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Adjuvant radiotherapy for breast cancer

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Background and history

Radiotherapy involves the delivery of ionising radiation in an attempt to kill malignant cells. Radiotherapy is frequently used in the management of early breast cancer. The radiotherapeutic management of early breast cancer accounts for 20–40% of available resources in most UK radiotherapy departments.

Postmastectomy radiotherapy was one of the first medical interventions to be tested in prospective trials. These began around 50 years ago and have left a rich legacy of randomised evidence which has established the role of radiotherapy in patient management and provided insights into the natural history of breast cancer. Long-term follow-up of these trials demonstrated that locoregional therapy can improve breast cancer mortality and overall survival. Consequently early breast cancer cannot be considered as a disease whose outcome is solely determined by the presence or absence of micrometastatic disease at the time of diagnosis. Local as well as systemic therapy has the ability to improve survival.

Adjuvant radiotherapy, whether given after breast-conserving surgery (BCS) or mastectomy substantially reduces local recurrence rates and contributes to the improved outcomes in the management of early breast cancer that we have seen over the last 10–20 years, but, like systemic adjuvant treatment, it is ultimately a treatment given for the risk, rather than the existence, of recurrence. This of course means that thousands of patients with early breast cancer are irradiated unnecessarily as they would not have suffered recurrence without radiotherapy or they still develop recurrence despite its use.

The search for reliable prognostic factors for recurrence and markers of tumour sensitivity will help to identify those who benefit most from this treatment.

Planning and treatment delivery

Modern radiotherapy for early breast cancer differs from the practice of 15–20 years ago. Radiotherapy planning allows the precise definition and contouring of target volumes requiring irradiation and organs that should be spared. This allows the delivery of a near homogenous dose of radiation and modern linear accelerators (linacs) have the facility for multileaf collimation and real-time on-treatment imaging to allow precise treatment delivery and verification (**Fig. 17.1**).

Inevitably the practice of radiotherapy involves compromise. Target volumes cannot be treated without the acceptance that some organs will receive a radiation dose, with the inherent consequences of the common short-term toxicities of radiotherapy and the small risks of more serious longer-term problems.

As is the case with systemic adjuvant therapies, the welcome improvements in treatment delivery create the well-known dilemma of ‘contemporary generalisability’ – namely whether (and by how much) the results of trials conducted decades previously should influence decision-making today, given the many other improvements that have taken place in management and the generally earlier presentation of patients.

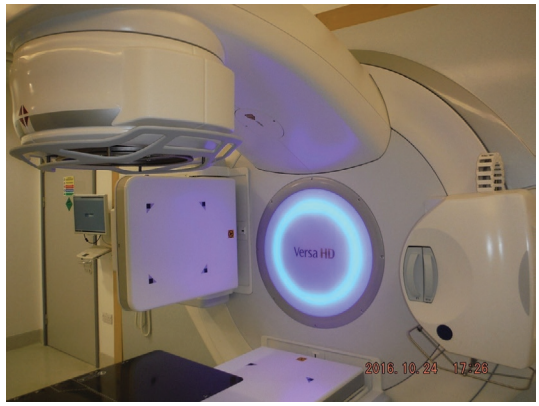


Figure 17.1 • A modern linear accelerator (LINAC) with facilities for multileaf collimation and on treatment imaging.

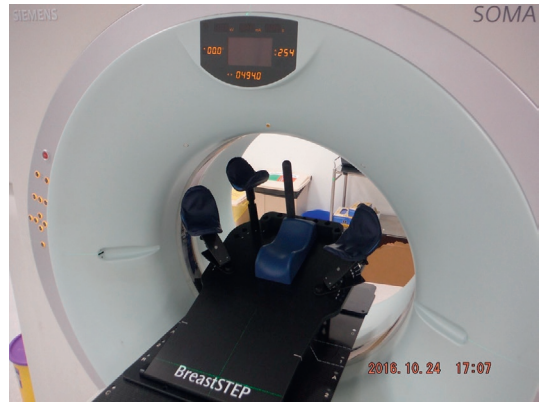


Figure 17.2 • CT simulator allows detailed 3D image acquisition for target volume and normal organ delineation.

Practicalities and treatment pathways

It is important to be aware of a possible need for postoperative radiotherapy when planning any surgical treatment and to discuss the pros and cons of radiotherapy in a preoperative multidisciplinary team (MDT) meeting with the clinical oncology team.

Factors that influence whether radiotherapy treatment is appropriate and practical include:

- Poor ipsilateral arm or shoulder movements
- The presence of a cardiac pacemaker or 'cardiac assist' device
- A very high BMI
- Significant comorbidities
- Previous radiotherapy
- Collagen vascular disease

It is particularly important to involve the clinical oncology team if immediate breast reconstruction for invasive breast cancer is being planned.

