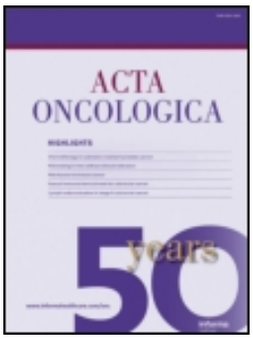

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ORIGINAL ARTICLE

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

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Abstract

Introduction. The EORTC 22922/10925 trial investigated the potential survival benefit and toxicity of elective irradiation of the internal mammary and medial supraclavicular (IM-MS) nodes Accrual completed in January 2004 and first results are expected in 2012. We present the toxicity reported until year 3 after treatment. *Patients and methods.* At each visit, toxicity was reported but severity was not graded routinely. Toxicity rates and performance status (PS) changes at three years were compared by χ^2 tests and logistic regression models in all the 3 866 of 4 004 patients eligible to the trial who received the allocated treatment. *Results.* Only lung (fibrosis; dyspnoea; pneumonitis; any lung toxicities) (4.3% vs. 1.3%; $p < 0.0001$) but not cardiac toxicity (0.3% vs. 0.4%; $p = 0.55$) significantly increased with IM-MS treatment. No significant worsening of the PS was observed ($p = 0.79$), suggesting that treatment-related toxicity does not impair patient's daily activities. *Conclusions.* IM-MS irradiation seems well tolerated and does not significantly impair WHO PS at three years. A follow-up period of at least 10 years is needed to determine whether cardiac toxicity is increased after radiotherapy.

Many studies on lymphatic drainage of the breast confirmed the importance of the Internal Mammary (IM) basin as a second draining route in breast cancer [1–3]. The incidence of lymph node (LN) metastasis of the internal mammary and medial supraclavicular (IM-MS) lymph node chain ranges between 4–9% in axillary node negative patients and 16–52% for axillary node positive patients [4–6]. A recent analysis of 2 269 Chinese breast cancer patients examined the subpopulation with high risk of internal mammary lymph nodes metastasis [7]. They described incidences of IM metastasis in more than 20% of patients with the following conditions: (1) patients with four or more positive axillary LN, (2) Patients with medial tumour and positive axillary LN, (3) Patients with T3 tumour and younger than 35 years, (4) Patients with T2 tumour and positive axillary LN and (5) Patients with T2 tumour and medial tumour.

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IM lymph node dissection was therefore performed in a number of institutes in the 1950s and 1960s. This radical surgical procedure was abandoned in the 1970s because several studies showed that this approach did not improve survival [8]. How to interpret today the clinical relevance of the historic rates of IM lymph node involvement in view of the greater proportion of screen-detected cancers, the improved imaging for detection of IM-nodes involvement, the increasing use of adjuvant systemic therapy and the newer radiotherapy techniques is unclear.

The interest for an elective treatment of the IM-MS nodes was renewed after the publication of several prospective randomised trials that demonstrated a favourable outcome after elective loco-regional irradiation [9,10]. In operable breast cancer however, the role of regional radiotherapy of the IM-MS chain remains controversial [8] since definite evidence supporting that elective irradiation of especially the IM nodes improves overall survival is lacking. Whether the expected benefit of elective irradiation of the IM-MS nodes counterbalances a possible increase of the risk of late toxicity is still unresolved [5].

The Radiation Oncology Group and the Breast Cancer Group of the European Organisation for Research and Treatment of Cancer (EORTC) therefore initiated a large randomised phase III multicentre trial (EORTC 22922/10925) assessing the impact of elective IM-MS lymph node irradiation on overall survival in patients with localised, stage I–III, breast cancer with medially or centrally located tumours and/or axillary lymph node invasion. This trial that recruited patients between July 1996 and January 2004, enrolled 4 004 women with unilateral breast cancer after breast and axillary surgery. The first analysis of the primary endpoint, overall survival at 10 years, will be performed about eight years after recruitment of the last patient, which is expected to be in 2012. Extensive reviews on the study population [11], on the radiotherapy techniques [12] as well as on the quality assurance program [13–15] have already been published.

We present here the toxicity reported up to three years after treatment as well as the change in WHO performance status (PS) between entry and year 3 post-treatment.

