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Optimising CT guided radiotherapy for breast cancer

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Chapter 2

Current technological clinical practise in breast radiotherapy; results of a survey in EORTC-Radiation Oncology Group affiliated institutions

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Abstract

Purpose: To determine the current technological clinical practise of radiation therapy of the breast in Europe.

Materials and Methods: A survey was conducted between August 2008 and January 2009 on behalf of the Breast Working Party within the EORTC Radiation Oncology Group. The questionnaire comprised 32 questions on 4 main topics: fractionation schedules, treatment planning methods, volume definitions and position verification procedures.

Results: Sixty-eight institutions out of 16 countries responded (a response rate of 47%). The standard fraction dose was generally 2 Gy for both whole breast and lumpectomy cavity (boost) treatment, although a 2.67 Gy boost fraction dose is routinely given in the United Kingdom. A simultaneously integrated boost fractionation is implemented in 23% of the institutions and is the standard choice of fractionation in a third of these institutions. The main boost modality was electrons in 55%, photons in 47% and brachytherapy in 3% of the institutions (equal use of photon and electron irradiation in 5% of the institutions). All institutions used computed tomography guided treatment planning. Wide variations are seen in the definition of the breast and boost target volumes, with margins around the lumpectomy cavity ranging from 0-30 mm. Inverse planned intensity modulated radiotherapy (IMRT) is available in 27% and breath-hold techniques in 19% of the institutions. The number of patients treated with IMRT and breath-hold varied per institution. Electronic portal imaging for patient set-up is used by 92% of the institutions.

Conclusion: This survey has established precise details of radiotherapy techniques currently implemented for breast irradiation in Europe.

Introduction

Randomised controlled trials are regarded to be the foundation for evidence-based medicine. They have shown to improve the various standards of care. With respect to the treatment of cancer, improving treatment standards by conducting clinical trials is an important goal of the European Organisation for Research and Treatment of Cancer (EORTC). To date, many successful trials have been conducted by the EORTC-Radiation Oncology Group (ROG), including trials in the field of radiotherapy for breast cancer. Based on these and other trials, adjuvant radiotherapy to the breast is now considered part of the standard of care in breast conserving therapy.

In the past 20-30 years there is a growing awareness of the necessity of homogeneity in radiation treatment across institutions, especially when a particular treatment is being evaluated in clinical trials. Not only should radiotherapy be applied according to international standards, but also the various components within the radiotherapy process, such as target volume and organs at risk definitions, dose-fractionation schedule, overall treatment time, applied techniques, etc., should be described and performed in a consistent and thus comparable manner. These details can potentially have an important influence on trial outcome and accounts for the fact that nowadays quality assurance is part of any radiotherapy trial [1-3].

Breast cancer radiotherapy techniques have evolved considerably over the last years, due to the wider availability of computed tomography (CT), the introduction of intensity modulated radiotherapy (IMRT) and the use of image guided radiotherapy (IGRT) techniques. When designing new breast cancer radiotherapy trials it is important to know to what extend participating radiotherapy institutions have implemented these techniques. Only a few surveys focussed specifically on the technological aspects of breast cancer irradiation [4-9]. Although some of these articles provide interesting data from either a specific European country or on a specific breast cancer radiotherapy technique, no general overview exists of breast irradiation techniques currently used in Europe. To generate such an overview, a

survey was conducted on behalf of the Breast Working Party within the EORTC-ROG.

Materials and Methods

A questionnaire was developed jointly by the radiotherapy departments of the University Medical Center Groningen (UMCG) and the Catharina Hospital in Eindhoven, The Netherlands. The questionnaire comprised 32 questions on 4 main topics: fractionation schedules, treatment planning methods, volume definitions and position verification procedures. The majority of the questions (23) were closed questions. Open questions were used to retrieve detailed information on the closed questions. For example, to determine the reason why certain clinical target volume (CTV) to planning target volume (PTV) margins were chosen. The closed questions included quantitative questions and multiple choice questions. When relevant, questions concentrated on whole breast irradiation, lumpectomy cavity (boost) irradiation, or both. The questionnaire was developed as a web-based application within the freeware tool Thesistools (www.thesistools.com). Using this web-based system, respondents were enabled to type in data and to select the appropriate answer from a list of predefined answers. Furthermore, this method allowed for easy access to the questionnaire and enabled convenient analysis of the collected data. The questionnaire was first tested by colleagues with expertise in the field of breast radiotherapy and adjustments were made based on their comments before it was distributed.

