Radiation Dose Homogeneity in an EORTC Multicenter Trial on Breast Irradiation

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The influence of the radiation dose on local control and cosmetic outcome in breast-conserving treatment for breast cancer is investigated in EORTC trial 22881/10882. In this study 50 Gy is administered to the whole breast, and the effect of an additional dose to the tumor-bearing area (boost dose) is evaluated. The purpose of this analysis is to document the dose homogeneity of the radiation dose as reported in the first 1915 treatment forms, received at the EORTC Data Center. The dose to the prescription Point (A) was within 95 and 110% of 50 Gy in all but 13 (99.3%) patients (median dose 50 Gy) and the minimum and maximum doses in the central plane of the breast were within 95% and 110% of the dose to point A in 82% of patients. The dose to the tumor excision area (point B) was within the homogeneity criteria in 97% of patients, and the boost doses were consistent with randomization in 93% of cases. These data, based on one-third of the randomized patients in trial 22881/10882, demonstrate a high level of homogeneity in radiation doses, despite a number of ambiguities in the protocol, which were efficiently clarified a few months after the beginning of the trial. This high level of consistency is a remarkable achievement given the number of centers, the number of patients, and the number of countries involved in this trial.

In most patients with 'operable' breast cancer, the standard treatment is presently a breast-sparing surgical procedure with radiation therapy (1–4). The local tumor control probability depends upon a number of prognostic factors: apart from histological type, tumor stage, age, size of excision and of irradiated volume, a very important determinant could be the radiation dose. In the NSABP study on breast-conserving therapy, after tumor excision, a local recurrence rate of 40% at 9 years was found without further treatment to the breast and 10% after 50 Gy whole breast irradiation (1). In another (European) study, after quadrantectomy, a 3% local recurrence rate at 5 years was reported in T1 tumors after 50 Gy whole breast irradiation and a boost dose of 10 Gy (5). In a study performed in The Netherlands, after a tumorectomy with a 1 cm margin, 2% of local recurrences were seen at 6 years after 50 Gy whole breast irradiation and a 25 Gy (interstitial) boost dose, irrespective of involvement of excision margins by the tumor (6).

While a higher radiation dose could result in a lower recurrence rate, it has been clearly demonstrated that cosmetic outcome is less favorable with increasing doses (7–13). Therefore, the EORTC Radiotherapy and Breast Cancer Cooperative Groups initiated a study investigating the role of the radiation dose to the breast after conserving therapy (trial Nos. 22881/10882). Patients were randomized to either receive a boost dose to the tumor bed or not after a dose of 50 Gy to the whole breast [after incomplete resection, randomization was between a low (10 Gy) and high boost dose (26 Gy)]. It was the aim of the study to investigate whether the boost dose has an effect on the recurrence rate, and to investigate the influence of this dose on the cosmetic outcome (14, 15).

A total of 32 institutions from 9 countries participated in the study, and between 1989 and 1996, 5569 patients were randomized. In a multicenter trial with such a high number of participants, uniformity of treatment is important for the reliability of the trial results. Since retrospective quality assurance (QA) studies in clinical trials have

demonstrated that variations in treatment quality occur, the need for prospective monitoring is obvious (16–18). To avoid treatment heterogeneity as much as possible, monitoring activity was started immediately after activation of the trial in 1989.

A QA program is imperative to gain insight into the exact modalities of treatment in different institutions and in the way these modalities are reported on the case report forms. The EORTC Radiotherapy Cooperative Group has a long tradition of QA: as early as 1982 site visits to institutions participating in EORTC radiotherapy trials took place. A medical team evaluated the infrastructure of these institutions (staffing, number of treatment machines, clinical files and radiotherapy charts), a team of physicists performed basic dosimetry checks on the radiotherapy equipment (19–21), and extensive dosimetry was carried out inside an anatomical phantom (22). In the present trial, extensive QA programs were similarly organized. This report presents an assessment of the documentation and the quality of reporting of radiotherapy data in a large subset of patients. Reported data on dose prescription and dose homogeneity are evaluated.