In most circumstances following an MDT decision to offer radiotherapy, consultation with the patient and informed consent, the next step is the organisation of a planning CT scan (**Fig. 17.2**) at which time positional parameters are recorded and permanent reference marks (tattoos) are usually placed to ensure consistent positioning and alignment throughout radiotherapy planning and treatment.

Following this procedure any changes to patient shape can be problematic. This can be an issue if there is a persistent postoperative seroma or wound healing problems. Similarly, inflation of any expander implant needs to be complete before radiotherapy is planned.

The clinical oncologist or appropriately trained therapy radiographer then delineates the appropriate target volume on the relevant dedicated CT data set:

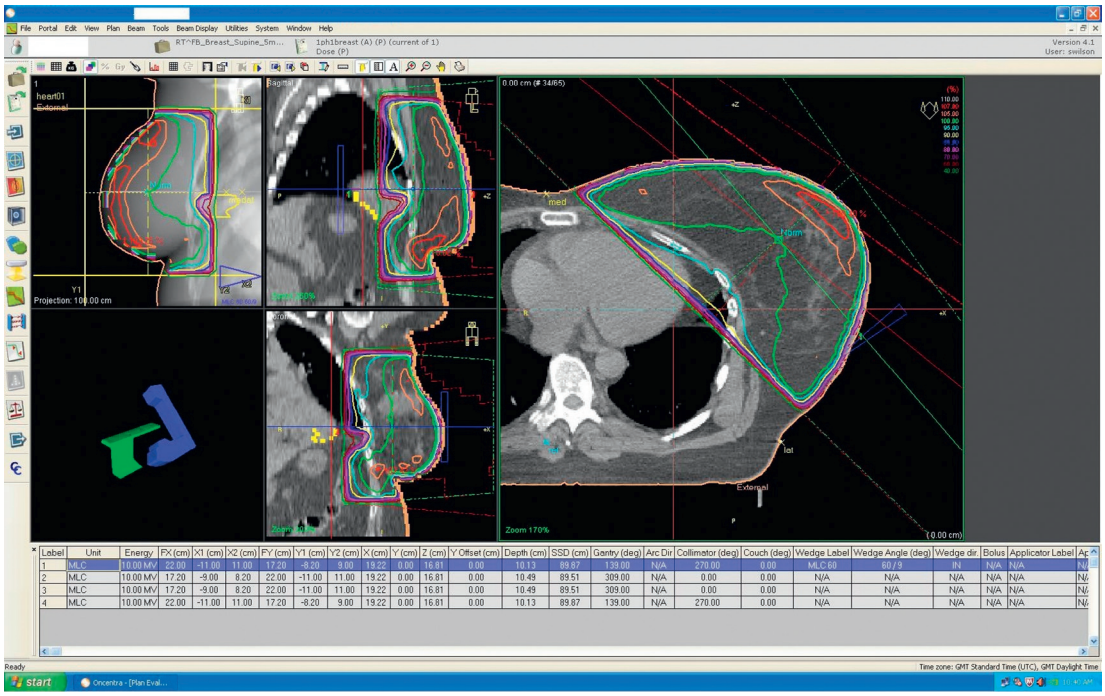
Intact breast or postmastectomy chest wall

± tumour 'bed' (boost volume) – following breast conservation
± regional nodal areas (axilla, supraclavicular region, internal mammary region).

Metal clip placement at the time of surgery at the limits of the tumour cavity and in the lower axilla is invaluable in delineation of the target volume particularly if a tumour bed radiotherapy 'boost' is planned (**Fig. 17.3**). Oncoplastic breast surgery with tissue rearrangement can complicate target volume definition in these circumstances and clip placement is particularly helpful.[1]

Following delineation of the target volume/s and any organs at risk (e.g. the heart) the treatment planning/physics team determine the optimum beam shapes, arrangements, energies and units of dose for each beam. The goal is to treat the target volume homogenously and limit, as far as possible, radiation to normal tissues. Compromises are inevitable. A very common arrangement to treat the breast or postmastectomy chest wall is to use tangential beams that 'glance across' these target volumes (Fig. 17.3).

It may take 1–2 weeks for treatment to start to allow time for careful treatment planning and the stringent quality assurance that accompanies this process. When treatment begins the patient will be set up in an identical position to that which was assumed for CT planning and each session takes usually 10–15 minutes, although only a fraction of this time is involved in the actual delivery of radiation. In most cases daily fractions are administered on weekdays.



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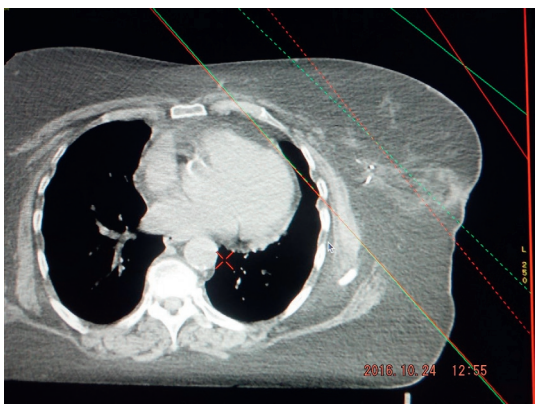

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Figure 17.3 • Conventional tangential beam arrangement for breast irradiation. Metallic clip insertion greatly improves the accuracy of tumour bed contouring. Advanced treatment planning allows a homogenous dose distribution and minimises dose to normal tissues.

