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Quality assurance of EORTC trial 22922/10925 investigating the role of internal mammary—medial supraclavicular irradiation in stage I-III breast cancer: the individual case review

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Abstract

To assess consistency among participants in an European Organisation for Research and Treatment of Cancer (EORTC) phase III trial randomising between irradiation and no irradiation of the internal mammary and medial supraclavicular (IM-MS) lymph nodes, all participating institutes were invited to send data from 3 patients in each arm as soon as they started accrual. The evaluation focused on eligibility, compliance with the radiotherapy guidelines, treatment techniques and dose prescription to the IM-MS region. Nineteen radiotherapy departments provided a total of 111 cases, all being eligible. Minor discrepancies were found in the surgery and pathology data in almost half the patients. Major radiotherapy protocol deviations were very limited: 2 cases of unwarranted irradiation of the supraclavicular region and a significant dose deviation to the internal mammary region in 5 patients. The most frequently observed minor protocol deviation was the absence of delineation of the target volumes in 80% of the patients. By detecting systematic protocol deviations in an early phase of the trial, recommendations made to all the participating institutes should improve the interinstitutional consistency and promote a high-quality treatment.

Keywords: Randomised clinical trial; Individual case review; Quality assurance; Breast cancer; Radiotherapy; Internal mammary chain

1. Introduction

In operable breast cancer (T0-3, N0-2, M0), the influence of regional lymph node involvement on prognosis is well known [1]. The incidence of lymph node invasion of the internal mammary chain ranges from 4% in axillary node-negative patients with upper lateral tumour location to 72% in axillary node-positive patients with lower medial tumour location [2–4]. In spite of this significant risk of tumoral involvement and several decades of a combination of surgery and radiotherapy in the local treatment of breast cancer, there remains an important controversy concerning the usefulness of irradiating the regional lymph node areas [5–12]. A meta-analysis of randomised trials of postoperative adjuvant radiotherapy, demonstrated a reduction of the long-term breast cancer death rate in the group of irradiated patients [13]. This was later confirmed in three randomised trials, which demonstrated the positive impact of adjuvant loco-regional irradiation, including the internal mammary and supraclavicular lymph node areas, on survival in high-risk patients [14–16]. The explanation of the observed

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advantage remains unclear: the prevention of local recurrences through irradiation of the chest wall, the prevention of regional recurrences through irradiation of the lymph nodes, or both. To date, only one randomised radiotherapy trial on the effectiveness of adjuvant internal mammary irradiation alone has been published [17]. The follow-up is too short and the number of patients too limited (270) to provide an answer on the usefulness of adjuvant irradiation of the internal mammary chain. The thin line between the advantages and the side-effects of internal mammary and medial supraclavicular (IM-MS) irradiation was very recently summarised in an editorial by Lievens and Van den Bogaert [18].

In May 1996, the Radiotherapy and the Breast Cancer Groups of the European Organisation for Research and Treatment of Cancer (EORTC) initiated a large phase III randomised multicentre trial. Its objective is to investigate whether adjuvant irradiation of the IM-MS lymph node chain for patients with localised breast cancer stage I-III with medially or centrally located tumours and/or axillary lymph node invasion after lumpectomy and axillary node dissection or modified radical mastectomy will significantly improve overall survival by at least 5% at 10 years [19]. Furthermore, the incidence of serious late side-effects on the heart and the lungs will be registered for patients treated with modern radiotherapy equipment and techniques for treatment preparation and treatment execution.

A large number of patients (3780) and a long follow-up (10 years) will be needed to answer the questions of this trial. To allow many radiotherapy institutes to participate in the trial and to accrue a large and representative sample of patients, a standard treatment technique for the IM-MS irradiation is recommended and described in the protocol (Fig. 1). In this technique, the IM-MS lymph node area is treated with mixed photon and electron beams matched to the tangential field borders of the breast or thoracic wall (which can alternatively be treated with a direct electron field). Individual anatomical localisation of the internal mammary nodes was not mandatory for the standard technique, but the use of a computed tomography (CT) scan, ultrasound or lymphoscintigraphy was recommended. This information can be used to select the most suitable electron beam energy, the dose prescription depth for the photon beam and the relative beam weights. In addition, the optimal beam dimensions depend on the location of the nodes. Several institutes have developed specific irradiation techniques for this indication [20]. These more complex treatment set-ups may be accepted in the trial, provided that they use individual localisation of the internal mammary nodes.

