# Optimal management of breast cancer with locoregional radiotherapy

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## Introduction

Radiotherapy of breast cancer has entered its modern, mature era, when its long-term benefit on locoregional control and survival has been demonstrated in large trials and meta-analyses. This article will review the available evidence of the effects of radiotherapy and the potential clinical, technical, and biological means of optimising its use, in the setting of the multidisciplinary management of breast cancer patients.

## Benefits and risks: effects of radiotherapy in breast cancer

As for all adjuvant treatments, the indications for locoregional radiotherapy rely on the optimal risk versus benefit ratio: benefit of the curative effects of radiotherapy, and risk of toxicity and long-term sequelae.

### *Benefits*

Numerous large retrospective studies with long follow-ups, prospective randomised trials, and meta-analyses brought evidence of the benefit of adjuvant radiotherapy, following mastectomy [1] or breast-conserving surgery (Table 1) in invasive breast cancer, as well as following breast-conserving surgery in pure ductal carcinoma *in situ* (Table 2). In most studies, a standard treatment regimen was applied delivering 50 Gy in 25 fractions over 5 weeks, or a close, equivalent regimen. General conclusions from these studies are summarised in Table 3.

Table 1
Local recurrences in randomised studies comparing breast conserving surgery alone and with post-operative radiotherapy

| Study | Treatment[a] | Number of patients | Follow-up (years) | Local recurrences | |
|---|---|---|---|---|---|
| | | | | No. | Relative reduction (%) |
| Fisher et al. (2002) [2] | T | 570 | 20 | 39 | |
| | T+RT | 567 | | 14 | 64 |
| Liljegren et al. (1999) [3] | T | 194 | 9 | 24 | |
| | T+RT | 187 | | 8.5 | 65 |
| Veronesi et al. (2001) [4] | Q | 273 | 9 | 23.5 | |
| | Q+RT | 294 | | 6 | 74 |
| Clark et al. (1996) [5] | T | 421 | 7 | 34 | |
| | T+RT | 416 | | 11 | 68 |
| Holli et al. (2001) [6] | T | 72 | 6.7 | 14 | |
| | T+RT | 80 | | 6 | 57 |
| Malmström et al. (2003) [7] | T | 587 | 5 | 14 | |
| | T+RT | 591 | | 4 | 71 |

[a] T: tumorectomy; RT: radiotherapy; Q: quadrantectomy.

Table 2
Randomised trial on radiotherapy following breast-conserving surgery for ductal carcinoma *in situ*

| Trial | Number of patients | Follow-up (years) | Absolute reduction with radiotherapy (%) | | |
|---|---|---|---|---|---|
| | | | All | Infiltrating | DCIS |
| NSABP B-17 (2001) [8] | 818 | 10 | 16 | 9 | 7 |
| EORTC 10853 (2000) [9] | 1010 | 4 | 7 | 4 | 3 |
| UKCCCR-DCIS (2003) [10] | 1701 | 5 | 8 | 3 | 4 |

Table 3
General conclusions from the studies comparing radiotherapy versus none after surgery

1. In small tumours, long-term outcome following breast-conserving surgery and whole-breast radiotherapy is equivalent to outcome after mastectomy.
2. Radiotherapy given after surgery for invasive cancer decreases the relative risk of recurrence by at least 66%, resulting in an absolute long-term (20 years) benefit of 20%.
3. This locoregional effect translates into an absolute survival benefit of 5–10%.
4. Following breast-conserving surgery for pure ductal carcinoma in situ, radiotherapy to the whole breast reduces the relative risk of ipsilateral recurrence by 50%, resulting in an absolute benefit of 7–8% at 5 years and 16% at 10 years.
5. The relative risk reduction is constant, meaning that the absolute benefit from radiotherapy will depend on the level of recurrence risk following surgery alone: the higher the risk, the higher the benefit.

