available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Quality assurance in breast cancer: EORTC experiences in the phase III trial on irradiation of the internal mammary nodes

Elena Musat[a,*], *Philip Poortmans*[b], *Walter Van den Bogaert*[c], *Henk Struikmans*[d], *Alain Fourquet*[e], *Harry Bartelink*[f], *Carine Kirkove*[g], *Volker Budach*[h], *Marianne Pierart*[a], *Laurence Collette*[a]

[a]EORTC, Avenue E. Mounierlaan, 83/11, 1200 Brussels, Belgium
[b]Dr. Bernard Verbeeten Institute, Tilburg, The Netherlands
[c]U.Z. Gasthuisberg, Leuven, Belgium
[d]Leids Medisch Centrum, Leiden, The Netherlands
[e]Radiotherapy, Institut Curie, Paris, France
[f]Radiotherapy, NCI-AVL, Amsterdam, The Netherlands
[g]Clinique St. Luc, Brussels, Belgium
[h]Klinikum Charite, Berlin, Germany

ARTICLE INFO

Article history:
Received 10 October 2006
Accepted 13 November 2006
Available online 19 January 2007

Keywords:
Breast cancer
Internal mammary lymph nodes
Radiotherapy
Randomised

ABSTRACT

The EORTC 22922/10925 trial randomly compares irradiation or no irradiation of the internal mammary and medio supraclavicular (IM-MS) nodes for stage I–III breast cancer. We report on the characteristics of 4004 participating patients, aspects of quality assurance and compliance to protocol treatment. The actual population has intermediate-risk disease: 51.8% stage II, 56% positive axillary nodes. The allocated treatment was not followed in 3.2% in the IM-MS irradiation arm versus 2% in the no IM-MS irradiation arm. In the IM-MS arm, there were major deviations for dose in 0.8%, surgery-to-radiotherapy time interval in 3.9% and in overall treatment time in 0.9% cases. Major deviations were found in 7.9% patients in the IM-MS group and in 2% patients in the no IM-MS group. In the final trial analysis, a sensitivity analysis should evaluate the subgroup of patients receiving an optimal treatment to verify the robustness of the results and the true impact of IM-MS irradiation.

1. Introduction

The value of irradiating specific anatomical regions in breast cancer patients (such as chest irradiation after mastectomy for intermediate risk patients, tumour bed 'boost' after breast conserving therapy and regional lymph node treatment) in terms of efficacy and toxicity remains controversial. The EORTC Radiation Oncology and Breast Cancer Groups initiated several trials to investigate the value of irradiation of different target volumes. The EORTC 22922-10925 trial investigates the role of internal mammary and medial supraclavicular lymph node (IM-MS) irradiation. To ensure

* *Corresponding author:* Tel.: +32 2 774 16 81; fax: +32 2 772 38 10.
E-mail address: elena.musat@eortc.be (E. Musat).
URL: http://www.eortc.be (E. Musat).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.11.015

compliance with the protocol treatment, the study was subjected to a quality assurance programme that consisted of a dummy run and individual case reviews.[1,2] The final results of trial 22922-10925 will only become available in the next few years. We report here on the patient, tumour and treatment characteristics in this trial and we assess the compliance with the protocol treatment as treatment deviations may affect the overall outcome especially of the group randomised to IM-MS irradiation.

2. Methods

Between August 1996 and December 2003, 4004 women with unilateral breast cancer were enrolled in the study, after breast and axillary surgery. The trial's primary objective was to assess the impact of elective IM-MS lymph node irradiation on overall survival. The study size was calculated to provide 80% probability of detecting a 4% improvement from 75% to 79% in 10-year overall survival.

2.1. Eligibility

Women from 18 to 75 years old, with unilateral, operable breast cancer of clinical stage Tx, T0-T3, N0-N2, M0 (UICC 1992 TNM classification) assessed prior to any systemic treatment were eligible. The primary tumour had to be located either in the medial or the central quadrant (irrespective of the axillary status) or externally in the presence of axillary node invasion. Signed informed consent was required before patient randomisation in accordance with national and local requirements. Patients were stratified according to institution, menopausal status, tumour location, pathological T and N stage, and sequence of radiotherapy and chemotherapy treatment.