MATERIAL AND METHODS

Trial design

The EORTC trial 22881/10882 was a phase III study started in 1989 and closed in 1996, in which 5569 patients were entered. The goal was to assess the role of the boost dose, in terms of local control and cosmesis. The whole breast was irradiated to a dose of 50 Gy after surgery in all patients. When the excision was microscopically complete, the patients were randomly assigned to no further irradiation or a boost dose (16 Gy for external or 15 Gy for interstitial boost modalities). In the event of a microscopically incomplete resection, the randomization was between a low boost dose, 10 Gy, or a higher dose, 26 Gy (25 Gy for interstitial therapy). Both interstitial therapy and external irradiation were allowed for the boost dose.

Data collection. Three different Case Report Forms (CRFs) had to be completed: an on-study form after randomization, a radiotherapy form after treatment completion and a follow-up form annually thereafter.

On the radiotherapy form, information on the radiation doses and techniques were reported. For the whole breast irradiation, the dose in point A (ICRU reference point) and point B (tumor bed) were requested, as well as the number of fractions given to the whole breast, the radiation quality used and the minimum and maximum doses in three planes through the breast.

Information on the boost technique was mandatory, and in the case of electrons or accelerator photon beams, the energy had to be specified. If the boost dose was given with external beam irradiation, the dose and the number of fractions had to be reported. Concerning interstitial boost therapy, the dose and the reference dose rate had to be stated.

Protocol specifications regarding whole breast irradiation

Treatment technique. Treatment to the whole breast had to be given by two tangential opposing fields, ventro-medial and dorso-lateral, preferably with dorsal beam edge alignment (with a maximum angle of 10° between the axes) to minimize the dose to the lung. The use of wedge filters or compensators was advised. Beam trimmers and/or a half-beam device could be used. The two tangential fields had to be treated with equal weights. Application of lung density corrections was recommended in the dose calculation procedure.

Cobalt-60 gamma-ray beams with a minimum SSD of 80 cm, or x-ray beams in the range of 4 to 8 MV were acceptable.

Dose and dose specification. The dose to the whole breast (50 Gy) had to be specified at point A, in agreement with ICRU Report 29, later replaced by Report 50 (23). Point A was defined as the intersection of the beam axes, provided that this was a relevant point in the target volume (Fig. 1). When the intersection of the beam axes was not a relevant point (as in half-beam techniques), point A was chosen in the central plane, on the line perpendicular to the dorsal beam edge, 2/3 from the line between the dorsal beam edge and the skin (Fig. 1). The 50 Gy to point A had to be given in 5 weeks, in 25 fractions of 2 Gy, 5 days a week. Both tangential fields had to be treated in the same treatment session.

Patient contours. Three transverse sections had to be determined, perpendicular to the treatment table, either by computed tomography or with other contour devices. The central plane was taken through the center of the target volume equidistant from the cranial and caudal borders of the fields covering the whole breast. This plane contained the axes of the two tangential beams that intersect at point A. The tumor plane should be taken through the center of the primary tumor site. This plane had to be chosen in the middle of the scar of the tumorectomy, or through the

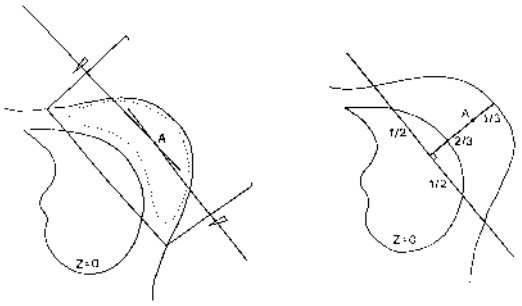

Fig. 1. Tangential breast irradiation: Point A is the intersection of the beam axes. Half-beam techniques: Point A is at mid-separation, perpendicular to the dorsal beam edge, at 2/3 from beam edge to skin.

center of the tumor excision area marked by a clip. The tumor plane contained point B, located in the center of the primary tumor excision area. The border plane was taken through a level 2 cm from the cranio-caudal border of the target volume (within the breast tissue), in the opposite direction to the tumor plane. If the tumor plane was closer than 2 cm to the central plane, then a separate section was excluded and the tumor plane was assumed to coincide with the central plane. In this case both inferior and superior border planes were determined. The target areas in each transverse section, as well as Points A and B had to be clearly indicated, and the primary tumor site area had also to be drawn in the tumor plane. Point B had to be indicated even in patients receiving no boost. The maximum and minimum doses were estimated within the target volume for all three planes.