*Risks and toxicity*

The principal organs at risk involved in a standard breast (or chest wall) radiation treatment are the normal ipsilateral breast tissue, the skin, the contralateral breast, the ipsilateral lung, and heart when the left breast is involved. Regional lymph nodes irradiation can also induce cardiovascular toxicity, brachial plexus neuropathy, lymphedema and shoulder stiffness.

Radiotherapy of the preserved breast can induce normal tissue fibrosis, gland retraction, pain, skin pigmentation and telangiectasias. These effects are responsible for cosmetic impairment (breast deformation and asymmetry). They depend (a) on the total radiation dose, heterogeneity of dose distribution and the resulting dose per fraction received in a given volume, (b) on the quality of surgery and the occurrence of complications, and (c) on concurrent treatments. In addition, breast irradiation increases the long-time risk of secondary sarcomas: the 15-year cumulative risk varies from 0.1 to 0.3% [11]. Cardiovascular radiation-induced toxicity has been related to a long-term increase in mortality in patients receiving radiotherapy [1]. It was shown that this effect was related to the dose, dose per fraction, volume of heart irradiated [12], and side of the treated breast. Acute pneumonitis, chronic pneumonitis, and increased risk of lung cancer are possible radiation-induced complications in patients treated for breast cancer: the risk increases with dose, dose per fraction, lung volume involved, pre-existing pulmonary condition, and smoking.

No evidence of increased contralateral breast cancer incidence was shown in patients who received radiotherapy to one breast or chest wall, compared to those who did not [4].

## Technical improvements and prevention of radiation-induced toxicity

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview suggested that the survival improvement related to adjuvant radiotherapy was annihilated by the induction of long-term cardiovascular mortality. Recent data showed that the incidence of cardiovascular morbidity [13] is decreasing as a consequence of technical improvement in imaging and radiation techniques. In addition, a recent study of the Surveillance, Epidemiology and End Results (SEER) data showed that the increased mortality ratio between left versus right breast cancer irradiation was not any more significantly different in trials conducted between 1985 and 1990, compared to earlier trials where this ratio was significantly increased [14]. Several guidelines and technical improvement can be used to reduce this toxicity:

*Guidelines and standards in quality assurance*

Dose homogeneity within the treated volume (breast) is defined by the International Commission on Radiation Units and Measurements (ICRU) criteria [15,16]: the dose should be comprised between 95% and 107% of the prescribed dose in any points of the treatment volume [defined as the planned treatment volume (PTV)]. Normal Tissues Complications Probabilities (NTCPs), which relate to volume of an organ at risk included in a defined isodose, using a standard or biologically equivalent treatment regimen, can be used to predict the risk of long-term complications [17–19]. A simple relationship was established between measurements of heart distances on a simulation film and the cardiac NTCP, as well as measurements of the ipsilateral lung distances and lung NTCP [20–22]. For example, 20 mm of the maximum heart distance included in the treatment field when 50 Gy in 25 fractions are delivered to the breast, would result in a 2% long-term cardiac NTCP (mortality).

*Treatment set-up positions*

The standard treatment set-up for breast irradiation is the dorsal supine position. Patients usually lie on a specifically designed board, with their ipsilateral arm abducted at a minimum angle of 90°. This position allows irradiation of the breast using two opposed parallel beams, treated at each fraction and equally weighed. In order to properly encompass the breast volume while complying with the dose homogeneity guidelines, the posterior limit of the beams should be tangent to the chest wall and include part of the ipsilateral lung. In patients with large, pendulous breasts, achieving a satisfactory dose distribution can be very difficult, hence resulting in areas of over dosage leading to severe acute reactions and long-term sequelae. In addition, because of particular anatomies and large breast volume, an unacceptable amount of lung volume may need to be irradiated. Alternative treatment set-ups were designed, such as the prone position [23–25] or the lateral position [26,27], allowing a satisfactory dose distribution and avoiding lung irradiation, using simple techniques. They can be utilised in patients with pre-existing impaired respiratory capacity. However, these techniques can be used only when the regional lymph nodes do not need to be treated.