Irradiation of the skin, underlying ribs and some lung tissue is unavoidable but with modern treatments it can be limited and long-term problems are rare. Trying to avoid cardiac irradiation without shielding target volume (and thus increasing the risk of recurrence) can be difficult and a number of technical developments, including the delivery of radiotherapy when the breath is held in deep inspiration ('deep inspiration breath hold' [DIBH]), are employed in some centres to achieve this.[2] For most women being considered for radiotherapy today, the absolute 30-year risk of having a major coronary event as a result of the radiotherapy is <2% so in almost all cases the benefits of the radiotherapy far outweigh the risks.[3]

Radiotherapy after breast-conserving surgery

Invasive cancer

The use of whole-breast radiotherapy after breast-conserving surgery for invasive cancer has been the default intervention for decades since randomised trials that compared mastectomy with breast-conserving surgery and breast irradiation (BCS + RT) were completed and published. These randomised trials are now a routine and accepted part of the history of developments in breast surgical oncology but in their time they were controversial and

revolutionary. They established beyond question the long-term safety of breast conservation. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient level meta-analysis of these studies has confirmed that overall and breast cancer-related mortality were not affected by the type of local treatment employed, but that there was a moderate increase in local recurrence risk in the BCS + RT group.[4] The higher risk of local recurrence in these early trials has not translated into a detriment in breast cancer mortality, possibly because of the opportunity to treat within-breast recurrence after BCS + RT by further surgery (usually mastectomy), which is often curative.

Trials of BCS + RT vs BCS without radiotherapy have shown that radiotherapy is associated with a substantial reduction in within-breast recurrence and a modest reduction in breast cancer deaths. The effect of radiotherapy on first recurrence is seen within 5 years of treatment; the effect on breast cancer deaths is not seen until 10–15 years (**Fig. 17.4**).[4]

One of the great powers of individual patient-level meta-analysis is the ability to explore treatment effects in subgroups, given the large number of patients involved. The EBCTCG meta-analysis of BCS vs BCS + RT revealed that radiotherapy produced similar proportional reductions in recurrence risk, irrespective of tumour size, grade, ER status, degree of nodal involvement or patient age. The absolute benefits of radiotherapy were however, different for patients with different tumour characteristics.[4] The greater the risk of breast cancer recurrence, the greater is the absolute benefit from radiotherapy.

Some patients are at low risk of recurrence, e.g. older patients, with smaller, lower-grade, ER-positive tumours. Some other patients may be at higher risk of radiation-induced morbidity. In some of these women, the benefit of radiotherapy is only small and it may be reasonable to consider the omission of radiotherapy.[5,6]

Irrespective of the effect of radiotherapy following BCS, within-breast recurrence rates have fallen substantially over the last 10–20 years and for many women irradiated in the 2000s, 5-year risks of within-breast recurrence are around only 1–2%.[7] These low recurrence rates may be due to the rising incidence of lower-risk (often screen-detected) cancer, improved surgery, greater pathological rigour, the routine achievement of adequate margins and an increasing use of systemic adjuvant therapy that reduces local (as well as systemic) recurrence risk.[8]

Despite the success of breast conservation in early breast cancer over the last 5–10 years we have witnessed an increasing use of both therapeutic and prophylactic mastectomy, particularly in the USA.[9] This probably relates to concerns about genetic predisposition in younger patients, the use of advanced breast imaging (particularly MRI), a greater access to reconstructive surgery and possibly the existence of misconceptions about contralateral breast cancer risk. In many ways this seems a retrograde step given the proven success of oncologically safe organ preservation afforded by modern locoregional treatment.

Radiotherapy 'boost'

Despite whole-breast radiotherapy, within-breast recurrence does still occur and in an effort to reduce this risk further it is common practice to recommend a boost of radiotherapy to the tumour-bearing part of the breast, where most within-breast occurrences occur.