2.2. Protocol treatment

Before entry, patients had undergone either mastectomy or breast conserving surgery, with axillary surgery. A 'sentinel node' procedure without further complete axillary surgery was allowed when the sentinel node was proved to be negative.

Irradiation of the IM-MS field had to be done using mixed beams at the recommended doses of 26 Gy of photons with a maximum of 10 MV energy and 24 Gy electrons with 12–14 MeV beam energy. This gave a total dose of 50 Gy over a 5-week period, with 2 Gy per fraction (in 5 fractions per week) to be delivered at the International Commission on Radiation Units and Measurements (ICRU) reference point. Splitting the IM-MS field in two and treating the medial supraclavicular field with photons only was allowed.

The choice of an additional 'boost' after breast conserving therapy was left to the discretion of the local investigator and the total dose (to the breast including the boost dose) was recorded. Thoracic wall irradiation after mastectomy or axillary field irradiation was left to the choice of the investigator according to local procedures.

The surgery-to-randomisation time interval had to be a maximum of 8 weeks. The surgery-to-radiotherapy time interval had to be 8 weeks (not exceeding 11 weeks) without adjuvant chemotherapy and 6 months (not exceeding 8 months) when adjuvant chemotherapy was given. The overall treatment time had to be a maximum of 6 weeks, not exceeding 7 weeks.

2.3. Definition of compliance parameters

Non-compliance to the protocol consists of: patient ineligibility, refusal of the allocated treatment, withdrawal of the informed consent, missing treatment information. In both arms, partial volume IM-MS irradiation is considered as both *protocol non-compliance* and *treatment deviation*.

The recommended treatment, the acceptable variation and the *treatment deviations* for the total radiotherapy dose, volume and timing are described in Table 1. Variation in planning methods between centres and the individualisation of the treatment to the patient anatomy are not considered as deviations.

3. Results

This report includes all randomised patients (2002 in the no IM-MS arm and 2002 in the IM-MS arm). Fifteen patients in the no IM-MS radiation group and 16 patients in the IM-MS radiation group were ineligible. The reasons for ineligibility were: inadequate tumour size (4 patients), node category (1), tumour location (6) histology (1) and presence of either distant metastases (3), concurrent disease (16) or other malignancy (1). Treatment data were not available for seven patients.

3.1. Patient and tumour characteristics

The patient and tumour characteristics were well balanced between the two groups (Table 2). The median age was 54

Table 1 – Definition of treatment compliance

IM-MS arm
Recommended treatment
Dose 48–53 Gy (ICRU 50)
Treated volume IM-MS
Surgery-to-radiotherapy time interval
Without adjuvant chemotherapy ⩽8 weeks
With adjuvant chemotherapy ⩽6 months
Overall treatment time ⩽45 days
Acceptable treatment variation
Dose 45–47 Gy and 54–55 Gy
Surgery-to-radiotherapy time interval
Without adjuvant chemotherapy 9–11 weeks
With adjuvant chemotherapy 6–8 months
Overall treatment time 46–48 days
Treatment deviations
Dose <45 Gy or >55 Gy
Treated volume
Only MS irradiation
No IM-MS irradiation
Surgery-to-radiotherapy time interval
Without adjuvant chemotherapy ⩾12 weeks
With adjuvant chemotherapy ⩾9 months
Overall treatment time ⩾49 days