*Respiratory gating techniques*

One way to limit irradiation to the ipsilateral lung volume or, in some circumstances, the heart, is to deliver treatment according to the respiratory movements. Two techniques are being experimented: one synchronises treatment delivery to the respiratory cycle, the radiation being given during the expiratory phase [28]. The other technique, called deep inspiration breath hold technique (DIBH), delivers radiation when the patient achieves a voluntary, stable inspiratory apnea, thus decreasing the amount of lung tissue included in the field while increasing the volume of air [29–32]. Their use in routine is not yet validated.

*Intensity modulation radiotherapy (IMRT) in breast cancer*

Technical developments, the availability of high energy machines with high beam outputs, the use of multi-leaf collimators and sophisticated mathematical algorithms in most treatment planning systems, allow us to tailor treatment to each patient situation and achieve optimal dose distribution within the target volumes while limiting the dose to organs at risk. In breast cancer radiotherapy, the advantage of using IMRT in routine practice is still being investigated: although it may provide a theoretical advantage, it is limited by various constraints. Advantages include the possibility to improve the homogeneity of dose distribution and, in theory, modulate the dose per fraction to tailor treatment to the biological characteristics of the tumour. Typical whole-breast (and nodes) IMRT would require the use of multiple fields (not only opposed tangents), thus increasing unnecessary low dose irradiation to normal tissues such as the contralateral breast, contralateral lung which may induce a long-term radiation-induced carcinogenesis [33]. In addition, this treatment planning of IMRT is still time-consuming, which prevents its use in routine in most radiation oncology departments where breast cancer treatment represents a large workload. New approaches with simplified versions of IMRT are in development to circumvent these drawbacks [34–37].

## Reduction of treatment constraints: new radiation treatment regimen

The standard treatment radiation therapy course extends over a period of 5 weeks, 5 days per week, extending to almost 7 weeks if an additional dose is given (boost). Constraints of this regimen are economical, social, physical and psychological. Patients with breast cancer often represent the largest number in radiation therapy departments: the insufficient number of treatment machines in some European countries or regions [38] is responsible for waiting lists which

concern breast cancer patients. Distance to the closest radiation therapy facility may be large, hence inducing high transportation costs and time consumption for patients who continue working during treatment. Elderly patients with co-morbidities can face large difficulties to travel every day to the treatment centre.

Various alternatives have been experimented to overcome these constraints. Some are still experimental and should wait the long-term, mature results of large prospective trials to be accepted as standard of care. Others were confirmed by trials.

*Hypofractionated treatment regimens*

The rationale for using hypofractionation (i.e. a smaller number of fractions, with higher doses and a shortened overall treatment time) relies on the equivalence of late effects of radiation on normal tissue, based on a linear-quadratic model of dose–effect relationship.

A large Canadian trial [39] has compared the standard regimen of 50 Gy/25 fractions (fx) over 35 elapsed days to a shortened regimen of 42 Gy/16 fx over 22 days, in patients with small breast cancers treated with breast-conserving surgery. This trial accrued 1234 patients over a 3-year period. Five-year local recurrence-free survival rate was 97.2% in the short regimen and 96.8% in the standard regimen. Cosmetic scoring was equivalent. The trial characteristics with about 1/4 of the patients under the age of 50, less than 20% with histological grade III, and few with tumours larger than 2 cm, suggest a group at relatively low risk of recurrence. A trial was conducted in the UK [40] on 1410 patients, comparing three treatment regimens (50 Gy in 25 fractions, 39 Gy in 13 fractions, or 42.9 Gy in 13 fractions, over 5 weeks). The results at 5 years showed no differences in terms of complications, sequelae and cosmetic appearance.

Retrospective studies have reported long-term results of a regimen delivering 32.5 Gy/5 fx/28 days, in elderly patients with impaired mobility, and suggested that this treatment using only five fractions could be equivalent to standard regimen [41,42]. Prospective trials testing this are ongoing.