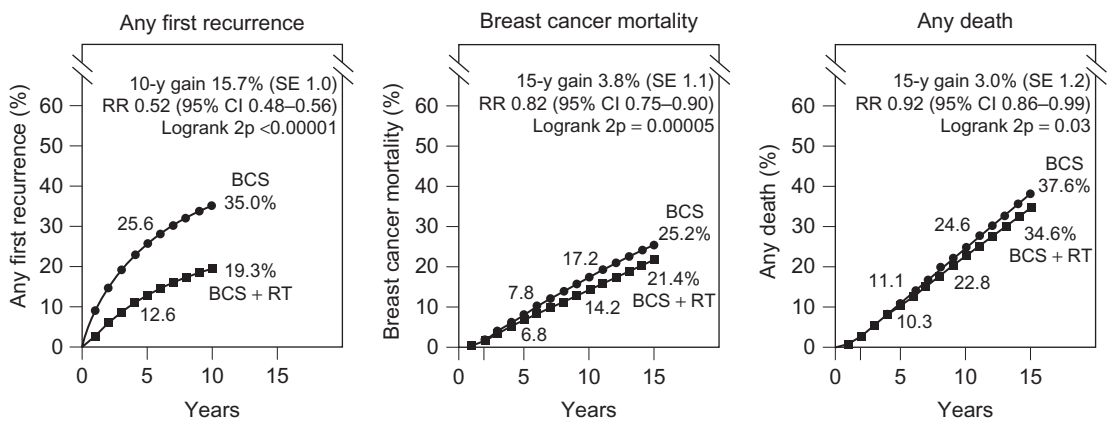

Figure 17.4 • The effect of radiotherapy on recurrence, breast cancer mortality and all-cause mortality (10 801 women (67% pathologically node-negative) in 17 trials).
Reproduced with permission from EBCTCG. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707–60.

If there is a higher risk of recurrence by virtue of young patient age (the most important prognostic factor for within-breast recurrence) or pathological indicators of higher risk (margin involvement, significant in situ disease, ER negativity or tumour size) then a tumour bed boost is often recommended. There are a number of radiotherapy techniques that can be used to deliver boost radiotherapy, including external beam radiotherapy (usually given over 5–8 days), intraoperative radiotherapy and brachytherapy (e.g. the use of implanted iridium wires).

The largest randomised trial of the use of a radiotherapy boost is the EORTC boost trial, in which 5318 patients <70 years of age with T1/2, N0/1 early breast cancer treated with wide local excision and axillary node clearance received 50 Gy in 25 fractions of whole-breast radiotherapy and were randomised to a 16-Gy electron boost or no boost. Age was a powerful prognostic factor for recurrence and in patients under 40 years a radiotherapy boost decreased the risk of local recurrence at 10 years from 23.9% to 13.5%. Margin status did not influence recurrence risk. Cosmesis was worse in patients who had received a boost.[10]

A radiotherapy boost seems reasonable in circumstances where there is a higher-than-average risk of within-breast recurrence – particularly in younger (<50 years) patients.[11] The use of a boost remains controversial given the falling rates of within-breast recurrence seen recently and the greater use of systemic therapy, that also reduces the risk of local failure. There exists a marked variability in the use of boost radiotherapy.

Ductal carcinoma in situ (DCIS)

DCIS is an increasingly common disease that is largely identified by mammographic screening. Around 25% of 'breast cancers' detected mammographically represent DCIS.

Many aspects of the management of DCIS are controversial due to limitations in knowledge of its natural history. The effect of whole-breast radiotherapy following BCS was tested in five individual randomised trials, four of which were combined in a meta-analysis conducted by the EBCTCG. Radiotherapy approximately halved the risk of within-breast recurrence of in-situ or invasive disease but it had no effect on breast cancer mortality (**Fig. 17.5**).[12]

The use of radiotherapy for DCIS is variable. An analysis of patterns of care from the UK Sloane Project has confirmed a wide variability in radiotherapy practice.[13] There are ongoing efforts to develop an improved means of selecting radiotherapy by the use of a molecular pathological profile or the identification of a risk score developed from routine demographic and pathological data. A number of nomograms to predict the benefit of radiotherapy can be used to aid decision-making and the (modified) van Nuys Index is one of the most widely used. This index uses tumour size, margin proximity, pathological classification (grade and the presence of comedo necrosis) and age to predict the benefit from radiotherapy.[14]