The Quality Assurance (QA) programme of the EORTC Radiotherapy Group aims to test the ability of the participating institutes to comply with the protocol guidelines. The variations in the dose delivered to the target volumes due to uncertainties in treatment planning systems (TPS) and in the calibration of the treatment machines were investigated by the general EORTC Radiotherapy Group QA procedures for institutional infrastructure. In the early phase of clinical trials, various QA procedures were performed to check protocol compliance and to detect and correct possible ambiguities in the protocol, which might introduce systematic protocol deviations [21–26]. In EORTC trial 22922/10925, the specific QA programme consists of (i) control of data consistency at the EORTC Data Centre by a double data entry procedure in the database, (ii) a dummy run procedure, (iii) an individual case review procedure (ICR) and (iv) mailed TLD electron dosimetry. The evaluation of the dummy run has already been reported, indicating a number of deviations in treatment set-up and dose prescription [27]. Based on the dummy run, a thorough evaluation of the irradiation techniques used in the 22922/10925 EORTC trial for the irradiation of the internal mammary and medial supraclavicular lymph node chain was also reported [20]. The external audit of electron beams using TLD dosimetry was performed by the EQUAL-ESTRO structure [28].

The current paper describes the outcome of the analysis of the individual case review from the 19 major participating institutes accruing 77% of the patients. The objective was to evaluate data consistency and to detect deviations from the protocol guidelines in a selection of patients accrued in the early phase of the trial.

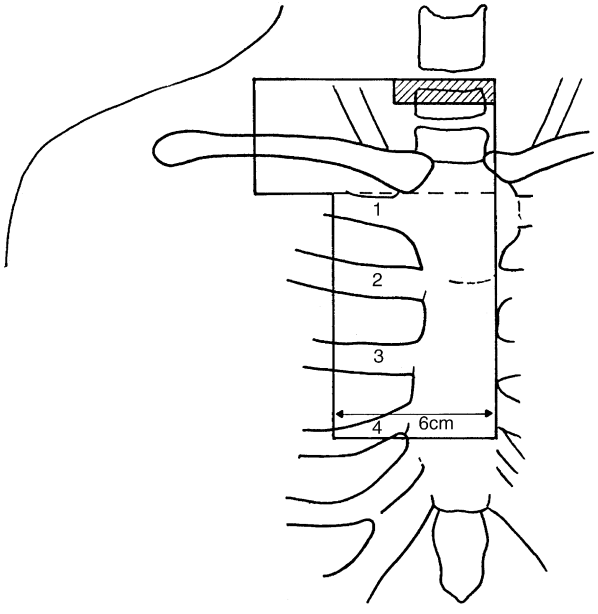

Fig. 1. Recommended standard technique for internal mammary and medial supraclavicular irradiation (IM-MS).

2. Patients and methods

All participating institutes were invited at the onset of the trial to send six complete patients' records (3 patients with irradiation of the IM-MS and 3 without) including the surgical and pathology report, radiation treatment charts, treatment planning calculations and plots, as well as information on the primary tumour site and adjuvant systemic treatment. To facilitate and improve the evaluation, several case report forms (CRF) collected at the EORTC Data Centre were used. All data from the participating institutes were mailed to Tilburg where they were checked within weeks of receipt by the co-ordinating radiation oncologist. This allowed a quick detection of possible protocol deviations and enabled a prompt response to the participating institutes in the form of a letter and a copy of the Evaluation-CRF (E-CRF), developed and used for the evaluation of each individual patient (Table 1). In some cases, participants were asked to clarify or to complete the information supplied. At several of the bi-annual meetings of the EORTC Radiotherapy Group, an overview of the findings of the ICR was presented and discussed. Based on the results of the ICR, as well as of the dummy run, a letter with recommendations to improve compliance with the protocol was sent to all participants, including those who did not yet participate in the QA programme. Furthermore, a revised protocol was introduced in May 1999, including several improvements and clarifications based upon the findings of the QA procedures.

Table 1
Items scored on the evaluation case report form used for the individual case review.