Patients and methods

Radiotherapy protocol

The prescribed dose was 50 Gy in 25 fractions of 2 Gy; 26 Gy was delivered with photons (minimum energy of Co-60 and maximum energy of 10 MV), and 24 Gy was delivered with electrons. To enable many radiotherapy institutes to participate in the trial and to accrue a large and representative sample of patients, a standard treatment technique with one anterior field for the IM-MS irradiation was recommended. The IM-MS lymph node area had to be treated with mixed photon and electron beams matched to the tangential field borders of the breast or thoracic wall (which could alternatively be treated with a direct electron field). Several institutes had developed specific irradiation techniques in this indication [12]. These more complex treatment set-ups were accepted in the trial, provided that they took into account the individual localisation of the internal mammary nodes [12,13].

The defined organs at risk were the lungs and the heart. No specific constraints were however defined in the protocol as the irradiated lung and heart volumes were considered as limited by the use of the mixed beam technique.

This study was subjected to an intensive quality assurance programme consisting of a dummy run and individual case review. The results of this procedure were already previously reported [11–15].

The protocol contained no guidelines which patients were to receive adjuvant treatment (hormonotherapy, chemotherapy).

Data collection

At the time of randomisation, data on WHO performance status (PS), tumour characteristics, number of positive axillary nodes and on adjuvant systemic treatment were collected for each patient. The following details concerning the radiotherapy were collected after completion of treatment: duration and interruption of radiotherapy, total dose, number of fractions and the technique used for IM-MS chain treatment. Yearly follow-up visit documented PS, presence of lung fibrosis, presence of cardiac fibrosis, presence of other toxicity and evidence of cardiac disease. Other toxicities and cardiac disease were to be detailed in free text.

Thoracic x-ray was obtained as a part of the yearly loco-regional evaluation in the protocol. Ejection fraction study was optional.

Statistical methods

The analysis was conducted in the per protocol population of patients who were eligible to the protocol and followed the randomly allocated IM-MS treatment policy. Patients with partial IM-MS irradiation were also excluded.

The percentage of patients with any toxicity reported in the first three years after treatment was compared between the two treatment arms by means of χ^2 tests. The events reported as free text were also grouped by category for descriptive purposes. The rates of individual events related to "lung toxicity" as well as the rates of any lung-related toxicity, the rates of cardiac disease, cardiac fibrosis and those of any skin-related toxicities were also formally compared by means of χ^2 tests between the treatment groups. To adjust the risk of false positive findings for the multiplicity of the tests, a nominal significance level of 0.01 was used.

Furthermore, changes in WHO performance status between randomisation and year 3 of the follow-up were assessed as no change, improvement or worsening. To avoid confounding the worsening of the PS related by the deterioration due to progressive disease, patients with disease progression reported within three years of entry on study were excluded from the analysis. Because patients with WHO PS of 0 at entry could not improve their performance status, we studied the probability of PS deterioration. Univariate and multivariate logistic regression models were used to assess the impact of treatment arm (IM-MS vs. no IM-MS), laterality of the breast cancer (left vs. right), adjuvant hormonotherapy (yes vs. none reported), neo-adjuvant chemotherapy (yes vs. no), age (<45 years vs. 45-<55 years vs. 55-<65 vs. ≥65 y), type of surgery (lumpectomy vs. mastectomy), tumour size (in centimetres), pathological axillary nodal status (pN+ vs. pN0), oestrogen and progesterone receptor status (positive vs. negative) and menopausal status (post-menopausal/artificial menopause vs. pre-menopausal) as possible predictors of the worsening of the PS. Statistical significance in these models was set at 5%.

Furthermore, we assessed the correlation between the presence of toxicity and the deterioration of the performance status using univariate logistic regression models as above mentioned.

Because of the very large sample size, the statistical power is very high and statistical significance may not necessarily indicate clinically meaningful differences.

Results

We report on the prospectively collected data from 3 866 of the 4 004 patients randomised (97%) in the IM-MS EORTC study 22922/10925 who were eligible and followed the allocated treatment policy (no IM-MS irradiation: N = 1944 vs. IM-MS irradiation: N = 1922). Complete follow-up documentation up to year 3 was available for 95.3% of the

Table I. Patient characteristics.