*Partial breast irradiation (PBI) and accelerated fractionation regimens*

The technique of partial breast irradiation was initially designed for patients operated with breast-conserving surgery as an alternative to the standard, but sometimes unpractical, 5-week whole-breast radiation regimen. Because its cost in time or resource [43] is sometimes critical, it may deprive some women of the possibility of breast conservation. PBI is associated with accelerated treatment regimen, using hypofractionation, in order to shorten the overall treatment time. The aim of PBI is to direct radiation to the surgical site only, with a predefined margin of normal tissue, thus avoiding treating the whole mammary gland, and preventing unnecessary irradiation of other organs.

Various techniques are tested, which include: low-dose rate brachytherapy [44,45], high dose rate brachytherapy [46,47], single-dose intra-operative external radiotherapy with electrons [48] or orthovoltage photons [49], and hypofractionated external radiotherapy [50]. The current treatment schemes allow delivering radiation to the surgical tumour bed with a predefined margin, with treatment time extending from one single fraction to 10 fractions, twice daily, over 5 days.

One randomised trial was conducted in the UK [51], comparing PBI with electrons and a conventional fractionation to standard whole-breast radiotherapy. This trial showed a significantly higher rate of recurrence in patients treated with partial breast irradiation. More recent data, with various treatment techniques, came from non-randomised studies in selected groups of patients. These studies suggest that PBI could be an alternative to standard treatment in some patients, but more mature results are needed, in large numbers with long enough follow-up to confirm the equivalence of effects, both on local control and on the long-term toxicity that may be associated with hypofractionation. Such studies are ongoing in Europe and in North America.

Irradiation of the tumour bed only represents a major paradigmatic shift from the original concept of breast conservation with whole-breast irradiation. Whole-breast treatment is considered mandatory to ensure a high probability of local control, because of the high probability of residual disease in the breast after surgery. This paradigm was based on retrospective histological studies of mastectomies carried out for small tumours. In these studies [52–56], residual tumour foci were found in the vicinity of the tumour site or at distance (more than 20 mm). In some studies, multi-focality or multi-centricity was identified.

Therefore, partial breast irradiation should not be used in routine practice until the results of prospective trials are available. Patients with identified risk factors for recurrence, and those with possible multi-focal disease (invasive lobular type) should not be included in these trials.

Table 4
Local recurrences in randomised studies comparing breast-conserving surgery with systemic treatment (chemotherapy and/or hormonotherapy) and the same combination with post-operative radiotherapy

| Study | | Number of patients | Treatment | Follow up (years) | Breast recurrences | |
|---|---|---|---|---|---|---|
| | | | | | % | % risk reduction |
| Forrest et al. (1996) [64] | | 294 | TAM or CMF | 6 | 24.5 | |
| | | 291 | +RT | | 5.8 | 76 |
| Fisher et al. (2002) [65] | ⩽10 mm | 334 | TAM | 7 | 16.5 | |
| | | 332 | RT + placebo | | 9.3 | 49 |
| | | 334 | TAM + RT | | 2.8 | 81[b]/63[c] |
| Hughes et al. (2004) [66] | ⩾70 years | 319 | TAM | 5 | 4 | |
| | | 317 | +RT | | 1 | 75 |
| Fyles et al. (2004) [67] | ⩾50 years | 383 | TAM | 6 | 5.9 | |
| | | 386 | +RT | | 0.4 | 92 |

[a] TAM: tamoxifen; CMF: cyclophosphamide, methotrexate, fluoro-uracil; RT: radiotherapy.
[b] TAM + RT vs TAM.
[c] TAM + RT vs RT + placebo.

## Improvement of therapeutic effects of radiotherapy

### *Breast conservation*

Numerous studies have shown that age is the most influencing factor for local recurrence following breast-conserving surgery and radiotherapy, both in invasive and in situ cancers (reviewed in Refs. [57,58]): a younger age at diagnosis is associated with a higher rate of ipsilateral recurrence. Other factors such as high grade, negative hormone receptors status, and high proliferation were found to be associated with a higher risk. Marginal involvement was found to be a strong predictor of breast failure in DCIS, but less so in invasive cancer.