Dose homogeneity. While the dose distribution (isodose pattern) was calculated for the central plane, it was necessary to provide additional information on dose distributions in the tumor and the border plane. The target and tumor volumes had always to be described in all three planes. For the initial 50 Gy to the whole breast, the minimal dose in any point in the three sections had to be not more than 5% lower than the nominal dose at point A. The maximum dose in these sections (minimum area 2 cm^2) had not to exceed the nominal dose at point A by more than 10%.

Initial protocol specifications regarding the boost irradiation

Primary tumor site volume and point B. This volume represented the site of the primary tumor, with a safety margin of 1.5 cm around the primary tumor after obtaining microscopically clear margins and of 3 cm after an incomplete excision (or in the case of invasive cancer with an extensive carcinoma in situ component). This volume had to be treated by the boost. The center of this volume was defined as point B.

Treatment techniques. The following techniques were accepted: two (tangential or wedged pair) external photon beams, electron beams, and interstitial therapy. Interstitial therapy was given in a single or in several planes, depending on the primary tumor site volume and according to the rules of the Paris system.

Radiation quality and dose. For external therapy technique, Cobalt-60 beams with a minimum SSD of 80 cm, or x-ray beams in the range of 4 to 10 MV were accepted. The external boost dose had to be 10, 15 and 25 Gy in fractions of 2 Gy, defined in point B, the center of the tumor excision area. For electrons, the dose was defined as the maximum given dose, the tumor region being within the 85% isodose line. For interstitial therapy, ^{192}Ir wires and Cesium-137 needles were accepted. Radium needles had to be avoided. The dose with Iridium wires had to be prescribed according to the Paris system, specified at 85% of the average basal dose, with a recommended dose rate of 10 Gy per day.

Amendments to the protocol after the start of the trial

While checking the first CRFs received at the Data Center in December 1989, six months after the initiation of the trial, some ambiguities in the protocol were detected, resulting in recommendations sent to the participating centers in June 1990.

One of the topics was the exact definition of the boost dose. It is obvious that in the whole breast irradiation, the dose to point B is in most cases different from point A, the difference depending on treatment technique, shape of the breast and distance between A and B. In patients randomized to receive a boost dose, two different interpretations of the dose prescription were seen. Either the boost dose was given to point B regardless of the above described difference, and therefore added to the dose to point A, or the boost dose to point B could be adjusted (compensating for the difference between A and B), so the total dose to point B became exactly 60, 65 or 75 Gy. This was done in some institutions, having the facility to calculate off-axis doses in complicated volumes.

In the recommendations, the first solution was advised. It was stressed that: 'The center of the tumor excision area is defined as point B, in which the booster dose is specified. Point B has, by definition, a different location in the breast for every patient, and so does not always receive exactly 50 Gy from the whole breast irradiation. The dose from the boost irradiation should, however, be added to the dose in point A and should not be compensated for any dose variation in point B by adding or leaving out boost fractions.'

The first individual case review with five participating institutions, held in October 1990, revealed some additional difficulties, resulting in a second set of recommendations sent in January 1991. Amongst other recommendations, the exact boost dose was adapted according to the modality used. In the initial protocol, boost doses of 10, 15 and 25 Gy were requested, together with a fraction size of 2 Gy for the external boost modalities. Since 15 and 25 Gy cannot be delivered in fractions of exactly 2 Gy, different fractionation schemes were used in practice, with a varying number of fractions, doses per fraction and total boost doses. Therefore, the total boost dose was recommended to be 10, 16 and 26 Gy for external beam modalities and 10, 15 and 25 Gy for interstitial therapy.