Eligibility
Histologically-confirmed invasive adenocarcinoma?
Breast cancer pTx, pT0-T3, the International Union Against Cancer (UICC) Classification 1992?
Breast cancer pN0-N2, UICC Classification 1992?
Absence of distant metastases?
Mastectomy or breast-conserving surgery and axillary dissection?
Lateral/N1-2 or centromedial/N0-1-2 tumour location?
Woman $<$ or = 75 years?
Written informed consent?
Surgery
Was surgery performed according to protocol?
Type of breast surgery on OSF according to pathology report?
Axillary surgery on OSF according to pathology report?
Pathology
Primary adenocarcinoma of the breast?
Tumour size and T-stage on OSF corresponds with pathology report?
Number of positive lymph nodes on OSF corresponds with pathology report?
Number of examined lymph nodes on OSF corresponds with pathology report?
Radiotherapy
Dose specification according to ICRU Report 50?
Dose homogeneity according to ICRU Report 50?
IM-MS nodes treated according to randomisation arm?
Target volume internal mammary and medial supraclavicular (IM-MS) nodes drawn on patient contour?
Target volume breast or thoracic wall drawn on patient contour?
IM-MS technique used:...
IM-point individual anatomical information?
Dose at IM-point or 3 cm lateral/deep from midline minimal 85%?
Dose in Gy at IM-point or 3 cm lateral/deep from midline:...
IM-MS electron energy conform protocol?
Dose specification of MS nodes at 3 cm depth?
IM-MS dose fractionation scheme 50 Gy in 25 fractions?
Time interval between surgery and radiotherapy respected?
Number of days between date of surgery and first fraction of radiotherapy:...
Date of first irradiation on OSF coincides with treatment chart?
Overall treatment time IM-MS 5 weeks (maximum 6 weeks)?
Overall radiotherapy treatment time in days:...
Megavoltage film or electronic portal imaging of IM-MS field?
Systemic therapy
Systemic therapy given corresponds with OSF?
Type of systemic therapy: 1 = hormonal therapy, 2 = chemotherapy, 3 = both
Information on date of first cycle of chemotherapy?
Information on treatment scheme of chemotherapy?

OSF = on study form.

As displayed in Table 1, the evaluation focused on the eligibility to the protocol (8 items), surgery (breast and axilla) (3 items), pathology (4 items), radiotherapy (18 items) and systemic therapy (4 items). Some space for additional comments was allowed on the E-CRF. All items were scored for all patients on the dedicated E-CRF and collected in a spreadsheet. Depending on the specific item, the score could be qualitative (yes, no, unknown) or quantitative (dose or number of days). For the evaluation of the calculated dose to the IM lymph node region, a reference point was defined at the cranial or central (whichever was the most relevant for the specific patient) treatment-planning slice through the breast target volume, representing an estimation of the anatomical location of the IM lymph nodes. Results were analysed for the entire group of patients and also per participating centre and per treatment arm.

Treatment according to the other randomisation arm and over- or under dose at the IM point were defined as major protocol deviations. All other deviations were considered as being minor deviations, including the absence of delineation of target volumes because the advised standard treatment technique did not oblige the use of individual anatomical information.

3. Results

By January 2003, over 3300 patients were accrued by 45 institutes in 12 different countries. Nineteen radiotherapy departments, responsible for the accrual of 77% of the patients, participated in this ICR (Table 2). Eighteen out of those 19 institutes sent 3 cases per randomisation arm (six records per institute), while one institute sent only 3 cases (1 case without IM-MS irradiation, and 2 cases with IM-MS irradiation). Therefore, a total of 111 cases was available for evaluation, 55 cases in arm 1 and 56 cases in arm 2.

3.1. Eligibility

All 111 patients were fully eligible, without any item being incomplete. 88 patients (79%) were treated with breast-conserving techniques. Only 23 of the 111 patients (21%) were treated with a modified radical mastectomy.

3.2. Surgery

In 1 patient, the type of breast surgery reported was not in agreement with the pathology report: on the CRF, a mastectomy was reported whereas, according to the pathology file and the other patient and treatment data, it was clear that a tumorectomy and a re-excision had been done. In another patient, some items were not correctly specified on the CRF, one pathology report was missing and in 2 patients some of the surgical details were not available. In 15 out of the 19 centres (79%), all data were present and correctly reported.