By using the EORTC-ROG membership mailing list, e-mails were sent with the request to complete the questionnaire. The invitation e-mail was successfully delivered to representatives of 145 EORTC-ROG institutions spread over 26 countries. Although the questionnaire was also attached as a Microsoft Word document, respondents were encouraged to use the web link provided in the e-mail to complete the questionnaire online on the web. A personal code was needed to gain access to the questionnaire as well as adding data on later occasions. The questionnaire was first distributed in August 2008 and reminders were sent in

September and December of the same year. Results were analysed per institution and statistics were calculated for all institutions together.

Results

Response

The response rate was 47% (68 / 145 institutions). It included responses from 16 countries: Austria (2); Belgium (6); France (12); Germany (4); Hungary (1); Israel (1); Italy (5); Lithuania (1); The Netherlands (17); Poland (1); Portugal (1); Slovenia (1); Spain (3); Sweden (1); Switzerland (7); and United Kingdom (5). The main results of the survey are summarised in Table 1.

Table 1. Condensed overview of percentages of institutions applying specific techniques

Application	Percentages of institutes
Standard fractionation schedule	Breast 25 x 2 Gy: 72%; Boost 5-10 x 2 Gy: 83%
CT-based treatment plan	Breast: 100%; Photon boost: 100%
Conformal technique based on CT defined targets	Breast: 90%; Photon boost: 96%
Inverse planned IMRT	Breast: 27%; Photon boost: 14%
Boost delivery modality	Sequential: 98%; Concomitant: 14%; SIB: 23%
Main boost modality ^a	Electrons: 55%; Photons: 47%; Brachytherapy: 3%
Patient setup verification	92%
Partial breast irradiation ^b	21% (<5% of patients)
Prone position irradiation ^b	12% (<1% of patients ^c)
Breath-hold ^b	19% (1-30% of patients)

Abbreviations: CT = computer tomography; IMRT = intensity modulated radiation therapy; SIB = simultaneously integrated boost.

^a Equal use of photon and electron irradiation in 5% of the institutions.

^b The response on these questions was limited (see paragraph on new technologies).

^c One institution treats 8% of their patients in prone position.

Fractionation schedules

For whole breast radiotherapy, the most common institutions' standard fractionation schedule is 25 fractions of 2 Gy (72% of the institutions). Four institutions customary prescribe 15 fractions of 2.67 Gy (4/5 institutions in the United Kingdom). A higher dose per fraction was also customary prescribed by

three other institutions: 22 times 2.3 Gy, 18 times 2.5 Gy or 17 times 2.5 Gy. All four responding institutions from Germany prescribe 28 fractions of 1.8 Gy. Eight institutions in The Netherlands have implemented a simultaneously integrated boost (SIB) fractionation schedule, five of which use this schedule as their standard schedule [10,11]. Seven of these institutions prescribe 28 fractions with a daily dose of 2.3 Gy delivered to the boost volume and 1.8 Gy to the remainder of the breast. The remaining institution prescribes 25 fractions of 2.75 Gy for the boost and 25 fractions of 2.0 Gy to the remainder of the breast. Seven non-Dutch institutions also apply a SIB, but only in a limited proportion of their patients. As for boost irradiation, most institutions (83%) use a sequential boost delivered with a standard daily fraction size of 2 Gy for 5 to 10 fractions (Figure 1).

