European Society for Therapeutic Radiology and Oncology (ESTRO) teaching course and workshop

E4. Radiotherapy in early breast cancer

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Introduction

The treatment of early breast cancer is a true multidisciplinary approach that involves sophisticated diagnostic procedures, ranging from molecular biology to modern imaging, and subsequently a treatment armamentarium involving surgery, radiotherapy and an increasingly wide spectrum of systemic therapy, including hormonal manipulation, chemotherapy and targeted therapy. The role of radiotherapy in this multidisciplinary activity has become larger and more complex because it has to adapt to advances in our knowledge of the disease and the consequences of changes in other procedures. Furthermore, the number of breast cancer patients who are subjected to radiotherapy is constantly increasing, due both to a larger number of patients and to a wider use of early detection programmes, which in turn result in more breast-conserving manoeuvres. It is therefore highly appropriate that a multidisciplinary meeting dealing with breast cancer also includes radiotherapy to an extent that reflects its importance in the daily-life treatment. This should, of course, take place mainly within the discussion and presentation of the scientific papers at the meeting, but in order to secure a good platform for such scientific discussions we have, prior to these activities, planned a teaching course and workshop dealing with pertinent issues within radiotherapy for early breast cancer. This workshop is organised by the European Society for Therapeutic Radiology and Oncology (ESTRO) and is aimed at introducing or updating both the young trainee and the experienced oncologist in the field of radiotherapy of breast cancer, covering both the clinical, biological and physical aspects.

That radiotherapy has had a major role in breast cancer over the years, and that furthermore a large number of well-conducted clinical trials have addressed the issue of both the indications and the techniques of application is evident from the most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of radiotherapy effects in early breast cancer [1]. The overview demonstrates convincingly for the first time in a meta-analysis that radiotherapy not only is an important partner in achieving loco-regional control, but also has significant influence on long-term survival in certain patient groups, and thus confirms the findings from some large mature clinical trials [2–4]. This survival benefit is achieved by proper indication of radiotherapy, and more importantly by using radiotherapy techniques that now can avoid the serious late effects that were seen with some older treatment methods, especially in the form of late cardiovascular morbidity and mortality.

The current problem is that while the experience of radiotherapy has been gathered over several decades and has created a platform for well-established indications, the whole scene of breast cancer treatment has changed. New approaches have emerged that deal both with changes in fractionation schedule, target volume (including partial breast cancer irradiation) and the interaction and time relationship with systemic therapy, and so has an altered approach towards treatment of the axilla, based on sentinel lymph node techniques. Some of these new concepts may certainly contribute to better cancer care, but some are also very experimental and may even turn out to be hazardous. Past experience has taught us that it takes many years to establish the proper indications and knowledge of the importance for the long-term outcome when we change procedures. The role of radiotherapy and the way it is practised is therefore in an interesting but potentially dangerous transition zone. We may gain and trim our treatment to become more beneficial, but it also carries the risk of losing already gained territories and in fact re-introducing potentially morbidity-increasing procedures (e.g. hypofractionation) [5]. The answer to many of these procedures will come from recently accomplished, ongoing or planned clinical trials, but unfortunately we will not have the proper and useful answers for several years. This rivalry between the nature of the disease, where it may take decades to get an outcome of a trial, and the constantly changing therapeutic strategy is the cursed and fascinating challenge of breast cancer treatment. It is probably most visible in the field of radiotherapy, because the potential morbidity of this treatment is also often late-occurring as it appears from

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recent data on cardiovascular effects and secondary cancer [6].

On this basis it is obvious that the planned teaching course and workshop will contain important and challenging topics. As indicated below, the aim is to present at least some of these in a way that may enhance the background to and understanding of the scientific approach to improving breast cancer treatment.

Effects of radiotherapy in early invasive breast cancer

It has long been assumed that by the time breast cancer cells reach axillary lymph nodes, the disease has spread via the bloodstream and is beyond cure by local measures. The systematic overview of radiotherapy trials by the EBCTCG published in 2000, and updated in 2005, presents direct evidence that lymphatic spread is the initial pathway of dissemination in a significant minority of patients [1,7]. Specifically, for every 100 node-positive patients randomised to radiotherapy after primary surgery, with or without adjuvant systemic therapies, there are up to 10 fewer deaths at 10 years compared with 100 women not given radiotherapy. Most of the benefit of radiotherapy is achieved by reducing recurrence risk at the primary site after microscopic complete tumour excision or mastectomy. Axillary recurrence is uncommon after complete axillary dissection, but the important observation is that patients with axillary metastases can be cured by local treatment. This outcome of several decades of clinical trials was offset in trials started before 1975 by an excess of non-breast cancer mortality in patients allocated radiotherapy due to excess cardiovascular mortality.