Increasing the radiation dosage to the tumour bed is a potential means of reducing the negative impact of risk factors: in locally advanced breast cancer, a dose–effect relationship was demonstrated in patients treated with radiotherapy alone [59,60]. Following breast-conserving surgery, three trials evaluated the benefit of an additional dose to the tumour bed ("boost"). A trial from Lyon [61], including 1024 patients, reported a significant 5-year risk reduction in patients receiving a 10-Gy boost to the tumour bed in addition to 50 Gy to the whole breast. A trial from Hungary [62] included only 207 women, and found a non-significant 4-year reduction in favour of a 16-Gy boost. The EORTC boost trial [63] included 5318 patients who were randomised to receive a 16-Gy additional dose to the tumour bed or none, following breast-conserving surgery with free margins and whole-breast radiotherapy to 50 Gy. At 5 years, there was a significant reduction of breast recurrences in favour of the additional dose group (4.3% vs 7.3%). The corresponding hazard ratio for the whole group over the period of study was 0.59. The observed difference in favour of an additional dose was significant only in women under 50 years. In young women under age 40, the absolute gain from a total dose of 66 Gy was 9.3%. However, there is no indication that the relative effect of additional dose depends on age, and differences in older age groups may become significant with longer follow-up. At present, a boost to the tumour bed should be recommended in all women below 51.

### *Following breast-conserving surgery, can radiotherapy be omitted in patients at very low risk of recurrence?*

#### *Invasive cancer*

Identification of patients who may not need radiotherapy following breast-conserving surgery remains a challenge. All trials investigating the benefit of radiotherapy on selected groups, usually with small tumours and free margins, demonstrated a significant reduction in the breast recurrence risk with radiotherapy. In the Milan trial [4], patients with tumours less than 25 mm were operated with a quadrantectomy, i.e. with wide margins of excision. The 10-year rates of ipsilateral breast recurrences were 23.5% without radiotherapy and 5.8% with. Four trials have tested the omission of

radiotherapy in patients with small tumours, or elderly patients, who were treated by Tamoxifen (Table 4). In all trials, whole-breast radiotherapy significantly reduced the rate of local recurrence. One trial included patients over 70 years of age receiving tamoxifen: the 5-year rates of recurrence were 4% without radiotherapy and 1% with radiotherapy. Thus, at present, all randomised trials and retrospective studies have failed to identify groups of patients who would not benefit from radiotherapy.

*Ductal carcinoma in situ*

Two large multi-centric trials have failed to identify risk factors that would help to select omission of radiotherapy. In the NSABP B-17 trial [68], radiotherapy benefited to all subgroups with various combination of comedo-necrosis and margins status. In the EORTC 10853 trial, treatment (radiotherapy vs none) was an independent predictor of breast failure when entered in a multi-factorial analysis including age, method of detection, margins status, histological subtype and architecture [69]. The UKDCIS trial failed to show any interaction between radiotherapy and tamoxifen on the risk of breast failure [10].

Retrospective studies have tried to identify groups where radiotherapy could be omitted. One study [70] suggested that radiotherapy was not beneficial when margins were greater than 10 mm. The French DCIS retrospective multi-centric study [71] identified age and margins status as the main predictors of local failure, both in patients treated with surgery alone and in those receiving radiotherapy. Radiotherapy significantly reduced the rate of breast failure in patients older than 60 with free margins.

*Post-mastectomy and regional nodes irradiation: which patients would benefit most?*

Several recent studies [72,73] have helped to identify new risk factors for chest wall recurrence after mastectomy. In addition to the classical indications for radiotherapy (axillary node involvement, pathological tumour size greater than 40 mm, skin and/or pectoralis involvement), a significantly higher risk of recurrence after mastectomy alone was found associated with macroscopic multi-focality or multi-centricity and young age.