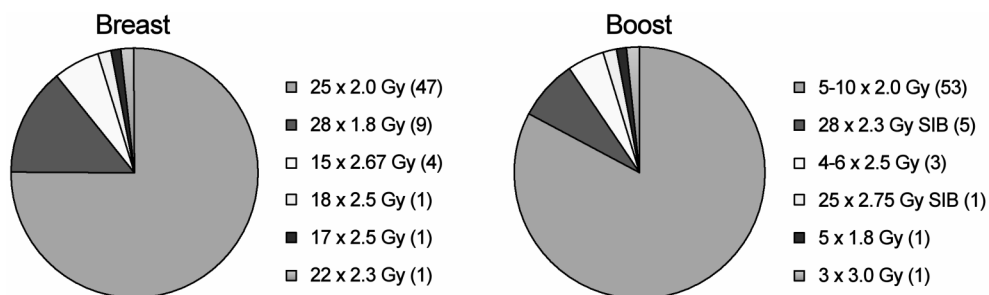


Figure 1. Fractionation schedules

Distribution of standard fraction sizes (in Gy) for breast (A) and boost (B) irradiation over institutions. Number of institutions is given in brackets. Simultaneously integrated boost (SIB) is planned and delivered simultaneously with whole breast plan.

Treatment planning methods

CT guided treatment planning was used in all responding institutions, with 4 institutions indicating to use body-outline contours in some of their patients. Specific questions were directed to the different treatment planning methods. With respect to CT guided boost planning, questions were restricted to irradiation by photon beams. CT is used for electron density-based dose calculations as well as

conformal planning based on the target volumes drawn on CT in the vast majority of institutions. In 10% and 4% of the institutions, use of CT is limited to electron density-based dose calculations for the breast and boost plans, respectively.

Manual optimisation of dose uniformity (forward planning) for breast and photon boost plans is performed in 89% and 85% of the institutions. Inverse planning (objective-based IMRT) is performed in 27% and 14% of the institutions, respectively, of which only 5 institutions use IMRT in more than 20% of their patients.

Boost treatment methods

Sequential delivery of the boost (after whole breast irradiation), is performed for some or all patients in 98% of the institutions, while a concomitant boost (a separately planned boost plan delivered on the same day as the whole breast irradiation) is used in 14% of the institutions. SIB is used in 23% of the institutions. More specifically, 8 Dutch institutions treat on average 72% of their patients with SIB, while 7 non-Dutch institutions treat on average 5% of their patients with SIB. The boost delivery method most commonly used (used in $\geq 50\%$ of the institutions' patients) is electron irradiation in 55%, photon irradiation in 47% and brachytherapy in 3% of the institutions (equal use of photon and electron irradiation in 5% of the institutions). When photon beams are used for boost delivery, the common number of different boost gantry angles is 2 (in 56% of the institutions) and 3 (in 35% of the institutions). Photon boost beam directions are tangential only (37%), non-tangential only (7%) or both tangential and non-tangential (in 56% of the institutions).

Target volume delineation

When breast target volume delineation is performed, various references and landmarks are used: radiopaque wires visible on CT are used in 59%, glandular breast tissue as visible on CT is used in 69% and bony structures as visible on CT are used in 28% of the institutions. For the purpose of boost target volume definition, surgical clips, when available, are used in 95% of the institutions, while

hematoma and seroma visible on CT are used in 49% of the institutions. Availability of surgical clips varies largely, between different countries but also within countries. No institution reported never to have clips available. On average, surgical clips are available in 56% of the patients. Large variations among institutions and countries are also observed with regard to the various margins used in breast and boost target volume definition. Zero, 5 and 10 mm are the most commonly used breast CTV to PTV margins (Table 2). Few institutions apply a larger margin of 15 mm (3 institutions) or 20 mm (2 institutions). The variation in margin from lumpectomy cavity to boost PTV is even more widespread, ranging from 0 to 30 mm. Twelve institutions (22%) take the resection free margin as stated in the pathology report into account in their margin. Ten out of these 12 institutions, all from The Netherlands, have the policy to use a margin of 20 mm minus the resection free margin when available.

Table 2. Margins applied for breast and boost planning target volumes

Breast CTV to breast PTV		Lumpectomy cavity to boost PTV ^a	
Margin	n=51 Institutions (%)	Margin	n=55 Institutions (%)
0 mm	22	0 mm	7
4 mm	2	5 mm	4
5 mm	29	10 mm	13
7 mm	4	15 mm	14
10 mm	27	20 mm	29
15 mm	6	25 mm	7
20 mm	4	30 mm	4
5 - 7 mm	2	15 mm minus ≤ 5 mm free margin	2
5 - 10 mm	2	20 mm minus free margin	18
7 - 10 mm	2	25 mm minus free margin	2

Abbreviations: CTV = clinical target volume; PTV = planning target volume.

