high risk of LRF are generally at even higher risk of distant dissemination. Therefore, almost all patients for whom loco-regional RT might be considered will also receive systemic treatment, which in itself also reduces LRF. In order to estimate the effects of loco-regional RT in the light of contemporary practice, a recent overview analysed all peer-reviewed published trials (with a median follow-up of at least 5 years) in which patients receiving adjuvant chemotherapy or tamoxifen (or both) were randomised to receive or not to receive such RT [7]. 6367 patients randomised in 18 studies initiated between 1973 and 1984 were analysed. RT was found to be associated with a 75% reduction in the odds of LRF, a 31% reduction in the odds of cancer recurrence, and a 17% reduction in the odds of death. In a multivariate analysis of treatment effect on survival, only beginning radiotherapy within 6 months of surgery and the use of megavoltage equipment were significant factors. These estimates from the systemic therapy meta-analysis are more optimistic than those from the EBCTCG Overview, but presumably are more pertinent to current practice. Regarding the reduction in odds of total recurrence and survival, the effects of RT seem similar in magnitude to those associated with systemic therapy [50,51].

7.2. Complications of PMRT

Unlike tangential breast irradiation, RT involving lymph nodal areas can cause serious toxicities, including arm lymph-oedema, brachial plexopathy, shoulder stiffness, and symptomatic lung reactions [9]. In addition, because a larger tissue volume is treated, comprehensive RT may potentially be associated with a significant increase in secondary neoplasms. According to the EBCTCG Overview, deaths from neoplasms other than breast cancer were slightly, but not significantly, increased in irradiated patients [2].

However, trial overviews indicate that increased cardiac and other vascular mortality is clearly the factor that has the greatest potential to minimise the net long-term survival benefit that patients derive from comprehensive RT [2,3]. Confirmatory data have also come from epidemiological studies, suggesting that patients irradiated for left-sided breast cancers may suffer increased mortality from myocardial infarction compared with patients irradiated for right-sided lesions [52]. Data from the Stockholm Trial suggest that excess cardiac mortality reflects the volume of heart irradiated to a high dose [53]. The use of fractions > 2 Gy may also be an adverse factor [54]. Irradiation of the great vessels (through internal mammary or supraclavicular fields) might be an additional cause of vascular morbidity [2], but clinical data are currently lacking. It is axiomatic that techniques for which the heart is not within the primary beam will not lead to excess cardiac morbidity. Even if the internal mammary nodes are treated, it is very likely that vascular morbidity can be minimised by appropriate treatment planning (particularly CT-based) and delivery techniques (e.g. incorporating electron beams) that limit as much as possible the

radiation exposure to the heart and great vessels. This notion has been confirmed by the combined analysis of more than 3000 patients randomised in the Danish Breast Cancer Co-operative Group Trials 82b and 82c (Table 2), in which no excess cardiac (or other non-cancer) mortality was observed after a median follow-up of 10 years [55]. Overview data suggest that such differences, if present, should have become apparent starting around 10 years [2]. In all trials started after 1975, there is no significant excess non-breast cancer mortality observed in irradiated patients [2], but there are only a limited number of patient-years of second-decade follow-up for patients in these newer trials.

Although longer-term confirmatory data is required from these newer studies, the weight of current evidence suggests that the marked increase in cardiac and other vascular mortality found in patients irradiated using old techniques is not likely to be observed with optimal contemporary RT practices. Despite this optimism, caution should be expressed regarding the unknown consequences of combinations of regional RT with newer cardiotoxic chemotherapy agents, such as anthracyclines and taxanes. This area requires careful study in this regard. The importance of long-term follow-up is apparent.

7.3. Which anatomical areas should be irradiated post-mastectomy?

This subject has been extensively reviewed [56]. Trials establishing that PMRT improves overall survival used comprehensive schedules encompassing both chest wall and nodal areas. Therefore, some investigators believe that comprehensive RT should always be prescribed in high-risk patients. However, the clinical benefit derived from adjuvant RT is presumed to be in direct proportion to the risk of LRF expected in the absence of irradiation. *Following modified radical mastectomy and systemic adjuvant therapy, LRF is most frequently observed in the skin flaps of the ipsilateral chest wall, considerably less frequently in the supra-/infra-clavicular areas, uncommonly in the axilla, and almost never in the internal mammary area* (Table 3). It follows that most of the benefit regarding loco-regional control stems from irradiation of the chest wall, and it is assumed (but not proven) that much of the survival benefit expected from adjuvant RT is also associated with this component of treatment [56]. Chest wall treatment is thus the cornerstone of postmastectomy irradiation.