Quality assurance procedures

Initially, a so-called 'Dummy Run' procedure was organized: three CT slices of a breast were sent to a number of

participating centers and treatment planning was done according to detailed specifications (24). In a number of Dutch institutions, a breast phantom was irradiated for dose comparison (25). Further, in vivo dosimetry was performed using mailed TLD dosimeters, giving information on individual patients (26–28). The first CRFs, received at the Data Center, were reviewed six months after the trial was started (29). Finally, an investigation of individual patient files, with comparison of clinical and physical reporting on the forms was organized in conjunction with the biannual group meetings (30). In a previous communication, the patient population entered in this trial was extensively discussed (31).

Population for the analysis of radiotherapy data reporting

From May to October 1993, an analysis of all available radiotherapy data was performed. The cut-off period was May 1993, with at the time 2672 patients randomized. Radiotherapy forms were available for 1915 patients from 25 institutions (82% of the expected forms at that time). Six patients were excluded from the analysis because of early treatment interruption: detection of metastases (2 patients), refusal to continue treatment (1), suspicion of residual disease and therefore mastectomy (2), and extreme skin reaction (1). The analysis of the whole breast irradiation was therefore performed on 1909 patient forms.

The dose to point B was available for 1749 patients. Two forms were excluded because of written errors, so the analysis of the boost dose and total dose in point B was performed on data from 1747 patients.

The total number of patients and centers per analysis may vary due to missing information for specific items on some of the CRFs.

RESULTS

Radiation quality whole breast

The radiation quality used for the treatment of the whole breast was reported in 1901 out of 1909 patients. An accelerator was used in the majority (1304) of patients, and Cobalt-60 in 597 cases. Thirteen institutions (13/25) treated patients with Cobalt-60, and in 23/25 centers accelerator photon beams were used. Cobalt-60 was the only modality in 2 institutions, only accelerator beams were applied in 12 centers, and both modalities were applied in the other 11 centers. In the large centers ($>$ 100 patients included in this analysis) where both Cobalt-60 and linear accelerators were used, it is interesting to note that most of the patients (59–94%) were treated on a Cobalt-machine. If accelerator photon beams were administered, the energy varied between 4 and 8 MV. Several institutions using accelerator photons (8/23) had more than one energy available. Two institutions reported using regularly an energy of 10 MV, while one center occasionally applied a beam of 16 to 18 MV.

Dose in point A and number of fractions

The dose specification at point A was available from 1906/1909 patients. In most patients (1590/1906, 83.5%) it was reported that exactly 50 Gy was administered, as recommended per protocol. In 99.3% of all patients, the dose ranged between 95 and 110% of 50 Gy (mean 50.2 Gy, median 50 Gy, SD 0.9 Gy). Only 13 patients (0.7%) received a dose either lower than 95% or higher than 110% of 50 Gy.

In the distribution of the dose reported in point A by institution (data not shown), a median dose of 50 Gy was reported in all but two institutions. In one of these two centers, the dose to point A was always below 50 Gy (median 47.5 Gy), while in the other, it was usually higher (median 52.2 Gy). In all other 23 centers, the dose was only very occasionally lower or higher than 50 Gy, as demonstrated by the mean dose, very near to 50 Gy (range 49.8–50.1) the median dose, equal to 50 Gy, and small standard deviations (0–1.4 Gy). Six of the 25 institutions reported to always administer 50 Gy in the prescription point.

The number of fractions was reported in 1903/1909 patients. As for the dose in point A, the majority of patients (1674/1903, 88%) received the whole breast irradiation in 25 fractions (mean 25.2, median 25) as per protocol. Treatment was reported to be administered in less than 25 fractions in 3% of the patients, in more fractions in 9%.

In the distribution of the number of fractions by institution (data not shown), it was seen that the median number was 25 in all but the above-mentioned two centers, one of which reported treating patients with fewer than 25 fractions (with total doses in point A less than 50 Gy), the other with more fractions (with total doses in point A usually higher than 50 Gy).

Dose homogeneity

Maximum and minimum doses in the three planes within the breast, as defined above, were available from 23 centers.

Minimum dose. In the *central plane* (1718 patients), containing the intersection of the beam axes (Point A), the mean of the minimum doses over all patients was 48 Gy (median 48 Gy, SD 2.3 Gy). In 82% of cases this dose was within 95 and 100% of the dose in Point A, in 18% it was lower than 95% (Fig. 2).