3.3. Pathology

The tumour size, as mentioned in the pathology report, was not correctly reported on the CRF in 14 patients (13%) and could not be evaluated in 8 other

Table 2
List of participants in the quality assurance programme of EORTC trial 22922/10925

City	Country	Institution	Local, responsible radiation oncologist and physicist
Bruxelles	Belgium	University Hospital Saint-Luc	C. Kirkhove, S. Vynckier
Leuven	Belgium	University Hospital	W. van den Bogaert, D. Huyskens
Santiago	Chile	Instituto de Radiomedicina	R. Arriagada, L. Schwartzman
Bordeaux	France	Institut Bergonié	J.-M. Dilhuydy, V. Lurie
Dijon	France	Centre G.-F.Leclerc	I. Barillot, S. Naudy
Grenoble	France	University Hospital	M. Bolla, A. Dusserre
Paris	France	Institut Curie	A. Fourquet
Villejuif	France	Institut Gustave Roussy	C. Le Pechoux
Berlin	Germany	University Hospital Charité	V. Budach, U. Jahn, J. Groll
Köln	Germany	University Hospital	R. Bongartz
Tübingen	Germany	University Hospital	M. Bamberg, N. Weidner, E. Herrmann
Como	Italy	Ospedale Sant'Anna	M. Valli, A. Monti, A. Ostinelli
Genève	Switzerland	University Hospital	J. Kurtz, Ph. Nouet
Lausanne	Switzerland	University Hospital	W. Jeanneret, H. Do
Zürich	Switzerland	University Hospital	Ch. Glanzmann, J.B. Davis
Amsterdam	The Netherlands	Nederlands Kanker Instituut	B. Pieters, C. Hurkmans
Deventer	The Netherlands	RTI Stedendriehoek e.o.	J. Immerzeel, A. van 't Riet
Tilburg	The Netherlands	Dr. Bernard Verbeeten Instituut	Ph. Poortmans, J. Venselaar
Utrecht	The Netherlands	University Medical Centre	H. Struikmans, J. Lagendijk

EORTC, European Organisation for Research and Treatment of Cancer.

cases (7%). The total number of tumour positive or of examined lymph nodes was not correctly reported in 1 and 5 patients, respectively, and could not be evaluated in 7 cases (6%) each. Supplementary remarks were: incorrectly specified items on the CRF in 17 patients (15%), there were missing pathology reports and missing CRF in 6 patients each (5%). In 1 case, immediate breast reconstruction with prosthesis was performed, but not reported. Only six centres (32%) complied completely for all their patients.

3.4. Radiotherapy

2 patients, randomised to arm 1, were not irradiated at all because of a lack of indication for post-mastectomy irradiation of the thoracic wall. For the same reason, 2 other patients, randomised to arm 2, were only treated in the IM-MS lymph node region. 2 patients, randomised to arm 1, were erroneously irradiated at the supraclavicular lymph node region.

Dose specification was not according to the International Commission on Radiation Units and Measurements (ICRU) Report 50 [29,30] in 10 cases (9%). Dose homogeneity was not within the prescribed limits for 1 patient and could not be evaluated for 2 patients. In 4 cases (7%), the fractionation schedule of IM-MS irradiation differed from the prescription of 25 daily fractions of 2 Gy (24–28 fractions of 1.8 – 2.25 Gy). The target volumes for the breast/thoracic wall and for the IM-MS lymph nodes were not drawn on the treatment plans in 87 (80%) and 64 (59%) of the patients, respectively. However, 95 patients (87%) had an individual localisation of the IM-MS nodes, either on CT scans (83 patients) or using ultrasonography, lymphoscintigraphy or combinations. In the 56 cases of irradiation of the IM-MS, most centres used the standard treatment technique as described in the study protocol (14 centres (74%) with 41 cases). However, for 32 of these 41 cases (78%), anatomical information was used to individualise the field set-up. Four centres (21%) with 12 patients developed an individualised treatment set-up. In one centre with 3 patients, the choice between the standard technique or a customised technique depended on the individual patient's anatomy. The specified maximum interval of 8 weeks between surgery and randomisation, unless chemotherapy was given in between, was not met in 10 cases (9%) from six centres. The overall treatment time of the IM-MS lymph nodes ranged from 25 to 55 days (mean = 38.3 ± 5.5): less than 6 weeks in 48 (86%) and less than 7 weeks in all 56 cases. In 22 cases (39%), information about portal imaging of the IM-MS field was missing. In all centres, at least one item on radiotherapy was missing or incompletely reported.