Post-mastectomy radiotherapy trials, as analysed in the EBCTCG overview, have shown that radiotherapy did not only decrease the rate of locoregional recurrence, but was associated with a significant long-term improvement of breast cancer specific survival. More recent large trials have shown that, by using modern radiotherapy techniques avoiding unnecessary cardiovascular irradiation, overall survival can be improved [74–76]. In all these trials, radiotherapy was delivered to the chest wall and regional lymph nodes, including the internal mammary chain, supraclavicular fossa and the whole axilla. Patients participating in these trials had locally advanced cancers, either with tumours larger than 5 cm, or with involved axilla.

A general consensus has emerged that regional nodes should be treated when more than three nodes are involved in the axilla. The benefit of regional nodes irradiation when 1–3 nodes are involved is still debated. The Danish Group [77] retrospectively studied the outcome of 1152 node positive patients, selected from both the pre-menopause and post-menopausal post-mastectomy radiotherapy trials, who had at least 8 nodes analysed. Results at 15 year showed that the highest survival improvement was observed in patients with small (T1–2) tumours compared to larger tumours, and in patients with 1–3 nodes involved compared to more than 3 nodes. Trials are ongoing in the USA and in Europe that will evaluate the impact of regional nodes irradiation on survival in patients with 1–3 pathologically involved axillary nodes.

According to surgical studies, the rate of involvement of the internal mammary lymph nodes (IMN) may vary from 5% to 45%. IMN involvement is increased in the presence of metastases in the axillary nodes, increases with tumour size, tumour location in the medial or central part of the breast, tumour extension in the peritumoral vessels, and young age. Retrospective studies gave contradictory results but these studies were often biased by multiple confounding factors. A multi-centric French study has included more than 1000 patients in a randomised trial, powered to detect a 5% survival difference at 10 years. The EORTC 22922/10925 trial closed in December 2004, following inclusion of more than 4000 patients after either mastectomy or breast-conserving surgery, with either central or medial tumours and negative axillary lymph nodes, or with involved axillary nodes whatever the location of the tumour. The endpoint will be the 10-year survival comparison.

## Effects of timing of irradiation on local control and survival

The steady increase in the number of women with breast cancer, combined with diagnosis at earlier stages and the increase of breast conservation, as well as the insufficient number of treatment machines

in many countries has increased the waiting list in numerous radiotherapy departments. The resulting lengthening of time-lapse before the initiation of locoregional radiotherapy has raised some concerns about its potential impact on local control and survival. In addition, the widening of indications of adjuvant chemotherapy, progressively extending from 3 to 6 or more months of treatment after surgery and before radiotherapy, has further increased this concern.

Several retrospective studies have tried to evaluate the impact of delaying radiotherapy. A systematic review of 21 observational studies published in the literature was conducted by Huang et al. [78], suggesting that delaying the initiation of radiotherapy over 8 weeks from surgery had an adverse impact on locoregional recurrence risk. A population-based study was conducted in the Yorkshire region in the United Kingdom [79], on 7800 patients with breast cancer treated with breast-conserving surgery and radiotherapy. The impact of delay of radiotherapy on survival was analysed in a multivariate study, with multiple demographic and clinical factors, as well as the delivery of chemotherapy. A trend towards worse survival was observed starting after 9 weeks of time interval between surgery and radiotherapy, which became significant after 20 weeks. On the other hand, a large Canadian study [80] with 6 years median follow-up showed no impact of delaying radiotherapy up to 20 weeks when adjusting to other prognostic factors, in a series of 1962 patients with low risk breast cancer treated with breast-conserving surgery.

Retrospective studies on delays in radiotherapy initiation in patients receiving chemotherapy are often biased and give contradictory results. One prospective trial [81] compared the sequencing of radiotherapy and chemotherapy following breast-conserving surgery. Two hundred and forty-four patients were randomised to receive 12 weeks of chemotherapy first, or radiotherapy first. Median follow-up of this study was 11.25 years. No significant difference in locoregional or distant recurrences, or in survival, was observed between the two arms.