Per protocol population		
	Treatment	
	No IM-MS (N=1944)	IM-MS (N=1922)
Age (years)		
Median	54.0	54.0
Range	22.0 - 75.0	19.0 - 75.0
< 45	346 (17.8)	354 (18.4)
45-<55	680 (35.0)	661 (34.4)
55-<65	582 (29.9)	579 (30.1)
>=65	336 (17.3)	328 (17.1)
Performance Status (PS)		
PS 0	1733 (89.1)	1725 (89.8)
PS 1	198 (10.2)	181 (9.4)
PS 2	7 (0.4)	5 (0.3)
Missing	6 (0.3)	11 (0.6)
Menopausal status		
Pre-menopausal	650 (33.4)	657 (34.2)
Peri-menopausal	151 (7.8)	133 (6.9)
Post menopausal	1080 (55.6)	1071 (55.7)
Artificial menopause	63 (3.2)	61 (3.2)
Type of breast surgery		
Mastectomy	447 (23.0)	454 (23.6)
Breast conserving	1497 (77.0)	1468 (76.4)
Pathological T *		
pT1	1180 (60.7)	1160 (60.4)
pT2	689 (35.4)	685 (35.6)
pT3	65 (3.3)	70 (3.6)
Missing	10 (0.5)	7 (0.4)
Pathological N (axilla)*		
pN0	877 (45.1)	855 (44.5)
pN1	848 (43.6)	822 (42.8)
pN2	182 (9.4)	188 (9.8)
pN3	37 (1.9)	57 (3.0)
Tumour stage*		
Stage I	658 (33.8)	654 (34.0)
Stage IIa	647 (33.3)	612 (31.8)
Stage IIb	376 (19.3)	374 (19.5)
Stage III	253 (13.0)	276 (14.4)
Missing	10 (0.5)	6 (0.3)
Combination of ER/PR status		
ER+, PR+	1066 (54.8)	1055 (54.9)
ER+, PR-/unknown	359 (18.5)	380 (19.8)
PG+, ER-/unknown	82 (4.2)	66 (3.4)
ER-, PR-	320 (16.5)	295 (15.3)
Missing	117 (6.0)	126 (6.6)
Adjuvant hormonal therapy		
None reported	775 (39.9)	786 (40.9)
yes	1169 (60.1)	1136 (59.1)
Adjvuant chemotherapy		
No chemotherapy	886 (45.6)	871 (45.3)
Adjuvant	243 (12.5)	242 (12.6)
Neo-adjuvant	815 (41.9)	809 (42.1)
Adjuvant treatment		
None	294 (15.1)	316 (16.4)
Chemotherapy	481 (24.7)	470 (24.5)
Hormonal therapy	592 (30.5)	555 (28.9)
Both	577 (29.7)	581 (30.2)

*Staging is according to UICC 1992
ER=Estrogen receptor, PR=progesterone receptor

patients. The characteristics of the patients included in this analysis are presented in Table I. At entry on study, 89.4% of the patients presented a WHO performance status of 0, 9.8% with WHO PS 1 and 12 patients had a WHO PS of 2 (0.3%), WHO PS was missing in 17 (0.4%). Further details on the total study population were previously published [11].

Toxicity within three years of treatment

The reported toxicity per treatment arm is summarised in Table II. Both study treatment arms were well tolerated with little toxicity: the most frequent reported toxicities were oedema (7.8% vs. 8.1%), skin fibrosis (8.3% vs. 8.5%), teleangectasia (1.5% vs. 2.3%) and lung fibrosis (0.9% vs. 2.8%) in the standard and the IM-MS arm, respectively.

There were no statistically significant differences between the two randomised groups in terms of cardiac fibrosis (0.3% vs. 0.4%; $p = 0.55$) nor in terms of presence of "cardiac disease" (1.4% vs. 1.6%; $p = 0.64$). Lung fibrosis (0.9% vs. 2.8%; $p < 0.0001$), dyspnoea (0.1% vs. 0.7%; $p = 0.0007$) and pneumonitis (0.1% vs. 0.7%; $p < 0.0012$) were statistically significantly increased in the IM-MS treatment arm. This translated into a significantly higher rate of "any lung" toxicities in the IM-MS treatment arm as compared to the control arm (4.3% vs. 1.3%; $p < 0.0001$). The observed difference represents an additional 57 cases of lung toxicity in the IM-MS arm.

No statistically significant difference could be observed in skin toxicity (including fibrosis, hyperpigmentation, teleangectasia as well as other skin toxicities; $p = 0.37$). The total number of events of toxicity reported up to year 3 amounts 21.8% in the standard treatment arm vs. 25.5% in the IM-MS arm (+67 cases, + 3.7%). This difference is statistically significant ($p = 0.006$).