Table 2 – Patient and tumour characteristics

Characteristic	No IM-MS N = 2002	IM-MS N = 2002
Median age	54.2	54.1
Range	22–75.9	19–75.9
Menopausal status N (%)		
Pre-menopausal	670 (33.5%)	678 (33.8%)
Peri-menopausal	153 (7.6%)	140 (7.0%)
Post-menopausal	1112 (55.6%)	1122 (56.0%)
Artificial menopause	66 (3.3%)	62 (3.0%)
Unknown	1 (0.0%)	
Type of breast surgery N (%)		
Mastectomy	479 (24%)	476 (23.8%)
BCT	1522 (76%)	1526 (76.2%)
Unknown	1 (0.0%)	
Number of examined axillary nodes N (%)		
<11	623 (31.1%)	557 (27.8%)
11–15	640 (32.0%)	702 (35.0%)
>15	735 (36.7%)	739 (36.9%)
Unknown	9 (0.4%)	5 (0.1%)
Stage (6th UICC classification) N (%)		
Stage I	664 (33.2%)	679 (34.0%)
Stage IIa	660 (33.0%)	635 (31.8%)
Stage IIb	385 (19.2%)	392 (19.6%)
Stage III	281 (14.0%)	285 (14.2%)
Unknown	12 (0.6%)	11 (0.6%)
Oestrogen and progesterone N (%)		
ER+ PR+	1091 (54.4%)	1088 (54.4%)
ER+ (PR- or unknown)	369 (18.4%)	395 (19.8%)
PR+ (ER- or unknown)	87 (4.4%)	70 (3.4%)
ER- PR-	335 (16.8%)	314 (15.6%)
Unknown	120 (6.0%)	135 (6.8%)

years (range 19–76). There were 41% peri- or pre-menopausal and 56% post-menopausal women. In total, 60.5% of the patients presented with pathological stage T1, 35.7% with pT2, 3.6% with pT3 and the status was unknown in 0.5%. 55.3% of patients presented with positive axillary nodes (Fig. 1) with a median of two (range, 1–59) positive nodes. According to UICC's 6th TNM classification, 33.5% of the patients presented with Stage I, 32.4% with Stage IIA, 19.4% with Stage IIB, 14% with Stage IIIA and stage was unknown in 0.6%.

3.2. *Loco-regional treatment*

The surgery-to-randomisation time interval of 8 weeks was respected in 99.7% of the patients. Twenty four percent of cases underwent mastectomy and 76% had breast-conserving surgery. Almost all patients (99.4%) having breast-conserving surgery received standard radiotherapy to the breast volume with a boost being added in 85% of these patients with a median total dose of 64 Gy (range, 20–76). The boost prescription was independent of patient age (Fig. 2). Among the patients who underwent mastectomy, 73% received thoracic wall irradiation and boost to the scar was added in 9% of these patients. The median dose to the thoracic wall after mastectomy was 50 Gy (range, 16–84).

In a large majority of the patients axillary surgery consisted of partial or complete dissection. A sentinel node procedure alone was performed in only 7% of patients. The median number of axillary nodes examined was 14 (range, 0–63). Axillary irradiation with a median dose of 50 Gy (range, 10–62) was given to 7% of patients who did not undergo a complete axillary dissection and who had positive lymph nodes. This depended on the procedures of the participating centre.

The characteristics of the radiotherapy given to the breast, chest and regional lymph node areas are summarised in Table 3. The characteristics of breast or chest and axillary nodes radiotherapy treatment are well balanced between the two arms. These include not only the total dose and treated volume but also the reported time intervals and delays.

3.3. *Adjuvant treatment*

Eighty four percent of the patients received adjuvant treatment with 25% receiving chemotherapy, 29% hormonotherapy and 30% both. The systemic adjuvant therapy, given according to the local rules, was well balanced between the two arms and was adapted to menopausal status, positive axillary nodes and oestrogens receptor status (Table 4).

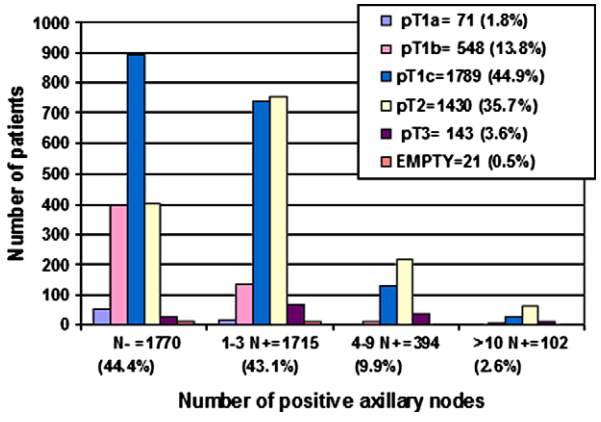

Fig. 1 – Pathological tumour size by number of positive axillary nodes.