Table 2
Vital status after 122 months' median follow-up of 3083 high-risk[a] patients randomised in Danish (DBCG) Trials 82b-c after modified mastectomy plus systemic therapy[b] to receive or not to receive 50 Gy local-regional RT [55]

	With RT	Without RT
Alive	766 (50%)	627 (41%)
Dead, cancer	710 (47%)	836 (55%)
Dead, cardiac	12 (0.8%)	13 (0.9%)
Dead, other	37 (2.4%)	45 (3%)

[a] pN+ or T3–4.
[b] Premenopausal: CMF chemotherapy; postmenopausal: tamoxifen.

Table 3
Sites of LRF at 10 years in 2016 node-positive patients treated in ECOG Trials by modified radical mastectomy and adjuvant chemotherapy (with or without tamoxifen), but without PMRT [57]

Site of LRF	*N* (%)
Chest wall	244 (12%)
Supra/infraclavicular	158 (8%)
Axilla	82 (4%)
Internal mammary	4 (0.2%)

Following axillary clearance, axillary failures are uncommon. Moreover, axillary RT markedly increases the incidence of arm oedema observed after axillary clearance [9]. Therefore, such irradiation is not recommended in patients having had axillary clearance, regardless of the extent of nodal involvement, unless there is good reason to suspect the presence of residual axillary disease. In patients having positive nodes in an axillary sampling, the risk of residual axillary disease is believed to justify axillary irradiation, and axillary sampling with selective RT in node-positive patients has been shown to be similarly effective for tumour control as axillary clearance [58]. The role of axillary RT in conjunction with sentinel node biopsy remains to be defined by future trials.

Quality objective	Outcome measure
• To reduce incidence of arm oedema	• Axillary RT is not recommended after level 2 or 3 axillary dissection regardless of the extent of nodal involvement, unless there is a good reason to suspect the presence of residual axillary disease (target 95%)

For patients with fewer than four positive nodes, the risk of supra-/infra-clavicular recurrence is generally well below 10% [57]. Considerations of local control thus do not justify a supra-clavicular radiation field unless a larger number of nodes is involved. However, this restrictive reasoning does not necessarily apply for node-positive patients having had less than a level 1-2 axillary dissection. Moreover, aside from a small risk of brachial plexus injury, the morbidity of normally-fractionated supra-clavicular RT is considered to be low,

and the consequences of recurrence in this area difficult to manage. However, it is possible that vascular injury associated with supra-clavicular RT may increase the incidence of cerebrovascular accidents in irradiated patients (EBCTCG 2000 Overview, unpublished).

Although substantial surgical data indicate that internal mammary nodes are often microscopically involved in patients with positive axillary nodes (particularly for tumours in the medial or central parts of the breast), clinical recurrence is rare, and RT of this area is never justified by local control considerations. There is no convincing evidence indicating that internal mammary treatment in itself improves survival [59]. Moreover, internal mammary irradiation is presumably the major contributor to the untoward cardiac complications associated with breast cancer RT. Prospective randomised trials are underway investigating the respective benefits and disadvantages of parasternal and supra-clavicular RT in this regard [13], and participation in such trials should be encouraged.