^a Lumpectomy cavity to boost PTV margin was binned using 5 mm increments and based on the summation of lumpectomy cavity to boost CTV margin and boost CTV to boost PTV margin.

Organs at risk delineation

Three-dimensional (3D) delineation of organs at risk (OAR) is performed in 95% of responding institutions. This involves delineation of the heart in 78%, ipsilateral lung in 92%, contralateral lung in 52%, and contralateral breast in 23% of the institutions that perform OAR delineation. Dose-volume histograms of

delineated OARs are used to decide on plan acceptance in relation to specific criteria in 88% of the responding institutions for all or selected patients. In addition, the 'Central Lung Distance' (CLD) and 'Maximum Heart Distance' (MHD [12]) are used as a criterion for treatment plan acceptance in 71% (max CLD 2-3 cm) and 59% (max MHD 1-1.5 cm) of responding institutions, respectively, in all or selected patients.

Position verification procedures

Some of the questions regarding position verification procedures had limited response. Eleven out of 28 institutions (39%) reported to use X-ray film for position verification, while 48 out of 52 institutions (92%) reported to use electronic portal imaging (EPI). In 4 institutions, both X-ray film and EPI are used, each in approximately 50% of the patients. Cone-beam CT is used in 7 out of the 23 institutions that responded to the corresponding question.

New technologies / strategies

Specific questions were added to identify the use of partial breast irradiation (PBI), irradiation in prone position, and breath-hold techniques. It appeared that PBI is used in 14 institutions spread over 13 countries, mostly in selected patients i.e., patients treated within clinical trials (generally <5% of the local population). Irradiation in prone position is rarely used. Eight institutions in 6 countries treat <1% of their patients with this technique, with the exception of one of these institutions, where 8% of patients are treated in prone position. Prone irradiation is used to irradiate pendulous breasts as a means to reduce lung exposure. Breath-hold techniques are used in 13 institutions spread over 8 countries in 1-30% of the patients. Patients selected for treatment with breath-hold techniques are mostly young patients that have a higher probability of cardiac complications due to involvement of the heart in the radiation fields.

Discussion

Fractionation schedules

The predominant dose per fraction size for breast irradiation is still 2 Gy in Europe, with only 3 institutions outside the UK using a higher fraction size. It is interesting to note that 4 out of the 5 UK institutions that responded, use a fractionation schedule of 15 fractions of 2.67 Gy, which is the fractionation schedule used in the UK START B trial [13]. Hypofractionation as such, despite the published results of clinical trials [14,15], does not seem to have been implemented in daily practise. Very recently, a few institutions in the Netherlands have introduced hypofractionation for selected patients and the discussion to incorporate the results into the national treatment guidelines has started (source: personal communication).

The prevalent fraction size for boost irradiation is also 2 Gy, although a wider variation in both fraction size and total dose exists compared to the whole breast fractionation schedule. The SIB technique has been remarkably rapid put into clinical practise in The Netherlands [10,11,16]. Eight out of 17 institutions perform this technique for some or all patients since it was first put into clinical use in The Netherlands at the UMCG in March 2005.

Treatment planning methods

The use of CT has increased rapidly in the last years and all institutions now routinely use CT scans for treatment planning. This is a major difference compared to the results found in e.g., a survey in the United Kingdom performed between 1997 and 1999 where only 2 out of 46 institutions used CT [5], and in an Australian survey published in 1999 where only 3 out of 11 institutions used CT [17]. CT is now used for delineation of target volumes and organs at risk, density corrections, shielding definition and manual or inverse plan optimisation. There are data available in the literature that suggest an advantage of (inversely optimised) IMRT over conventional (non-optimised) treatment of the breast with regard to a reduction in acute and late breast and skin toxicity [18-20]. It is therefore expected

that the use of IMRT will increase over the coming years as a means to improve dose homogeneity in the breast and to standardise treatment planning procedures. Partial breast irradiation could potentially show even more advantageous than IMRT in selected patients, since it allows much smaller volumes of the breast and surrounding normal tissues to be irradiated.