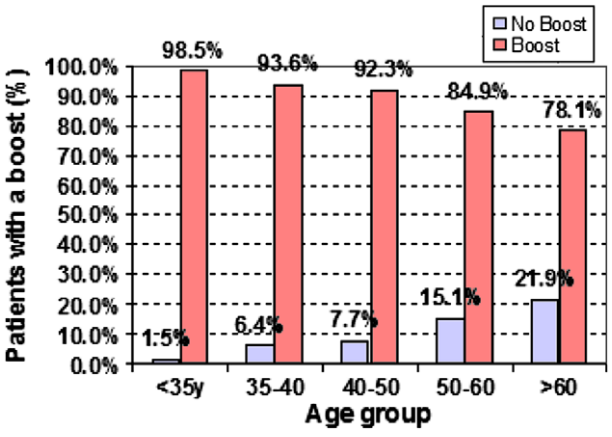

Fig. 2 – Boost prescription in BCT subgroup (3039 patients).

Table 3 – Radiotherapy volume and delivered dose

N (%)	No IM-MS Radiation group n = 2002	IM-MS Radiation group n = 2002
If BCT	1522	1525
Breast radiation	1515 (99.4)	1515 (99.4)
Total breast dose (Gy)	64 (22–76)	64 (20–76)
Number of fractions	30 (11–50)	30 (10–66)
Boost	1285 (84.4)	1308 (85.8)
If mastectomy	479	475
Chest wall radiation	349 (73.2)	349 (73.2)
Total chest wall dose (Gy)	50 (16–84)	50 (40–76)
Number of fractions	25 (13–39)	25 (19–38)
Boost	49 (10.2)	36 (7.6)
Axillary radiation	136 (6.8)	158 (7.8)
Total axillary dose (Gy)	50 (10–62)	50 (15–61)
Number of fractions	25 (5–34)	25 (1–32)
IM-MS radiation	20 (1.0)	1936 (96.7)
MS only radiation	21 (1.0)	8 (0.4)
No IM-MS radiation	1956 (97.7)	56 (2.8)
Unknown	5 (0.2)	2 (0.1)

Table 4 – Adjuvant systemic treatment by nodal and receptor status

Subgroup	No./total no. in the subgroup (%)	
	Pre-menopausal	Post-menopausal
Node-negative, ER-	N = 167	N = 181
None	41 (25%)	64 (35%)
Chemotherapy	107 (64%)	97 (54%)
Hormonal therapy	8 (5%)	17 (9%)
Both	11 (7%)	3 (2%)
Node-negative, ER+	N = 447	N = 889
None	169 (38%)	248 (28%)
Chemotherapy	36 (8%)	14 (2%)
Hormonal therapy	144 (32%)	522 (59%)
Both	98 (22%)	105 (12%)
Node-positive, ER-	N = 267	N = 231
None	0	11 (5%)
Chemotherapy	226 (85%)	174 (75%)
Hormonal therapy	2 (1%)	20 (9%)
Both	39 (15%)	26 (11%)
Node-positive, ER+	N = 667	N = 939
None	6 (1%)	6 (1%)
Chemotherapy	207 (31%)	58 (6%)
Hormonal therapy	48 (7%)	376 (40%)
Both	406 (61%)	499 (53%)

Patients with unknown receptor status have not been included in this table.