7.4. Selection of patients for PMRT

Because PMRT not only protects high-risk patients from LRF, but also reduces breast-cancer mortality and potentially improves their long-term overall survival, it is important to define which patients are appropriate candidates for such treatment. However, criteria regarding 'unacceptable' risk and 'significant' benefit are necessarily arbitrary. Formal cost-outcome analyses have been proposed as a potentially useful tool for addressing these aspects [60]. For the purposes of argument, an anticipated *10-year LRF rate of 20% is suggested as a threshold for recommending PMRT*. Under these circumstances, overview results suggest that RT produces an absolute long-term reduction in breast cancer mortality of approximately 5% [2,7]. Since newer studies suggest (but do not definitively prove) that any increase in non-breast cancer mortality associated with contemporary RT techniques is substantially less than 5% (or even non-existent [55]), a net overall survival benefit can reasonably be expected in such patients. It is assumed that PMRT in patients at lower risk would result in 'negligible' (i.e. less than 5%) survival benefit, but this remains to be proven. Certainly, *if an increase in non-breast cancer mortality could confidently be excluded, PMRT would also be recommended for patients at substantially lower risk of LRF (e.g. 10%)*.

Quality objective	Outcome measure
• To define which patients are appropriate candidates for PMRT	• PMRT is strongly recommended in patients whose expected loco-regional failure rate is 20% or more at 10 years

Patient selection, therefore, involves defining subgroups that (as a function of the quality of surgery and type of systemic therapy) have at least a 20% risk of LRF at 10 years. Even with 'optimal' surgery (modified radical mastectomy with level 2 or 3 clearance) and appropriate systemic treatment, node-positive patients with tumours larger than 5 cm or involving the skin or chest wall, and all patients with four or more positive nodes, are at more than 20% risk of LRF (Table 4) [56,57,61], and PMRT should be recommended. Patients with T1-2 tumours and less than four involved axillary nodes generally have LRF rates of less than 15% after modified radical mastectomy and appropriate systemic treatment [57,61]. However, subgroups at higher risk may include patients with larger tumours [61], lymphatic vessel invasion [62,63], extension of cancer cells beyond the lymph node capsule [63], gross tumour multicentricity [63], high histological grade [62], less than 10 examined lymph nodes [63], pectoral fascia invasion or close surgical margins [63]. There are currently no data supporting the use of PMRT in patients with negative axillary nodes, with the exception of advanced local tumour stage.

Selection criteria for PMRT assume a direct proportionality between LRF risk and absolute survival benefit. A 'negligible' survival improvement (or even a survival decrement) might be expected after RT in patients at low risk of LRF. However, it is possible that low-risk patients have more to lose from the metastatic re-seeding that may result from LRF, and that significant survival improvement could result from PMRT in patients whose risk of LRF is well below 20%. Although trials are underway to test this hypothesis, at present, PMRT is generally not recommended in patients at low risk of LRF.

Quality objective	Outcome measure
• To diminish the incidence of breast cancer recurrence after total mastectomy	• RT should be administered at least to the chest wall in node-positive patients with tumours clinically T3-T4 or involving the skin or chest wall, or with four or more positive nodes (minimum target: $>95\%$)

Table 4
10-year loco-regional recurrence rates in 2016 patients with T1–3 tumours and positive axillary nodes, randomised in ECOG Trials and receiving appropriate chemotherapy (with or without tamoxifen) after modified radical mastectomy, but without RT [57]

Positive nodes	% LRF		
	T1	T2	T3
1–3	12	12	31
4–7	20	27	45
>7	33	33	33

7.5. Irradiation of lymph nodal areas after breast conservation

In principle, the indications for nodal irradiation after conservation surgery should be identical to those following mastectomy. However, tangential breast irradiation not only encompasses the entire breast and underlying chest wall, but also a portion of the lymph nodes in the lower axilla and (to a variable extent) the internal mammary chain. As a consequence, a reduction of regional recurrence is observed after tangential RT alone, even without the use of RT beams specifically directed at lymph node areas [32]. It is unclear to what extent the addition of nodal fields in patients with breast-conserving therapy might contribute to improving overall survival. As indicated above, use of a separate infra-/supra-clavicular field may be justified in patients with four or more involved axillary nodes, or in node-positive patients following axillary sampling. Trials addressing the role of axillary irradiation in association with sentinel node biopsy are underway. The value of internal mammary RT is also under investigation in randomised trials.