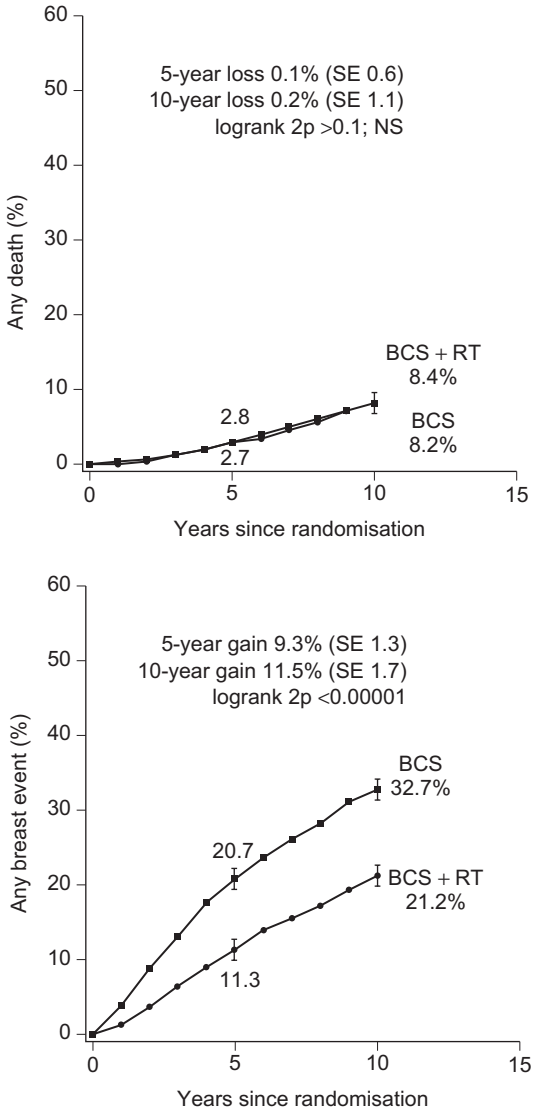

Figure 17.5 • The effect of radiotherapy on any breast event and all-cause mortality following BCS for DCIS. Reproduced with permission from EBCTCG. Overview of the randomised trials of radiotherapy in ductal carcinoma in situ (DCIS) of the breast. J Natl Cancer Inst Monogr 2010;41:162–77.

Partial breast radiotherapy after breast-conserving surgery

Most within-breast recurrences occur at the same site as the original index cancer. This has prompted studies to determine if irradiation of the 'tumour-bearing area' of the breast alone without treating the remainder of the breast is equivalent to routine whole-breast radiotherapy. This may be achieved in a number of ways: by planned (postoperative) external beam radiotherapy, by the use of external beam intraoperative radiotherapy where a single fraction of electrons is given after tumour excision but with the patient still anaesthetised, or by other intraoperative brachytherapy techniques. The administration of radiotherapy during or shortly after surgery has the potential to obviate the need for a course of postoperative external beam radiotherapy that could greatly reduce the inconvenience of treatment.

A number of trials have explored these options with mixed results and the use of partial breast radiotherapy is controversial, with a marked variability in opinion and practice. In the USA there is a much greater use of brachytherapy to deliver partial breast radiotherapy in lower-risk patients whereas this treatment is used much less frequently in the UK. A recently published review from the Cochrane collaboration concluded that there was insufficient evidence on which to base recommendations.[15] The recently published consensus statement from the Royal College of Radiologists suggests that partial breast radiotherapy may be considered where the risk of local recurrence is low.[11] Further data from ongoing clinical trials are needed.

Tailored radiotherapy

A further development in whole-breast radiotherapy involves tailoring the dose of radiotherapy within the breast according to the differences in site-specific recurrence risk. The risk of recurrence is highest in the original tumour-bearing region and lower in areas more distant from this. The UK IMPORT randomised trials involve a comparison of dose-escalated radiotherapy versus standard radiotherapy (IMPORT HIGH) in higher-risk disease[16] and of standard radiotherapy versus 'de-escalated' radiotherapy in lower-risk disease. This should help to determine the effects of de-escalation of dose in lower-risk patients and dose escalation in higher-risk disease.[17] Technical improvements in radiotherapy planning and treatment delivery have enabled different doses to be delivered to different parts of the breast and have allowed the development of these randomised trials. The participation of UK centres in these trials has been key to improved radiotherapy treatment delivery in routine clinical practice.

Radiotherapy after mastectomy

Postmastectomy radiotherapy (PMRT) was one of the very first of all medical interventions to be formally tested in randomised controlled trials (RCTs) in the late 1950s. Despite the availability of long-term follow-up from these RCTs, which were so innovative in their time, PMRT remains in many circumstances a controversial treatment where variability in practice, inconsistency between treatment guidelines and many grey areas of decision-making are prevalent.

There is also the ever-present problem of 'contemporary generalisability' to contend with. The older the RCT that defines the robust long-term effect of an intervention, the less relevant its results become in modern breast cancer care.

Despite this, some definitive conclusions can be reached and the ability to do this is in the most part because of the efforts of the EBCTCG in drawing together all of the world-wide randomised evidence at individual patient level.

PMRT in high-risk patients, particularly those with extensive nodal involvement (≥4 positive nodes), substantially improves the prospects of long-term locoregional control and also improves breast cancer mortality and (because breast cancer deaths dominate in these circumstances) overall survival. In node-negative patients PMRT is usually not required, locoregional recurrence is uncommon, there is no discernible impact on breast mortality and the level of toxicity from PMRT is close to, or exceeds, the small benefit of treatment. In 'intermediate'-risk disease (1 to 3 positive nodes) there is more uncertainty, but the EBCTCG meta-analysis in this group does show a significant benefit of radiotherapy in locoregional control and survival.[18]

Since these trials were conducted, breast cancer recurrence rates have reduced substantially so the absolute benefits of postmastectomy radiotherapy are likely to be lower for women today. Hence, recent randomised trials evaluating the role of PMRT in intermediate-risk disease are important. The UK SUPREMO trial has tested the role of radiotherapy in these circumstances. Recruitment is complete and the results from this trial will be available soon.