3.4. *Compliance to the randomised treatment*

The majority of the patients were treated according to the randomised arm (Table 3). Two percent of the patients who were not treated according to the randomisation arm belonged to the no IM-MS arm and 3.2% to the IM-MS arm. In the no IM-MS irradiation group, 20 patients received radiotherapy to the IM-MS chain and 21 received radiotherapy only to the MS volume. In the IM-MS irradiation group, eight patients received radiotherapy to the MS volume alone instead of the complete IM-MS chain and 56 patients did not receive planned IM-MS irradiation at all. The reasons for not receiving IM-MS treatment in these 56 patients were: treatment arm refusal (23), trial refusal (9), irradiation was not possible due to anatomical or technical reasons or to concurrent disease (24), and for three patients the reason was unknown.

3.5. *IM-MS radiation treatment (1936 patients)*

Details of IM-MS treatment compliance are reported in Table 5. Fifteen patients have deviations in the total delivered dose. The IM-MS treatment fulfilled the protocol recommendation with regards to the electron or photon energy in 67.8% of the patients. Treatment individualisation was reported in 623 cases and consisted of alternative techniques that used CT-based radiotherapy (494), variations in the recommended energy (679) and different electrons/photons ratio (360). The MS field was irradiated only with photons in 59% of patients, with a mean energy of 6 MV, which was allowed by the protocol.

There were major deviations in 3.9% of patients with regards to the surgery-to-radiotherapy time interval: 59 patients, without adjuvant chemotherapy, exceeded the allowed 11 weeks and amongst patients receiving adjuvant chemotherapy, 18 exceeded the maximum of 8 months allowed by the protocol. The overall irradiation duration was in accordance with the protocol with a median of 36 days (range, 0–60) in all but 19 patients (0.9%). All deviations in overall treatment time occurred in patients who had also other major treatment deviations. Overall the non-compliant patients in the experimental IM-MS radiotherapy arm were of lower risk than non-compliant patients in the observation arm.

4. Discussion and literature review

According to surgical studies the rate of involvement of the internal mammary lymph nodes varies between 5% and 45%.[3,4] The risk of involvement of the IM lymph node chain increases when axillary nodes are positive, with increasing tumour size, in tumours located in the medial or central part of the breast, when the tumour extends into peri-tumoural vessels and in younger patients.[5] Based on the risk of loco-regional recurrences, a general consensus emerges that regional lymph nodes should be treated when more than three axillary nodes are involved. However, whether to irradiate when 1–3 axillary nodes are involved, as well as which regions to irradiate, are still points to be debated. Published evidence is lacking as regards the efficacy of IM-MS irradiation in patients at risk of loco-regional relapse. Retrospective studies have produced conflicting results due to multiple biases.[6–8] One small prospective, non-randomised study of IM-MS irradiation versus no irradiation, in high risk breast cancer patients reports a benefit in terms of loco-regional control and disease-free survival at 6 years.[9] Another small randomised study reported only early toxicity data thus far.[10]

Table 5 – Compliance with the IM-MS treatment arm (treated patients N = 1936)

IM-MS irradiation	Mean (range)	Number of patients (%)		
		Recommended	Acceptable	Deviations
Total dose	50 (2–56) Gy	1874 (93.5)	52 (2.7)	15 (0.8)
Surgery-to-radiotherapy time interval	64 (16–411) days	1433 (71.8)	422 (21.1)	77 (3.9)
Without adjuvant chemotherapy	49 (16–193)	616 (30.9)	205 (10.1)	59 (3.0)
With adjuvant chemotherapy	139 (16–411)	817 (40.9)	221 (11.0)	18 (0.9)
Overall treatment time	36 (1–60) days	1893 (95.0)	21 (1.0)	19 (0.9)

The EORTC study will first be able to provide level I evidence of the specific contribution of IM-MS irradiation to long term disease control and survival and will document the long-term treatment toxicity. Compliance to the eligibility criteria and protocol guidelines was good. This study accrued patients at a lower-risk for IM-MS subclinical metastasis than initially anticipated. Considering that the absolute survival benefit of additional IM-MS irradiation may be lower in study population, it is quite important to ensure and report on quality of radiotherapy. Overall we observed 8.8% major deviations in 7.9% in the IM-MS treatment group of the patients and only 2% occurred in 2% of the patients in the no IM-MS group. This can be explained by the higher number of parameters evaluated in the IM-MS group. In daily clinical practice, this imbalance is also increased by a suboptimal dose distribution in the IM-MS region which may deviate from the prescribed dose.[1,2]