All other reported toxicities (mastitis, breast infection, radionecrosis, osteonecrosis, oedema, pain, dysphagia, fatigue, arm/shoulder function impairment, other) were equally distributed between the two treatment arms.

Change in performance status at three years after randomisation

The PS at baseline and at year 3 is summarised in Table III for all 3 866 patients. Since those whose disease progressed or were lost to follow-up were censored for the assessment of WHO PS at 3 years, 3 341 patients are included in this analysis (1 684 and 1 657, respectively). At year 3, the WHO PS was unchanged compared to baseline in the majority of patients in both arms: 83.4% in the standard treatment arm vs. 84.1% after IM-MS irradiation. It deteriorated in 141 of 1 944 (8.4%) vs. 144 of 1 657 (8.7%) of the patients in the standard and IM-MS treatment arm, respectively and improved in 8.3% vs. 7.2%, respectively. There was no significant difference between the two treatment arms ($p = 0.79$). Respectively 133 of 141 and 134 of 144 of the deteriorations of the PS were in the form of an increase from PS 0 to PS 1. Conversely, all improvements (139 and 119 patients, respectively) were in the form of decrease of an initial PS 1 to a PS of 0.

In the whole group, the univariate analysis revealed a statistically significant impact of the application of any adjuvant systemic treatment (OR = 0.39, CI: 0.30–0.52; $p < 0.0001$) on the risk of deterioration of the WHO PS and no significant difference between the two randomised treatment arms (OR=1.03, CI: 0.81–1.32, $p = 0.79$). In order to elucidate the apparently protective impact of adjuvant systemic treatment, we then separated the patient group who had received neo-adjuvant chemotherapy) from the others (i.e. no adjuvant chemotherapy and adjuvant chemotherapy). This was in order to avoid a possible differential effect of other factors in the group neo-adjuvant chemotherapy, which might have had an acute and temporary PS deterioration at the time of randomisation, due to the neo-adjuvant chemotherapy (see Table IV). These analyses revealed a statistically significant impact of adjuvant hormonotherapy in the patient group that did not receive neo-adjuvant chemotherapy (OR = 0.56, CI: 0.44–0.76; $p < 0.0001$) indicating a lower risk of deterioration of the WHO PS for the patients who received adjuvant hormonotherapy. This parameter was the only one that remained significant in a multivariate model. Oestrogen and progesterone receptor status were also significant in the univariate model (OR = 1.06, CI: 0.69–1.63; $p < 0.005$ vs. OR = 0.81, CI: 0.58–1.12; $p < 0.025$ respectively) but their effect vanished in the multivariate model. The other tested variables did not influence the evolution of the PS. In the group who received neo-adjuvant chemotherapy, only age was (borderline) statistically significant in the univariate analysis, and none of the factors was significant at the $p < 0.05$ significance level in the multivariate model. Table V displays a multivariate model combining all patients in one model, that also includes the factors that are nowadays considered in the decision to deliver neo-adjuvant chemotherapy or adjuvant hormonotherapy, namely disease stage, age, hormone receptor statuses, and menopausal status. The model confirms that in patients who have otherwise similar age, menopausal status, oestrogen and progesterone receptor status and disease stage, those who did receive either adjuvant hormonotherapy or neo-adjuvant chemotherapy, as appropriate