In modern practice the clinical oncologist within the breast MDT needs to use the available randomised evidence and the guidelines derived from this, in the context of the changes in surgical

treatments, particularly to the axilla. There are also important differences between radiotherapy practice today and that employed in the previous RCTs of PMRT. Most older trials of PMRT included irradiation of regional nodes including the internal mammary chain. These differences and the reduced toxicity of modern radiotherapy need to be factored into decision-making.

There are other risk factors for local recurrence after mastectomy, other than degree of nodal involvement (although this remains dominant). Extensive vascular invasion and larger tumour size also increase local recurrence risk. In these circumstances, the postmastectomy chest wall is the commonest site of local recurrence and PMRT should be considered.

A number of recent guidelines exist to support decision-making, including those from the Royal College of Radiologists (Faculty of Clinical Oncology) [11] and the American Society of Clinical Oncology.[19]

Radiotherapy and breast reconstruction

The increasing availability of breast reconstruction, whether performed at the same time as mastectomy or subsequently, means that there is a greater need to consider the practicalities and consequences when recommending radiotherapy in the situation of planned immediate reconstruction or whether breast reconstruction should be delayed if radiotherapy is likely.

An obvious but nevertheless critical principle is that oncological considerations of preventing recurrence and reducing mortality must take priority and that radiotherapy decision-making should not be affected by the choice to perform, or type of, reconstructive surgery.

Reconstructive and oncoplastic breast surgery are rapidly changing fields with a proliferation of new technologies and techniques that are used variably in different breast units. The oncologist is easily confused by this bewildering display of surgical complexity and apparent vast array of treatment options and must take refuge in some core principles which are listed below:

- The breast MDT is the ideal environment to discuss oncological and surgical management when breast reconstruction is a possibility.
- Oncology input is vital prior to any decision on immediate breast reconstruction, particularly for invasive disease.
- It is useful for the oncologist to provide some indication of the likely need for radiotherapy at the MDT prior to definitive surgical planning. This is informed by careful clinical, radiological and pathological nodal staging information (axillary cytology or sentinel lymph node biopsy).
- The use of a permanent silicone implant in irradiated tissue irrespective of whether the implant is in situ during radiotherapy or inserted subsequently leads to a high risk of capsular contracture which impairs the cosmetic result, may cause pain and often requires subsequent surgical revision.
- Autologous tissue (without an implant) tolerates radiotherapy used as adjuvant treatment in early breast cancer better. Latissimus dorsi flaps appear to tolerate radiotherapy better than lower abdominal flaps.

The use of metallic ports for the inflation of expander implants can on occasions cause problems if they are sited within tissue that will receive radiotherapy. These ports can affect radiation dose distribution although the clinical consequences of this are unclear.[20]

The use of chemotherapy must also be considered in the overall management plan. If it is clear that cytotoxic chemotherapy will be recommended, then an attractive option is to use neoadjuvant chemotherapy prior to definitive surgery. This has the advantages of allowing time for discussion and planning surgery and, in appropriate circumstances, arranging for referral for family history assessment and mutation analysis that may affect surgical management, if a mutation in one of the high penetrance breast cancer predisposition genes is identified.

This approach also takes advantage of the possibility of downstaging disease in the breast and axilla, is oncologically safe in that breast cancer mortality is unaltered by whether chemotherapy is given before or after surgery and finally has been shown to be associated overall with lower infection rates and better wound healing.[21] This approach does, however, require close surgical and oncological cooperation.[22]

Postmastectomy radiotherapy (PMRT) after neoadjuvant chemotherapy (NACT)

In the circumstances of PMRT after mastectomy without preceding chemotherapy, data from large-scale randomised trials help us to define best practice. When making decisions about PMRT after

the preceding use of NACT we have none, and must therefore try to define appropriate treatment from non-randomised evidence.

A decision about whether radiotherapy should be recommended must be made on the basis of several factors, including: demographic factors, preoperative information on clinical and radiological stage, preoperative cytology or core biopsy results from the breast and axilla and on the basis of tumour response to chemotherapy (clinical, radiological and pathological response [pCR]).

Buchholz and colleagues at the MD Anderson Center found in their data set that advanced disease at presentation and positive lymph nodes after chemotherapy predicted for local recurrence and that pCR in these patients did not preclude the need for radiotherapy.[23]

Mamounas and colleagues reported on a combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 trials that were primarily designed to address scheduling and type of NACT. No radiotherapy was given in the NSABP studies after mastectomy irrespective of disease burden in NACT patients.

In mastectomy patients, pre-NACT clinical tumour size, clinical nodal status and pathological nodal status/breast tumour response were predictive of local recurrence. Chest wall and regional nodal recurrences after mastectomy were rare (1/94) and (3/94), respectively, in patients who achieved a pCR in the breast and lymph nodes irrespective of the pre-NACT clinical stage.[24]

The German Breast Group have addressed questions of systemic treatment and not the need for PMRT. In a pooled analysis of three randomised NACT trials involving 3481 patients with operable and locally advanced breast cancer the use of radiotherapy was associated with a significant benefit in terms of 5-year LR-free survival (90% vs 82%) and disease-free survival (75% vs 67%).