## Combination of radiotherapy with systemic treatments

### *Combination with chemotherapy*

The benefit of adding radiotherapy after adjuvant chemotherapy has been shown in a number of randomised studies. Whelan et al. [82] did a meta-analysis of 18 randomised trials, involving more than 6000 patients with node-positive breast cancers who received systemic treatment showing that locoregional radiotherapy reduced the risk of local recurrence (odds ratio 0.25; 95%CI: 0.19–0.34), and improved both disease-free (odds ratio 0.69; 95%CI: 0.58–0.83) and overall survival (odds ratio 0.83; 95%CI: 0.74–0.94). Two large randomised trials conducted in Denmark [75] and Canada [74] involving, respectively, 1708 and 318 patients showed that for high-risk patients (most of them were node positive) who received CMF regimen of chemotherapy (from 6 to 12 cycles) after mastectomy, locoregional radiotherapy decreased the rate of recurrences as well as improved specific and overall survivals.

Data about the possible adverse cosmetic effect of the combination of sequential radiotherapy and chemotherapy are scarce. However, its effect, if any, seems moderate [83,84]. The use of more effective, but also more toxic chemotherapy regimens based on anthracyclines or taxanes need to be assessed both in terms of acute skin toxicity and long-term cardiac and pulmonary complications.

### *Combination with hormonal therapy*

Three recent studies [85–87] assessed whether the sequencing (concurrent vs sequential) of radiotherapy and hormonal therapy with Tamoxifen could affect outcome in breast cancer patients. All concluded in the absence of an adverse effect on local or systemic control.

No data are currently available on the combined effects of radiotherapy and treatment with aromatase inhibitors.

## Future: biological predictive profiles and molecular targeting

Optimisation of radiotherapy in breast cancer would, ideally, not only be achieved by identifying prognostic factors for failure following treatment, but also more efficiently by identifying predictive markers of radiation sensitivity in the tumour of an individual patient. This would allow screening patients to whom radiotherapy would be of no benefit, to increase the total dose in patients who will benefit, and could help to develop drugs directed at specific molecular targets in order to overcome radiation resistances.

Few studies at present have looked for gene expression profiles as predictive markers of recurrence following breast cancer radiotherapy, and several studies are ongoing. Retrospective studies [88–91] suggest that breast cancer occurring in BRCA1 and BRCA2 mutation carriers, genes that are involved in

DNA double strand break repair mechanisms, would be more radiosensitive than in sporadic cases.

Preclinical studies strongly suggest that the effects of radiotherapy could be increased by the concurrent use of targeted inhibitors of mechanisms involved in radiation resistance (proliferation [92], apoptotic inhibition [93,94], angiogenesis [95,96]), and clinical studies are under way with trastuzumab [97].

## Conclusions

Locoregional radiotherapy is an efficient treatment of breast cancer, reducing the rates of recurrence following surgery by two thirds, hence improving long-term survival. They are proportional, meaning that the relative risk reduction with radiotherapy is independent from the known clinical or biological factors, as well as from systemic treatment of breast cancer. Therefore, the decision to use radiotherapy in an individual patient should rely on the estimated absolute benefit for a defined risk group, taking into account the risk of complications and sequelae. There is evidence that the therapeutic ratio (benefit/complications) can be further improved by increasing the dose to the tumour bed after breast-conserving surgery and whole-breast irradiation to 50 Gy, and by reducing the risk of complications. This latter can be achieved by a better definition and coverage of the target volume and a better way to spare the surrounding tissues, made possible by the use of modern radiotherapy. Because radiotherapy using standard treatment schemes can achieve high rates of local control, new treatment modalities should be used with caution, and validated by clinical trials with sufficient power to detect small differences and long enough follow-up.

Finally, the identification of biological markers of prognosis and response to treatment will hopefully allow optimisation of radiotherapy delivered to each individual patient.

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