In the *tumor/second border plane* (1624 patients), containing the tumor bed (Point B), the mean of the minimum doses was 47.8 Gy (median 48 Gy, SD 2.5 Gy). In 70% of cases this dose was within 95 and 110% of the dose to Point A, in 30% lower than 95%.

In a single institution, the minimum doses reported in the central plane were above 50 Gy (mean 51.1 Gy, median 52 Gy, SD 2.2 Gy, the dose in point A also being

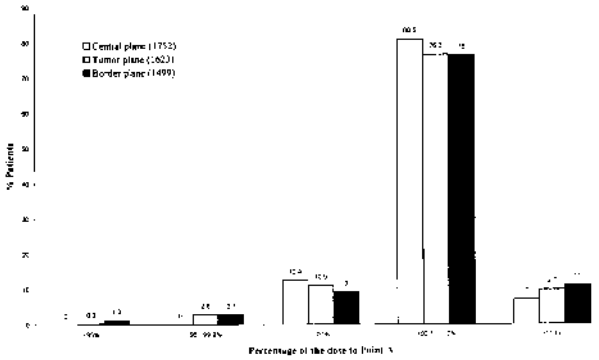

Fig. 2. Distribution of the maximum doses reported for the three planes through the breast (central plane, tumor plane and border plane) as a percentage of the dose reported at Point A.

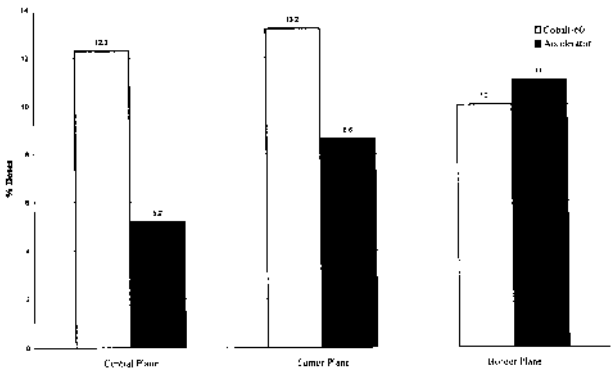

Fig. 3. Percentage of maximum doses exceeding 110% of the dose reported at Point A, in the three planes through the breast, according to radiation quality.

higher than 50 Gy), and the minimum doses in the tumor/second border plane were equally higher than 50 Gy (mean 50.4 Gy, median 50 Gy, SD 4.2 Gy).

In the *border plane* (1497 patients), the mean of the minimum doses was 47.9 Gy (median 48 Gy, SD 3 Gy). In 72.5% of cases this dose was within 95 and 110% of the dose in Point A, in 27.5% of cases it was lower than 95%.

In 19/23 centers, a minimum dose lower than 95% of the dose in Point A was reported for at least one case. No difference in distribution of the minimum dose was observed according to radiation quality.

Maximum dose. In the central plane (1754 patients), the mean maximum dose was 52.5 Gy for all patients (median 52.2, SD 1.8 Gy). In 93% of the cases this dose was within 100 and 110% of the dose in Point A, in 7% it was higher than 110%.

In the *tumor/second border plane* (1 624 patients), the mean maximum dose was 52.8 Gy (median 52.5 Gy, SD 2.2 Gy). In 90% of cases this dose was within 95 and 110% of the dose in Point A, in 10% it was higher than 110%.

In the *border plane* (1500 patients), the average maximum dose was 52.8 Gy (median 52.5 Gy, SD 2.7 Gy). This dose was within 95 and 110% of the dose in Point A in 88% of cases, higher than 110% in 11% and lower than 95% in 1%.

The maximum doses according to radiation quality are described in Fig. 3. More patients treated with Cobalt-60 than with accelerator had maximum doses higher than 110% of the dose to Point A.

Dose to point B (whole breast irradiation)

The dose component of the total breast irradiation to point B (the center of the tumor excision area), was reported in 1747/1909 patients.

The distribution of the reported doses showed a mean dose of 50.5 Gy (median 50 Gy, SD 2.1 Gy). In 737 patients (42%) the dose to point B was exactly 50 Gy. In 693 of these patients, the dose reported to point A was also 50 Gy.