7.6. RT and breast reconstruction

Close collaboration between breast and plastic surgeons and the oncologist is required in selecting patients for reconstruction, as the need for appropriate adjuvant radiation and systemic therapy should be the overriding concern. There are limited data defining and quantifying the effects of radiotherapy on the results of reconstructive surgery. Much of the data come from retrospectively analysed surgical series, in which small sample size and the heterogeneity of patient populations preclude firm recommendations about the integration of radiotherapy and reconstructive surgery [56]. Moreover, details of radiotherapy are often too scanty to allow correlation between the radiation technique and risk of complications.

With these caveats, for patients undergoing reconstruction with prostheses (implants or tissue expanders), most of the evidence suggests that complications are more frequent and cosmesis is poorer with the addition of radiation [64]. RT can lead to a hardening of implants by capsular contracture, and leakage or rupture of expanders may occur. Despite the higher complication rate with expanders/implants, patient satisfaction and the perception of an aesthetic outcome may not necessarily differ between irradiated and non-irradiated patients [65]. In general, however, reconstruction with implants should be avoided where there is a high likelihood of radiotherapy being required.

Compared with its effect on implant results, radiotherapy seems to have no significant effect on the viability and a relatively minor effect on the cosmetic outcome of reconstruction with myocutaneous flaps, irrespective of whether radiotherapy is given before or after surgery [66–68]. There is some evidence that the risk of late complications may be significantly higher among patients undergoing immediate as opposed to delayed transverse rectus abdominis myocutaneous (TRAM) flap reconstruction [67]. Nonetheless, one might opt for immediate autogenous reconstruction if the patient accepts that the risk of complications is likely to be higher and the cosmetic results poorer than those expected in the absence of irradiation. These disadvantages have to be balanced against the psychological benefit of primary surgery and immediate reconstruction as a single procedure.

8. Conclusions and future directions

As applied to the curative treatment of breast cancer, RT is complex and technically challenging. Optimal use of this modality requires close collaboration between the radiation oncologist and all other members of the multidisciplinary breast cancer team, into which the radiation oncologist needs to be fully integrated.

Current breast-conserving therapy techniques provide uncomplicated local control and acceptable cosmesis in a large majority of patients. Breast irradiation is the standard of care following breast-conserving surgery for invasive cancers, because omission of RT in unselected patients will result in a 4-fold increase in IBTR, is prejudicial to the goal of breast conservation, and increases the percentage of patients suffering from uncontrolled loco-regional disease and distant metastases. However, since the majority of IBTRs are observed in the immediate vicinity of the primary tumour bed, the 'gold standard' of whole-breast irradiation has been questioned. Although mature data from a randomised trial indicate that unselected patients are not adequately treated when RT is limited to the affected quadrant [69], it might be possible to establish criteria allowing selection of appropriate patients whose tumours are truly of limited extent [70]. Recent data from groups using localised brachytherapy [71], or various innovative intra-operative irradiation techniques [72], have been published. However, these studies have rather short follow-up, and the proportion of IBTRs that are outside the primary tumour quadrant tends to increase with long-term observation.

Since breast irradiation is costly, inconvenient, and not without side-effects (usually minor), the research question of defining subgroups of patients in whom breast irradiation might be omitted retains its currency. However, low-risk subgroups have not yet been clearly defined, as it is difficult to reliably identify patients with IBTR risk much below 20% at 10 years [73]. Selection criteria include age 60 years or older, small tumour size, low grade, negative nodes, positive hormone receptors

(allowing tamoxifen therapy), wide excision margins, and absence of morphological features predictive of multifocality (lobular histology, extensive intraductal component, lymph vessel invasion) [73]. As screen-detected cancers often fit this description, it is hoped that many such patients will be able to forego breast irradiation without danger. It is possible that newer imaging techniques, such as magnetic resonance imaging, might help identify patients not needing breast irradiation. Prospective studies addressing these aspects are being carried out [74,75].