Effects of radiotherapy in ductal carcinoma *in situ*

Pure ductal carcinoma *in situ* (DCIS) of the breast represents 15–20% of all newly diagnosed breast cancers. Of these, 60–70% can be treated with breast-conserving surgery; three large multicentric prospective randomised trials provided evidence that the addition of whole-breast radiotherapy to surgery halved the rate of ipsilateral breast recurrences, with follow-ups ranging from 5 to 11 years [8–10]. Most patients in these trials received a dose of 50 Gy in 25 fractions, and few had an additional dose in the tumour bed. This 50% relative risk reduction with radiotherapy was observed in *in situ* recurrences as well as in invasive recurrences. Retrospective analyses have identified various risk factors following breast-conserving treatments, with age being the strongest predictor of breast recurrence [11,12]. The randomised trials failed to identify subgroups of patients who would not benefit significantly from whole-breast radiotherapy [13,14]. Though no specific trial has evaluated the benefit of increasing the radiation dose to the primary tumour site in DCIS, the similarities of the patterns of failure with invasive cancer would suggest a benefit, particularly in young patients. In addition, two trials showed that the effects of radiotherapy were independent of the potential effects of tamoxifen on breast recurrences [8,10]. As in invasive breast cancer, the results from the trials suggest that the effects of radiotherapy in DCIS are proportional, the magnitude of the benefit depending on the baseline risk without radiotherapy. Treatment decisions should be based on the risk factors of recurrence, and the magnitude of the expected benefit from radiotherapy should be weighed against the risk of long-term complications and sequelae following the delivery of radiotherapy using modern techniques.

Biological aspects of curative radiotherapy for breast cancer

There are fairly reliable dose–response data for the control of clinical and subclinical disease that suggest a halving of local recurrence for a 16 Gy increment in total dose above 50 Gy delivered in 2.0 Gy fractions [15]. There is no evidence for a time dependency for local control of breast cancer by radiotherapy, although this has not been tested in randomised trials. Where fraction size dependency is concerned, data suggest that breast cancer may be more sensitive to fraction size than hitherto assumed, and not significantly different from the sensitivity of the dose-limiting normal tissues [16]. If confirmed, this would have potentially important implications for fractionation regimens and for strategies of dose escalation using techniques of intensity modulated radiotherapy. However, radiotherapy is delivered, attention must be paid to factors that enhance late normal tissue responses, including scheduling with respect to surgery and cytotoxic chemotherapy. Co-morbidities may contribute to inter-patient variation, and there is increasing interest in genetic factors that predispose to late adverse effects, including polymorphisms in the vicinity of genes regulating radiation responses [17,18].

Radiotherapy planning, delivery and verification

Understanding the biological processes relevant to the responses of breast cancer and the normal tissues to radiotherapy should impact on the technological approach to the planning and delivery of radiotherapy. Having

decided what structures to irradiate, target volume localisation is traditionally based on the surface anatomy of the post-mastectomy chest wall, conserved breast, axilla, supraclavicular fossa and internal mammary chain [19]. Target volume localisation is increasingly supplemented by three-dimensional imaging that relates surface marks to internal structures, especially critical non-target tissues such as lung and heart. X-ray computed tomography (CT) has its problems however. Localisation of the tumour bed cannot be performed unless titanium clips are inserted at the time of surgery, for example, and the upper limits of the breast can be difficult to define without inspection and palpation. Forward planning appears to be just as effective as more complex reverse planning approaches, with three-dimensional dosimetry calculated and delivered using multiple static fields [20]. Increasingly, real-time verification of field placement and dose are being introduced into routine practice, with or without respiratory gating.

The course will comprise a number of introductory speeches, followed by a dialogue between the presenter, the experienced faculty and the participants. We have therefore allocated ample time for questions and discussion, and have also chosen to present some of the topics in the form of case histories that invite discussion of day-to-day problems.

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