In 47% of 815 patients, the dose to point B was reported to be exactly the same as the dose to point A. This dose was 50 Gy in 693 patients (85%), more than 50 Gy in 101 patients (12%) and lower than 50 Gy in 21 patients (3%).

The homogeneity criteria were fulfilled in 97% of patients (reported dose within 95–110% of the dose to point A). These criteria were equally fulfilled with accelerators as with Cobalt-60 beams, but relative doses tended to be higher with Cobalt-60 (Fig. 4).

Boost

Treatment and technique. Information on the boost dose was available for 1747 patients from 22 centers. The resections were reported to be complete in 1642 (94%) of these cases, whereas in 105 (6%) patients they were incomplete. A total of 939 patients received a boost. External boosts were administered in 801, interstitial boosts in 137 cases.

Electrons were used in 20/22 centers, Cobalt-60 in 8/22, accelerator photons in 12/22 and interstitial therapy in 9/22 centers. In 6 institutions, only electron beams, and in a single center, only photons were applied. In 15 centers, a combination of different techniques was used: electrons and interstitial therapy in 2 centers, electrons and photons in 5, and electrons, photons and interstitial therapy in 8 centers.

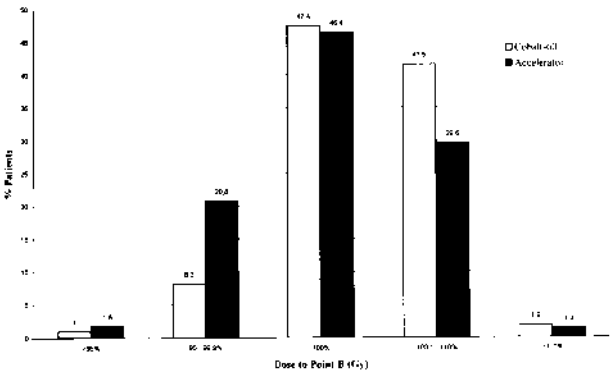

Fig. 4. Dose to Point B as a percentage of the dose at Point A: distribution according to radiation quality.

Electron energies varied from 4 to 20 MeV (mostly 9, 10 and 12 MeV), photon energies between 4 and 18 MV (usually 4 to 8 MV). In 6/12 centers, different photon energies were used. The same energy was usually applied for the boost and the whole breast irradiation.

Boost doses. In the 1642 patients with a *complete resection*, 816 were randomized to receive no boost, but 16 of them were reported to have received a boost. In the 826 patients randomized to receive a 15/16 Gy boost, 737 received a dose between 14 and 17 Gy, 81 received doses lower than 14 or higher than 17 Gy, 7 received no boost and in 1 patient no dose was reported. Of the 81 patients, 8 had an interstitial and 73 an external boost. In a few (4) cases, the deviating doses were equal to those requested in other treatment arms (10 Gy and 25 Gy). The other doses varied considerably: usually between 11 and 14 Gy (63 patients), between 17 and 20 Gy (12 patients) or exactly 6 Gy (2 patients). In total, 88/825 patients (10.7%) received a more or less different radiation dose than they were assigned to at randomization, but only 23 patients actually received a different treatment (boost or no boost).

In the 105 patients with incomplete resection, 49 were randomized to receive a 10 Gy boost. A dose between 9 and 11 Gy was reported in 42 patients, in 6 patients a deviating dose was reported, ranging from 11 Gy to 25 Gy [11 Gy in 1 patient, doses as requested in other treatment arms (16 Gy and 25 Gy) in 3 patients, 20 Gy (1 patient) and 23 Gy (1 patient)]. One patient did not receive a boost. In this group, 7/49 (14.3%) of the boost doses were not according to the requested dose. In the 56 patients randomized to receive 25/26 Gy, 7 (12.5%) were reported to have received a different dose. Three patients received 24 Gy, the other four received a dose as requested in other treatment arms (10 and 15 Gy).

In *total*, 118/1746 (7%) of all patients did not receive the exact dose they were randomized for, in 52 (47%) of these patients, however, the difference was within 1 Gy of the requested dose. Eight of the 118 patients did not have a boost dose although it should have been given, in 110 patients the dose was not exactly as required.