3.5. Dose to the IM-MS lymph node region

In the 56 cases of irradiation of the IM-MS, we had sufficient information to recalculate the dose to the IM lymph node area in 45 patients (80%). The median dose in this group was 49.25 Gy. It was at least 85% of the prescribed dose of 50 Gy in 44 patients (98%). In 37 cases (66%), the dose to the MS lymph

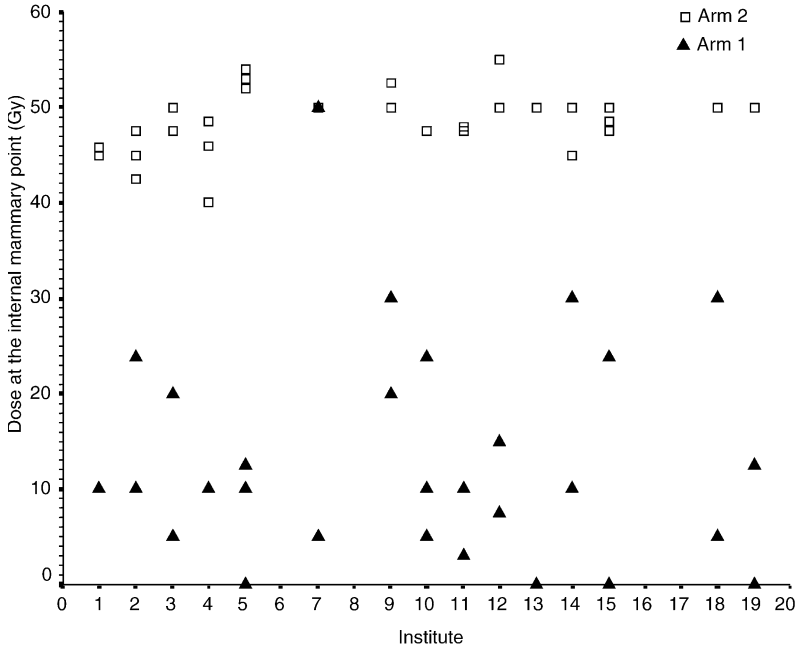

Fig. 2. Dose at the internal mammary point stratified by institute and per randomisation arm. The mean dose (±standard deviation) in arm 1 was 12.8±11.7 Gray (Gy) and in arm 2, 48.7±3.3 Gy.

nodes was prescribed at the 3-cm depth as specified in the protocol, in 17 cases (30%) it was prescribed at a different depth (in general at the depth of Dmax) and in 2 cases (4%) it was not retrievable. In the 55 patients randomised to arm 1, i.e. without irradiation of the IM-MS, the dose to the IM lymph node area could be recalculated in 42 patients (76%). The median dose here was 9 Gy. For 9 patients (21%), this dose was more than 25% of 50 Gy and for 4 patients (10%) even in excess of 50%. The dose to the IM lymph node area is displayed in Fig. 2.

3.6. Systemic therapy

Guidelines on systemic therapy were not included in this protocol. However, institutes had to specify their general policies concerning adjuvant treatment. All data were present and correctly reported for all patients in nine centres (47%). Information on adjuvant systemic treatment was not complete for 13 patients (12%). The treatment given according to the patient file did not correspond to the CRF in 7 patients (7%). 27 patients (24%) received chemotherapy only, 32 (29%) hormonal therapy only, and 23 (21%) a combination of hormonal and chemotherapy. Only 20 patients (18%) did not receive any adjuvant systemic treatment.

4. Discussion

EORTC 22922-10925 trial investigates the impact of elective irradiation of the internal mammary and medial supraclavicular lymph node chain on long-term survival for patients with localised breast cancer stage I-III with medially or centrally located tumours and/or axillary lymph node invasion after lumpectomy and axillary node dissection or modified radical mastectomy. To guarantee the accrual of a large number of patients within an acceptable period of time, the participation of a large number of radiotherapy departments is necessary. Therefore, treatment set-up guidelines in the protocol were not very strictly defined. A simple treatment technique was suggested, but more complex treatment set-up techniques were also allowed. At the time of activation of the protocol, a QA committee was formed in order to initiate the necessary procedures to guarantee the quality of the data by limiting the inter-institutional variability and by detecting potential systematic protocol deviations which may be due to possible ambiguities in the protocol guidelines. The dummy run procedure has already shown a significant number of minor deviations from protocol guidelines [27]. In this paper, the results from the individual case review procedure are described. Both eligibility as well as protocol compliance was evaluated for 3 patients randomised to each of the two treatment arms.