The recent EBCTCG meta-analysis brought strong evidence that radiotherapy improves overall survival in both post-mastectomy and breast conserving therapy as a consequence of better loco-regional control. This supports previous meta-analyses of published data.[11,12] In post mastectomy patients, large randomised trials using correct radiotherapy techniques that are nevertheless considered nowadays as suboptimal, have shown that survival is improved.[13,14] Newer techniques, that are currently being introduced, decreased the risk of late cardiac mortality that in older trials partially obscured the beneficial effects of radiotherapy.[15,16] The EBCTCG analysis by irradiated volume failed to identify which part of the target volume caused the favourable effects on survival.[17] Consequently, until the EORTC trial reports efficacy data, uncertainties remain about the contribution of the specific components of the IM-MS irradiated volume in the management of patients with low- and intermediate-risk breast cancer.

4.1. *Total dose and treated volume*

The total dose and the irradiated volume remain the most important factors influencing the effects of breast cancer radiotherapy. According to Denham,[18] 40 to 60 Gy offers the greatest chance to control microscopic residual disease with acceptable toxicity. An optimal treatment plan further requires that the dose homogeneity within the treated volume ranges between 95% to 107% of the prescribed dose.[19]

Two analyses investigated the optimal radiotherapy treatment for breast cancer. Van de Steene *et al.*[20] analyses of published data of radiotherapy in stage I–II breast cancer concluded that after a long follow-up overall survival is increased in large trials using optimal radiotherapy. The meta-analysis of 36 randomised trials by Gebsky *et al.*[21] addressed the specific issue of the optimal biological equivalent dose to the optimal target volume for breast cancer, in trials that included mainly post-mastectomy patients. At 10 years, based on 13 available data comparisons, they were able to show that trials using optimal radiotherapy had a 6.4% absolute increase in survival when compared with suboptimal radiotherapy. The authors also analysed the previously published 10 years EBCTCG results including 23 randomised trials. They observed a survival benefit even at 5 and 10 years associated with optimal radiotherapy compared to trials using suboptimal radiotherapy. These results suggest that optimal radiotherapy must be given to ensure the expected benefit.

We report an inappropriate treatment of the IM-MS target volume in 3.2% patients in the IM-MS irradiation arm and in 2% in the control arm. These deviations may impact on the long term results of the trial and should be taken into account when performing the final analysis. There was also a major deviation in the total dose in 15 patients of which 14 were under-treated (<45 Gy) and one over-treated (>55 Gy). These deviations occurred in so few patients that it is not expected to have an impact on the study results. We also report smaller variations by 5% to 10% of the planned dose (45–49 Gy) in 53 cases. This dose range can still be considered as sufficient[18,21] and thus was judged as acceptable.

4.2. *Surgery-to-radiotherapy time interval*

The impact of the time interval between surgery and initiation of loco-regional radiotherapy in daily clinical practice has raised concern about its potential impact on local control and survival. Moreover, the duration of adjuvant chemotherapy has further increased this time interval.[22] For ethical reasons, a randomised comparison of shorter versus longer time intervals between surgery and radiotherapy cannot be envisaged, but several retrospective studies have attempted to address this question. Huang *et al.*[23] conducted a systematic review of 21 observational studies published in the literature. The results suggest that a delay of greater than 8 weeks between surgery and the initiation of radiotherapy increases the risk of loco-regional recurrence. Survival data has been reported by Hershman *et al.* on 13,906 women of 65 years and older with early breast cancer with no adjuvant chemotherapy registered to the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.[24] There were 3% of pa-