Total dose in point B

The total dose in point B (the sum of the dose in point B reported from the whole breast irradiation and the boost dose) was fairly homogeneous in the four different dose levels that were possible in the trial, with the exception of a few outlying doses.

After *complete resection* (Fig. 5), in the group without boost the mean total dose to point B was 50.8 Gy (median 50.8 Gy, SD 2.8 Gy), while in the 15/16 Gy boost group the mean dose was 65.9 Gy (median 66 Gy, SD 2.7 Gy).

After incomplete resection, in the group randomized for a 10 Gy boost the mean dose was 61.3 Gy (median 60.3 Gy, SD 4.5 Gy), while in the 25/26 Gy boost group the mean dose was 75.3 Gy (median 76 Gy, SD 3.9 Gy).

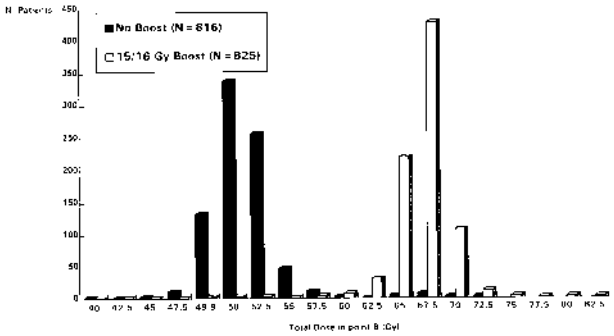

Fig. 5. Distribution of the total dose reported at Point B, per randomization arm, in patients with complete tumor resection.

DISCUSSION

A precise and clear protocol is a prerequisite for treatment to be performed and reported in a uniform way by all investigators participating in a multicenter trial. In this study on the role of the boost dose in breast irradiation (EORTC 22881/10882), the most important dosimetric parameters are the total dose to the breast and the dose administered to the primary tumor bed, both possibly influencing local control as well as cosmetic result after treatment. The reliability of the results of the trial depends on the homogeneity of treatment throughout the different participating institutions. Since it is to be expected that some differences will exist, it seems relevant to evaluate the extent of these differences, in order to understand the causes and to take these into consideration when analyzing treatment results.

Dose to point A

In the definition of the dose to the whole breast, the ICRU method was recommended since it is a very specific and uniform dose specification (at the intersection of the beam axes for tangential fields). It was considered to be the best method to compare the data on dose and dose homogeneity. The repartition of the reported doses, however, delivered to point A, show a spread around the required 50 Gy. The most important cause of this spread is that ICRU recommendations of dose prescription at the intersection point were not routinely used in every institution. Indeed, in some centers, the dose was prescribed on an isodose, usually the one surrounding the target volume. This explains the variation in reported dose to point A, depending on the value of the chosen isodose. Another reason for the spread of the dose in A is that in some institutions different treatment set-ups from those specified in the protocol were applied, which were accepted on a case-by-case basis by the trial coordinator before the trial started. In one of these set-ups, point A cannot be defined, the patient not being treated supine, and other dose calculation methods were used in these patients.

Number of fractions

The dose to the whole breast was to be divided into 25 fractions. The number differed from 25 in 229/1903 patients, in most (196) of these cases the dose in point A was also different from 50 Gy. In some centers, other treatment schemes were administered than the requested 25 times 2 Gy. Since the dose per fraction was not collected on the forms, the exact treatment schemes could not be totally reconstructed. Another reason, occasionally reported on the forms, was machine breakdown, resulting in treatments being given in fewer fractions per week with a higher dose per fraction.

The dose to point A and the dose per fraction (related to the number of fractions) are of particular importance since the dose level is not only influencing the local recurrence rate but also the cosmetic outcome (7–11, 13).