4.1. Eligibility

All 111 patients were eligible for participation in this trial according to the inclusion and exclusion criteria defined in the protocol. Concerning the details on surgery, only one item in 1 patient was not correctly specified. In 4 patients, less important deviations or missing information were noted. For pathology data, a total of 20 deviations in 18 patients was found. One centre forgot to send evaluation data on this item for all their patients, with missing data on four items in a further 3 patients. We conclude, therefore, that compliance to the eligibility criteria of the trial and participation to the QA programme was excellent in the majority of the patients of the 19 centres who participated in the ICR. The 26 centres that did not participate included only 23% of all randomised patients. Nevertheless, their participation to the QA should be encouraged to cover as much as possible the smaller centres with less experience in the participation of clinical trials. Remarkably, all patients from seven of the centres were treated with a breast-conserving approach, which might suggest a kind of patient selection by those participants.

4.2. Protocol compliance

The number of major protocol deviations encountered was very limited. In the early phase of the trial, 2 patients randomised to arm 1 received radiotherapy to the supraclavicular area. After having highlighted this point during meetings of the EORTC radiotherapy group and in the list of recommendations sent to all participants, this was not encountered again. The dose calculated at the IM point was in the vast majority of the cases according to the randomisation arm: at least 85% of the prescribed dose in all but 1 of the patients randomised to arm 2 and in only 4 patients randomised to arm 1, was it more than 50% of the prescribed dose of 50 Gy in 25 fractions. Depending on the individual patient's anatomy, but especially when the thoracic wall was treated with one or more electron beams, it was difficult to avoid giving part of the dose also to the IM lymph node area for patients randomised into arm 1. Suggestions made to the participants to decrease the dose at the IM point included an adaptation of the field set-up and the local use of tissue equivalent material.

Only three of the participating centres irradiated the IM-MS lymph node region without the use of individual anatomical information. They all followed strictly the standard treatment set-up technique as described in the trial guidelines. Centres using customised anatomical localisation of the internal mammary nodes were encouraged to adapt the electron beam energy, the prescription depth for the photon beam and the relative beam weights according to the patient's anatomy when using the standard technique. Five of the participating

institutes used more complex and highly individualised treatment set-ups techniques developed specifically for this indication.

A rather typical feature when using the standard technique for IM-MS irradiation together with breast/chest wall irradiation is the matching of the field junctions. Most of the institutes using the standard technique individualise the choice of an exact match or an overlap based on patient- and tumour-related characteristics. A modification of the standard technique was used in 11 cases, resulting in an improved dose distribution at the field junction [20]. Remarkably, only a minority of the participants clearly delineated the target volumes. Even with the actual CT-based patient anatomy clearly visible on the screen of the TPS, the absence of delineated target volumes might hamper proper treatment prescription and evaluation. Therefore, when writing future protocols, more attention should be paid to the proper definition and delineation of target volumes. The simplest way might be to recommend a strict adherence to the ICRU guidelines, although discrepancies will always occur because of the different interpretation of the clinical data by different clinicians.

In this individual case review, a high compliance to the patient-inclusion criteria was found. A number of potentially systematic deviations from the protocol or from general guidelines, which might lead to a false-negative result of the end point, were nevertheless detected. This may indicate that even in protocols where, for reasons of accrual, the radiotherapy guidelines are kept as simple as possible, a more precise prescription of the procedures may be necessary.

Only 19 of the 45 participating institutes completed the ICR. However, since the 19 participants are the ones with the highest accrual (77%), this can be judged as being of less importance. Moreover, by providing recommendations regularly to all participants, the ICR will have worked (like the dummy run) as oil spreading on the water. Both QA procedures were performed in the early phase of the trial, before a significant number of patients was accrued. This enabled the study coordinators and the QA committee to give recommendations for improvements to the participants individually as well as during the meetings of the EORTC Radiotherapy Group. A summary of all recommendations was soon sent to all participants and already in May 1999, less than 3 years after the start of the trial and before the accrual of one-third of the patients needed, a revision of the trial protocol was written and distributed. By doing so, participating institutes, including those which had not yet participated to the QA programme or did not actually start patient accrual, were encouraged to improve the compliance to the trial protocol and to refine the radiotherapy techniques used. This should lead to an improvement of the dose distribution of the radiotherapy of the IM-MS and to a decrease in the inter-institutional dose variation, thereby strengthening the reliability of the final trial results.

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