In association with appropriate systemic therapy, loco-regional RT after mastectomy in high-risk patients significantly reduces the total risk of cancer recurrence and improves overall survival. Unlike breast irradiation, comprehensive loco-regional RT is associated with potentially serious toxicity. In particular, scrupulous treatment planning is required in order to minimise radiation exposure to the heart and great vessels. In patients having a LRF risk of 20% or more after modified radical mastectomy, an absolute reduction in long-term breast cancer mortality of approximately 5% can be expected from comprehensive RT with modern techniques. This benefit is expected to be substantially greater than any potential increase in intercurrent mortality associated with contemporary RT practices, and a net improvement in overall survival can thus be expected. Tumours larger than 5 cm or involving skin or chest wall, and those with four or more positive axillary nodes are associated with a loco-regional recurrence risk of 20% or more, despite adequate systemic therapy. Such patients should receive PMRT. For T1–2 tumours with less than four positive nodes, further research will be required to determine which patients derive sufficient benefit regarding loco-regional control or survival to justify PMRT. Although it is unclear which anatomical component of comprehensive RT contributes most to the survival improvement, adequate irradiation of the chest wall is of primary importance for tumour control. After level I-II axillary dissection, radiotherapy should generally not include the axilla (risk of arm oedema). RT techniques must evolve to keep abreast of developments in surgical oncology, including lymphatic mapping. The use of sentinel node techniques may lead to a re-definition of the indications for peripheral nodal irradiation, including RT to the axilla and the internal mammary chain.

In addition to refining the indications for the more selective use of adjuvant RT, future radiation oncology research will investigate the use of newer techniques of medical imagery, treatment planning, and beam delivery for optimising breast cancer treatment. This will result in improved target dose homogeneity and better protection of normal tissues, with corresponding reductions in breast fibrosis and other symptomatic treatment-induced side-effects. High-precision techniques, such as intensity modulated photon beams and proton beam treatment, may prove to be advantageous in a substantial proportion of complex breast cancer cases. Altered dose and fractionation schedules will be tested in the hope of making RT more effective or more convenient for patients. Radiobiological research may allow the identification of patients with abnormal radiosensitivity who are at risk for untoward late effects of treatment, and should identify molecules that increase the antitumour effect of RT. Radiation oncologists are thus optimistic regarding the future possibilities of providing breast cancer patients with even greater clinical benefits, whilst substantially reducing the inconveniences and untoward effects associated with radiation treatment.

9. Participants

H. Bartelink, Amsterdam. L. Cataliotti, Florence. J. Cuzick, London. J. Dunst, Halle. M. Ewertz, Aalborg. J. Fodor, Budapest. A. Fourquet, Paris. M. Greco, Milan. J. Hammer, Linz. J. Jassem, Gdansk. I. Kunkler, Edinburgh. R. Orecchia, Milan. A. Ponti, Turin. P. Romestaing, Pierre Benite. E. van Limbergen, Leuven. J. Yarnold, Sutton.

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Appendix

Radiotherapy

No Yes Unknown

Department _____
Date of RT appointment /___/___/___/
Date of first radiotherapy /___/___/___/
Scheduled date of last radiotherapy /___/___/___/
Actual date of last radiotherapy /___/___/___/

RT dose per fraction __.__**Gy**
Reason for departure from conventional RT fraction:

_____

Total dose _____**Gy** **Boost dose** _____**Gy**

Irradiated volumes

Breast
No Yes Unknown
(1) - Cobalt 60
(2) - X-MV
(3) - Other: .....
(9) - Unknown

RT boost
No Yes Unknown
(1) - Electron
(2) - X-MV
(3) - Interstitial brachytherapy
(4) - Other: .....
(9) - Unknown

Chest wall
No Yes Unknown
(1) - Cobalt 60 (2) - X-MV
(3) - Roentgen (4) - Electron
(5) - Contact brachytherapy
(6) - Other: .....
(9) - Unknown

Internal mammary nodes
No Yes Unknown
(1) - Cobalt 60
(2) -X-MV
(3) - Electron
(4) - Other: .....
(9) - Unknown

Axilla

(0) - No
(1) - Yes, apex
(2) - Yes, all axilla
(3) - Yes, unknown site
(9) - Unknown

Supra/infra clavicular nodes
No Yes Unknown
(1) - Cobalt 60
(2) - X-MV
(3) - Other:
.....
(9) - Unknown

Interruption to therapy

No Yes Unknown

Reason: .....

Central Lung Distance

mm .....

Maximum Heart Distance

mm .....

CLD and MHD measurements

(1) - By simulator
(2) - Average port-film measurements

Notes

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