Dose homogeneity to whole breast

Information on the degree of dose homogeneity is equally important, since inhomogeneity can significantly influence the quality of the cosmetic result (32, 10, 13). The criteria requested by the protocol, that the minimal dose in any point in the three sections should not be more than 5% lower than the nominal dose at point A and that the maximum dose in these sections (minimum area 2 cm^2) should not exceed by more than 10% the nominal dose at point A, are considered worldwide to be well achievable (33). While homogeneity in the central plane was obtained according to the protocol in 82% of patients, some outlying minimum and maximum doses are reported. Some degree of dose heterogeneity is to be expected in relation to the natural breast size, for instance in some cases, the dose to the cranial border region can be fairly high because of 'missing tissue', especially in large breasts. Estimation of maximum and minimum doses on the isodose plots can be difficult in some cases, especially when uncertainty exists as to the exact delineation of the target volume.

The dose to point B, the center of the tumor excision area, is usually different from the dose in point A, except when both points are fairly close. In 47% of patients, the dose in point B was reported to be exactly the same as that in point A. While in many cases, this is indeed so, in other cases the dose in B was actually not calculated, either because of incapacity of the planning system to calculate off-axis doses, or because of lack of time to calculate the dose distribution in more than one plane.

Radiation quality

Radiation quality influences the dose distribution to some extent: in patients treated with Cobalt-60, a larger proportion had maximum doses higher than 110% of the dose in point A, and doses in point B in the range of 100–110% compared to photons from accelerators. The reasons for this discrepancy are the higher proportion of institutions using dose prescription on a specific isodose, and a lower proportion of patients treated with wedge filters in the group of patients treated with Cobalt-60.

It is known that, especially in large breasts, dose distributions with Cobalt-60 beams tend to be more heterogeneous for purely physical reasons, thereby increasing the risk of fibrosis in some areas of the breast (9, 10).

Dose to tumor bed

While the heterogeneity expected in the dose to the whole breast is limited, more differences can be expected in the dose distribution in the tumor bed when a boost is added. The reported total boost doses and numbers of boost fractions in the different treatment arms are indeed spread over a certain range. This has several causes. In the first version of the protocol, a dose of 10, 15 or 25 Gy was prescribed, with for the external boost modalities a fraction size of 2 Gy. This inconsistency in the protocol resulted in different fractionation schemes being used, with varying numbers of fractions, doses per fraction and total boost doses. When this was discovered, a letter was sent to the participating institutions, recommending total boost doses of 10, 16 and 26 Gy for the external beam modalities, resulting in better dose uniformity. However, a few different total boost doses were also reported, not justifiable by a misinterpretation of the protocol regarding the exact definition of the boost dose.

Interpretation of dose prescription of boost dose

In most patients, 'the whole breast dose' to point A and B is different. In patients randomized to receive a boost dose, two different interpretations of the prescription in the protocol for the boost dose were possible: either the dose was given to point B regardless of this difference, and therefore added to the dose to point A, or the boost dose to point B could be adjusted, compensating for the difference between A and B, so the total dose to point B could be exactly 60, 65 or 75 Gy. This was initially done in some institutions, having the facility to calculate off-axis doses in complicated volumes. In the recommendations sent to the institutions later on, it was stressed that this second option should not be followed, but to add a fixed boost dose to the dose in point A and not to compensate for any dose variation in point B by adding or leaving out boost fractions, or adapting the dose in interstitial boosts. Although the concept of compensation was the most attractive at first sight, it was decided not to perform it, because of the larger differences it would create in total dose to the tumor area: some participating institutions were using planning systems capable of calculating off-axis doses, necessary to calculate the dose in B if B is not in (or near to) the central plane; other institutions did not have this facility and could thus not compensate for dose deviations in B. Therefore, for the sake of a more homogeneous dose,

it was decided to add a fixed boost dose to the dose in point A.

CONCLUSION

Data on heterogeneity will have to be taken into account when the trial results are interpreted. Both local control and cosmetic outcome could be influenced by the actual dose given to the prescription point, the tumor bed and the whole breast, so a detailed knowledge and evaluation of these factors in individual patients is indispensable in cases of local recurrence or unfavorable cosmetic results.

In this megastudy, because of early quality assurance procedures and analysis of reported data, ambiguities were elucidated in the protocol and new guidelines were added to the protocol after discussion during the biannual group meetings in a very early stage of the trial. These measures have proven to be successful, since the level of homogeneity is high, given the large number of patients and participating centers from different countries with different radiation technique traditions.

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