tients receiving radiotherapy after a 12 week time interval and these delays were associated with poor survival at 5 years of follow-up. The authors couldn't identify whether this association was due to confounding factors, such as poor health behaviours. Retrospective studies in patients receiving adjuvant chemotherapy are often biased and give contradictory results. A French retrospective study[25] reported the 9-year follow-up of 1831 early breast cancer patients with positive axillary nodes treated with breast conserving therapy. No effect on local relapse was observed when the radiotherapy was delayed to allow for adjuvant chemotherapy. To date, the question of the sequence of radiotherapy and chemotherapy after breast conserving surgery was addressed by only one prospective randomised trial on 244 patients.[26] The patients were randomised to receive either 12 weeks of chemotherapy or radiotherapy first. With a median follow-up of 11.25 years, this study showed no significant difference in loco-regional, distant recurrence or overall survival between the two arms. Unfortunately, the study is not sufficiently powered to rule out any differences with certainty. A population-based study[27] conducted in Yorkshire (UK) on 7800 patients with breast cancer treated with breast conserving therapy showed a trend towards worse survival whenever the time interval between surgery and radiotherapy exceeded 9 weeks, and a significantly worse survival when the delay was greater than 20 weeks, after adjustment for multiple demographic and clinical factors and the use of adjuvant chemotherapy. Therefore, the effect of prolonging the surgery-to-radiotherapy interval awaits confirmation from larger data sets. This effect should also be analysed in relation to the total delivered dose and, in breast conserving surgery, with the tumour resection margin status. Both factors can have a much larger impact than the possible negative effect of delaying the delivery of radiotherapy.[28]

Until proven otherwise, we followed the protocol guidelines and considered that surgery-to-radiotherapy intervals longer than 12 weeks in the absence of adjuvant chemotherapy[29] and longer than 8 months with adjuvant chemotherapy are unacceptable. In our study we found 3.9% of such unacceptable deviations in the surgery-to-radiotherapy time interval. We report also 0.9% deviations in the overall treatment time and but these occurred in patients who had also other major treatment deviations.

4.3. *Reporting of the results*

A special problem of reporting results is to evaluate treatment efficacy according to adherence to treatment after randomisation. Levitt at al. have shown how introduction of minor errors and reclassifying small numbers of patients may substantially modify the conclusion of a clinical trial especially when a strict 5% or less significance level is used.[30] We found 8.8% major deviations in 7.9% of patients treated in the IM-MS group compared to 2% in the no IM-MS group. It is important that primary analysis in this trial to be performed on an intent-to-treat basis. Published data suggest that the patients should be analysed by optimal and suboptimal treatment delivery as subjective factor.[21] In the final analysis of this study the subgroup of patients receiving an optimal radiotherapy should be evaluated as a sensitivity analysis to assess the robustness of the results and to enhance the relevance of the delivery of an optimal treatment to strengthen its implementation in clinical practice.

Conflict of interest statement

None declared.

Acknowledgement

We gratefully acknowledge all participating investigators and patients. The 'Vlaamse Liga Tegen Kanker' supported this work through the Emmanuel van der Schueren Fellowship for Quality Assurance in radiotherapy.

This publication was supported by grants number 5U10 CA11488-34, 5U10 CA11488-35, 5U10 CA11488-36 from the US National Cancer Institute (Bethesda, Maryland, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