Boost treatment methods

The rapid introduction of SIB by Dutch institutions might be explained by the fact that in The Netherlands the majority of institutions participate in a prospectively randomised multi-centre trial, investigating the value of a 26 Gy versus the standard 16 Gy boost dose in patients ≤ 50 years of age (the “Young Boost Trial”). In that trial, the margins for CTV and PTV are carefully described and the SIB technique is proposed as one of the standard techniques.

In the case of an electron boost, (conformal) CT guided target definition and planning are rarely performed. This might be because a SIB using electron boost fields is much more challenging concerning treatment planning. Furthermore, incorporating both photons and electrons in every treatment session is quite labour intensive. Also target coverage, particularly at the deeper parts of the target volume, might be less adequate with electron beams than with CT-based photon techniques [21]. However, sub-analysis of the EORTC boost no-boost trial has not shown a difference in local recurrence rates between electron and photon boosts [22]. Thus, one might argue that electron irradiation is just as effective in preventing local recurrences. It should however be noted that also photon boosts in the aforementioned study were not CT-based in most cases.

Target volume delineation

Although CT seems to be the current standard for treatment planning, there is a very large variation in the definition of the target volumes; especially CTV to PTV margins applied for breast and boost vary significantly. Obviously, CT images do not provide good contrast for breast and boost delineation. Therefore, identification of the mammary gland by palpation for the purpose of CTV definition

remains an important reference for many radiation oncologists. Furthermore, the survey did not include questions regarding the rationale of the margins used, e.g., whether or not they are derived from studies on local position verification measurements. Still, it is observed that large variations in margins are seen in institutions that can be assumed to participate in EORTC-ROG clinical trials, in which margins are often prescribed as part of the trial protocol. Conversely, in The Netherlands, it seems that all institutions participating in the aforementioned Young Boost Trial use the same lumpectomy cavity to boost PTV margin.

Particularly in the case of highly conformal irradiation, such as advanced 3D conformal radiotherapy (3D-CRT)-SIB or IMRT-SIB, margin selection is becoming increasingly important. The introduction of CT guided treatment planning has shown to generally result in an increased boost target volume [22], stressing the importance even more to limit the CTV to PTV boost margins as much as possible. Furthermore, it has been shown previously that the boost volume may change during a course of radiotherapy [16]. As a result, adaptive treatment planning techniques aimed at minimising the boost margins while maintaining target coverage will probably become more important in the near future.

Position verification procedures

The majority of the institutions indicated to use EPI for patient set-up verification. This is in substantial contrast with results from a UK survey published in 2002, where only half of the institutions performed set-up verification [5].

New technologies and strategies

The increased use of breath-hold techniques, together with the high frequency of delineation of the heart as organ at risk and the frequent use of the maximum heart distance as criterion for plan acceptance indicates that the reduction of heart dose is a matter of concern in the treatment of many patients, and that methods to prevent late cardiac complications are used more frequently than before. Irradiation in prone position can also be used to reduce the dose to critical structures such as the heart. However, probably due to the limited applicability

(pendulous breasts) and practical limitations of this technique it is not yet used on a large scale. There also seems to be a reluctance to prescribe PBI as routine treatment to patients and only patients in trials receive such irradiation. However, the outcome of these clinical trials may eventually lead to an increased use of this technique.

Conclusions

This survey among European radiotherapy institutions has established that recent advances in radiotherapy technology are currently widely adopted for the treatment of breast cancer. All responding institutions reported to use CT guided treatment planning. 3D-CRT and EPI-based patient set-up verification are now in mainstream use, with IMRT techniques being used by 27% of the institutions. This indicates that new radiotherapy techniques, when being addressed in clinical trials, are feasible in the network of EORTC-ROG institutions. The boost is applied sequentially in 98% of the responding institutions. The SIB technique is used in 8 Dutch institutions that treat on average 72% of their patients with SIB, while 7 non-Dutch institutions treat on average 5% of their patients with SIB. Our survey also reveals considerable variations between institutions, especially in boost delineation and applied margins. When designing new radiotherapy trials, quality assurance should focus on these issues because we found these to have the most variability compared to other radiotherapy details. For Dutch institutions participating in the Young Boost Trial, we found that trial participation increases consistency among institutions with respect to the use of treatment methodology, ensuring high quality radiation treatment available for patients outside clinical trials.

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