Patients with clinically positive lymph nodes at diagnosis benefited most from radiotherapy and the risk of local recurrence was still significant at 14% in patients achieving a pCR.

This retrospective analysis concluded that patients managed without RT after neoadjuvant chemotherapy for breast cancer have a significantly worse outcome even if they achieved a pCR.[25]

In the absence of prospective randomised evidence it seems reasonable to recommend radiotherapy to all patients after BCS, to those presenting with locally advanced cancer and those with a significant residual burden of disease in the breast or lymph glands after mastectomy. Patients with lower-risk disease, particularly those who achieve a pCR with NACT, do not require radiotherapy after mastectomy.

Regional nodal irradiation

There has been much recent interest in the role of radiotherapy to regional nodal areas. Irradiation of regional lymphatics, however, is not a new treatment and was variably included in the original studies of postmastectomy radiotherapy, many of which started 50 or more years ago.

Two areas will be considered:

- The role of radiotherapy to the axilla as an alternative to axillary node clearance.
- 'Additional' radiotherapy to other regional nodal areas (supraclavicular region and internal mammary region).

Axillary radiotherapy

The widespread introduction of sentinel lymph node biopsy (SLNB) as a staging procedure for the clinically and radiologically node-negative axilla has focused attention on the management of the SLNB-positive axilla. It is generally accepted that SLNs containing isolated tumour cells or micrometastases (<2 mm deposits) mean that no further treatment is necessary to the axilla – either surgical or radiotherapeutic.

If the SLN is involved with macrometastatic disease (>2 mm deposits) then there is controversy on further axillary management. The ACOSOG Z11 trial reported no benefit from axillary node clearance in patients treated with BCS and SLNB with one or two involved SLNs. Disease-free survival, overall survival and axillary recurrence rates were the same in both patient groups but unsurprisingly lymphoedema was significantly worse in patients undergoing axillary node clearance.[26] Opinion over whether this single trial should be practice-changing varies, and although innovative and critically important, there are some methodological concerns that include small trial size and variable and uncontrolled radiotherapy practice. Further confirmatory trials including the UK POSNOC trial to support the practice of avoidance of axillary treatment in the macrometastatically SLN-positive axilla are in process but it will be some years before results of this trial are available.

An alternative to ANC is axillary radiotherapy. Older trials of axillary radiotherapy versus surgery and the much more recently published AMAROS trial conducted in the era of SLNB have demonstrated that breast cancer mortality, disease-free survival and axillary recurrence rates are the same between these two possible axillary treatments. Lymphoedema is significantly less

following axillary radiotherapy whereas short-term shoulder stiffness and reduced shoulder movements are more common with axillary radiotherapy.[27]

These results make axillary radiotherapy an attractive option in those patients with involved SLNs, particularly if radiotherapy to the intact breast or postmastectomy chest wall is required.

If axillary radiotherapy is recommended then it is preferable to treat the axilla using an anterior (and sometimes an additional posterior) field matched to the tangential beams used to treat the breast or post-mastectomy chest wall. Another way of irradiating the axilla is by using 'high tangents' (extending the superior border of the tangential fields used to treat the breast or postmastectomy chest wall) but this provides inconsistent treatment of the superior aspects of the axilla.

Axillary radiotherapy does potentially result in a loss of some prognostic information – namely the number of involved axillary nodes. Some have raised concerns that this could compromise decision-making for systemic treatment and post-mastectomy radiotherapy given the dominance of nodal involvement as a prognostic factor for local and systemic recurrence. In clinical practice this is rarely an issue as oncological decision-making is evolving and reliance on these stage-dependent prognostic factors reducing.

Regional nodal radiotherapy

The role of radiotherapy to the regional nodes, particularly the ipsilateral internal mammary nodes, is an ongoing controversy and it has not been possible, until recently, to define the contribution specifically from the irradiation of regional nodal areas.

The recent publications of two large studies (EORTC[28] and MA-20[29]) and the Danish DBCG cohort study[30] have shown modest improvements in disease-free survival and breast cancer mortality, particularly in higher-risk patients.

An individual patient meta-analysis would be of huge value in defining the benefits, toxicities and ideally the size of any treatment effect in different subgroups. However, the totality of the evidence does suggest a role for radiotherapy to the internal mammary and supraclavicular regions in higher-risk (multiple-node-positive) disease. Such treatment does require careful radiotherapy planning and delivery to avoid undue risk of toxicity, particularly in the case of radiotherapy to the left internal mammary nodes, given the concerns about increased cardiac doses that can occur.