REFERENCES

1. Poortmans P, Kouloulias V, Venselaar J, et al. 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. *Eur J Cancer* 2003;**39**(14):2035–42.
2. Poortmans P, Venselaar J, Struikmans H, et al. The potential impact of treatment variations on the results of radiotherapy of the internal mammary lymph node chain: a quality-assurance report on the dummy run of EORTC Phase III randomized trial 22922/10925 in Stage I–III breast cancer(1). *Int J Radiat Oncol Biol Phys* 2001;**49**(5):399–408.
3. Farrus B, Vidal-Sicart S, Velasco M, et al. Incidence of internal mammary node metastases after a sentinel lymph node technique in breast cancer and its implication in the radiotherapy plan. *Int J Radiat Oncol Biol Phys* 2004;**60**(3):715–21.
4. Galimberti V, Veronesi P, Arnone P, et al. Stage migration after biopsy of internal mammary chain lymph nodes in breast cancerpatients. *Ann Surg Oncol* 2002;**9**(9):924–8.
5. Lohrisch C, Jackson J, Jones A, Mates D, Olivotto IA. Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. *J Clin Oncol* 2000;**18**(15):2828–35.
6. Grabenbauer GG. Internal mammary nodes in invasive breast carcinoma. To treat or not to treat? *Strahlenther Onkol* 2004;**180**(11):690–4.
7. Fowble B, Hanlon A, Freedman G, et al. Internal mammary node irradiation neither decreases distant metastases nor improves survival in stage I and II breast cancer. *Int J Radiat Oncol Biol Phys* 2000;**47**(4):883–94.
8. Obedian E, Haffty BG. Internal mammary nodal irradiation in conservatively-managed breast cancer patients: Is there a benefit? *Int J Radiat Oncol Biol Phys* 1999;**44**(5):997–1003.
9. Stemmer SM, Rizel S, Hardan I, et al. The role of irradiation of the internal mammary lymph nodes in high-risk stage II to IIIA breast cancer patients after high-dose chemotherapy: a prospective sequential nonrandomized study. *J Clin Oncol* 2003;**21**(14):2713–8.

10. Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: Results of a randomized trial. *Radiother Oncol* 1995;**36**(3):172–6.
11. Levitt SH, Aeppli DM, Nierengarten ME. The impact of radiation on early breast carcinoma survival. *A Bayesian analysis. Cancer* 1996;**78**(5):1035–42.
12. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000;**18**(6):1220–9.
13. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;**97**(2):116–26.
14. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: Long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006;**24**(15): 2268–75.
15. Senkus-Konefka E, Jassem J. Complications of breast-cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2006;**18**(3):229–35.
16. EBCTCG. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000;**355**(9217):1757–70.
17. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2005;**366**(9503):2087–106.
18. Denham JW. The radiation dose-response relationship for control of primary breast cancer. *Radiother Oncol* 1986;**7**(2):107–23.
19. ICRU Report 50 - 62. Prescribing, recording, and reporting photon beam therapy. Bethesda, Maryland, USA; 1993, 1999.
20. Van de Steene J, Vinh-Hung V, Cutuli B, Storme G. Adjuvant radiotherapy for breast cancer: Effects of longer follow-up. *Radiother Oncol* 2004;**72**(1):35–43.
21. Gebski V, Lagleva M, Keech A, Simes J, Langlands AO. Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006;**98**(1):26–38.
22. Bowden SJ, Fernando IN, Burton A. Delaying radiotherapy for the delivery of adjuvant chemotherapy in the combined modality treatment of early breast cancer: Is it disadvantageous and could combined treatment be the answer? *Clin Oncol (R Coll Radiol)* 2006;**18**(3):247–56.
23. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol* 2003;**21**(3):555–63.
24. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI. Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int J Radiat Oncol Biol Phys* 2006;**65**(5):1353–60.
25. Benchalal M, Le Prise E, de Lafontan B, et al. Influence of the time between surgery and radiotherapy on local recurrence in patients with lymph node-positive, early-stage, invasive breast carcinoma undergoing breast-conserving surgery: Results of the French Adjuvant Study Group. *Cancer* 2005;**104**(2):240–50.
26. Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: Updated results of a prospective randomized trial. *J Clin Oncol* 2005;**23**(9):1934–40.
27. Mikeljevic JS, Haward R, Johnston C, et al. Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer* 2004;**90**(7):1343–8.
28. Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N Engl J Med* 1996;**334**(21):1356–61.
29. Jobsen JJ, van der Palen J, Ong F, Meerwaldt JH. Timing of radiotherapy and survival benefit in breast cancer. *Breast Cancer Res Treat* 2006;**99**(3):289–94.
30. Levitt SH, Aeppli DM, Potish RA, Lee CK, Nierengarten ME. Influences on inferences. Effect of errors in data on statistical evaluation. *Cancer* 1993;**72**(7):2075–82.