Within the UK an expert group convened by the Royal College of Radiologists (Faculty of Clinical Oncology) in 2016 provided a consensus view on this treatment and explored the resource challenges that implementation of regional radiotherapy will bring.[11]

Fractionation

The effect of radiotherapy on the tumour and normal organs in the thorax is related to several factors, including radiotherapy dose (Gy) but also the number of (usually) daily fractions of treatment which make up the total dose. A standard dose of adjuvant radiotherapy in early breast cancer is 40 Gy of radiotherapy given over 15 fractions (3 weeks). The total dose, without knowledge of fractionation and overall treatment time, is insufficient information to understand the biological effects both on cancer cells – essential to prevent recurrence – and on normal tissue – the cause of radiotherapy toxicity.

Dose and fractionation have largely been derived empirically on the basis of limited experimental data and reported outcomes in uncontrolled studies. Unsurprisingly, dose fractionation schedules that evolved were variable. A common and still prevalent belief was that smaller fraction size improved the therapeutic index, maintaining local control with a lower risk of toxicity. Prolonged radiotherapy schedules of 6-7 weeks of treatment were (and in some countries still are) in common use.

Mature results from randomised trials of dose/fractionation have shown that shorter, more convenient, less expensive, schedules are effective in maintaining local control and are both cost-effective and do not increase toxicity. These are now in routine use.[11,31] The use of even larger fraction sizes and the possibility of delivering routine external beam radiotherapy for early breast cancer in a single week is being tested in RCTs.[31]

Toxicity

Early toxicity

The acute toxicity of radiotherapy, starting most commonly during the second week of treatment, comprises mild fatigue and erythema of the skin. More unusually a dry cough, that is in almost all cases transient, can occur, often towards the end or shortly after treatment is completed.

Late toxicity

Longer-term toxicity after routine radiotherapy for early breast cancer includes rib tenderness (which is not unusual following mastectomy without radiotherapy). Longer-term pulmonary toxicity is very rare with modern tangential treatment.

The efforts of the EBCTCG in defining the benefits of radiotherapy for early breast cancer have been complemented by other colleagues in Oxford who have provided critical information on the incidence and mortality of cardiac disease and carcinogenesis consequent on breast radiotherapy. The number of cardiac deaths in the longer term is higher in patients treated with radiotherapy but the absolute effect is small, amounting <1% in most circumstances. A population-based, case-control study reported by Darby and colleagues has further demonstrated that the risk of major coronary events or cardiac death was related to mean heart dose with no apparent threshold. The increase started within 5 years of radiotherapy but continued in the longer term.[3] Cardiac doses have reduced considerably with more modern techniques. Nevertheless, greater understanding of this toxicity has prompted the development of radiotherapy techniques to spare cardiac tissue wherever possible.

There is also a small increase in the risk of lung cancer following breast irradiation. This occurs in the second decade after radiotherapy. Taylor and colleagues within EBCTCG found this to be very small in non-smokers but is much higher in those women who continue to smoke after radiotherapy.[32] Smoking status should be considered when making radiotherapy decisions in some patients.

The additional risks of other cancers (mostly sarcomas and oesophageal cancer) caused by breast radiotherapy are small and the great majority of the excess in non-breast cancer-related deaths are due to lung cancer and cardiac causes.[4]

Conclusion

Radiotherapy remains an integral component of management of early breast cancer. Understanding the benefits and toxicities of this treatment has greatly improved the therapeutic relationship of this treatment and guided its applicability in current management.

Key points

- The need for postoperative radiotherapy should be considered when planning surgical treatment at the operative multidisciplinary team (MDT) meeting.
- The clinical oncology team should be involved in discussions about patients having immediate breast reconstruction.
- Metal clip placement at the time of surgery at the limits of the tumour cavity and lower axilla is invaluable in delineation of the target volume, particularly if a tumour bed radiotherapy 'boost' is planned.
- The benefit of radiotherapy in reducing local recurrence is seen within 5 years of radiotherapy; the effect on breast cancer deaths is not seen until 10–15 years.
- Within-breast recurrence rates have fallen substantially following BCS over the last 10–20 years and 5-year risks of within-breast recurrence are around 1–2%.
- A radiotherapy boost seems reasonable in circumstances where there is a higher-than-average risk of within-breast recurrence – particularly in younger (<50 years) patients.
- Radiotherapy following breast-conserving surgery for DCIS halves the risk of within-breast recurrence of in situ or invasive disease but it has no effect on breast cancer mortality.
- Following neoadjuvant chemotherapy, it seems reasonable to recommend radiotherapy to all patients having BCS and to those presenting with locally advanced cancer and a significant residual burden of disease in the breast or lymph glands after mastectomy. Patients with lower-risk disease, particularly those who achieve a pCR with NACT, do not require radiotherapy after mastectomy.
- Axillary radiotherapy is an attractive alternative to axillary clearance in those with a positive SLNB if radiotherapy to the intact breast or postmastectomy chest wall is required.

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Recommended video:

- Breast radiotherapy – https://tinyurl.com/y8u57olx

Full references available at **http://expertconsult.inkling.com**

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