Table II. Toxicity up to year three according to treatment arm

	No IM-MS (N=1944) N (%)	IM-MS (N=1922) N (%)	P-value
Lung Fibrosis (to year 3)*	17 (0.9)	54 (2.8)	<0.0001
Cough	5 (0.3)	10 (0.5)	0.19
Dyspnoea	1 (0.1)	14 (0.7)	0.0007
Pneumonitis	1 (0.1)	13 (0.7)	0.0012
Pleuritis	5 (0.3)	2 (0.1)	0.26
Other lung toxicity	2 (0.1)	4 (0.2)	0.41
Any lung toxicity	**26 (1.3)**	**83 (4.3)**	**<0.0001**
Dermatitis	38 (2.0)	26 (1.4)	
Skin fibrosis			
Yes, unspecified	160 (8.2)	152 (7.9)	
Breast/chestwall	0 (0.0)	6 (0.3)	
Matchline	1 (0.1)	5 (0.3)	
Hyperpigmentation			
Yes, unspecified	55 (2.8)	56 (2.9)	
Parasternal	0 (0.0)	3 (0.2)	
Teleangectasia			
Yes, unspecified	27 (1.4)	41 (2.1)	
Parasternal	0 (0.0)	1 (0.1)	
Supraclavicular	1 (0.1)	2 (0.1)	
Skin - other	7 (0.4)	11 (0.6)	
Any (breast) skin toxicity	**246 (12.7)**	**262 (13.6)**	**0.37**
Cardiac fibrosis (to year 3)*	5 (0.3)	7 (0.4)	**0.55**
Evidence of cardiac disease (to year 3)*	28 (1.4)	31 (1.6)	**0.64**
Mastitis	7 (0.4)	6 (0.3)	
Breast Infection	4 (0.2)	3 (0.2)	
Radionecrosis	2 (0.1)	1 (0.1)	
Osteonecrosis	22 (1.1)	27 (1.4)	
Oedema			
Yes, unspecified	81 (4.2)	81 (4.2)	
Presternal	0 (0.0)	1 (0.1)	
Arm/hand	70 (3.6)	73 (3.8)	
Breast/chestwall pain	45 (2.3)	35 (1.8)	
Retrosternal pain	1 (0.1)	2 (0.1)	
Other pain	15 (0.8)	26 (1.4)	
Dysphagia	0 (0.0)	4 (0.2)	
Fatigue	20 (1.0)	22 (1.1)	
Arm or shoulder function impairment	8 (0.4)	1 (0.1)	
Other - unspecified	8 (0.4)	8 (0.4)	
Any toxicity (to year 3)	**424 (21.8)**	**491 (25.5)**	**0.006**

*pre printed item on case report forms

Table III. WHO performance status at baseline and at year for the non-progressive patients

Performance status at year 3	Baseline Performance status				
No IM-MS Group	Missing	Performance status 0	Performance status 1	Performance status 2	Total
Missing	1	223	29	2	255
Performance status 0	5	1370	135	3	1513
Performance status 1	0	133	33	1	167
Performance status 2	0	4	0	1	5
Performance status 3	0	1	1	0	2
Performance status 4	0	2	0	0	2
Total	6	1733	198	7	1944
IM-MS Group	Missing	Performance status 0	Performance status 1	Performance status 2	
Missing	4	224	30	0	258
Performance status 0	4	1361	114	4	1483
Performance status 1	3	134	33	1	171
Performance status 2	0	4	4	0	8
Performance status 3	0	1	0	0	1
Performance status 4	0	1	0	0	1
Total	11	1725	181	5	1922

(Missing: patients with missing performance status or with progression before the assessment time point
Blue=deterioration, orange=improvement

are at lower risk of PS deterioration at year 3 than those who did not. This PS deterioration however, was seen in only about 8.5% of the assessable patients who for the vast majority had a worsening from PS 0 to PS 1 (see Table III).

Correlation between toxicity and change in performance status at three years after randomisation

Table VI shows the univariate analysis relating the presence of any lung toxicity, lung fibrosis or evidence of cardiac disease within the first three years to the risk of deterioration of the WHO PS. The results indicate no statistically significant relationship between lung toxicity or lung fibrosis and the risk of deterioration of the performance status. Cardiac diseases on the contrary seem significantly correlated with a high risk of WHO PS deterioration (OR = 3.71, CI: 1.90–7.24, $p < 0.0001$). The impact of cardiac fibrosis could not be assessed because only 11 patients were reported as having this event. None of these 11 patients had a deterioration of the PS at three years.

Discussion

Radiation therapy is an integral part of the multimodality treatment of breast cancer. The Danish and the British Columbia trials have firmly established the survival advantage following radiotherapy in post mastectomy patients [10,16]. Furthermore, the EBCTCG meta-analysis has demonstrated that radiotherapy, besides improving local control rates, confers a survival benefit in breast conservation treatment as well as in post mastectomy patients [15]. Although they showed the importance of loco-regional control on survival outcomes, the Danish and British Columbia trials and the EBCTCG meta-analysis were unable to discern the direct contribution from IM-MS treatment. It was noted as well that the survival gains associated with improvements in loco-regional control may be diminished by RT-associated cardiac mortality [17–20]. The EORTC 22922/10925 trial investigates therefore if elective irradiation of the IM-MS chain improves overall survival at 10 years.

In our report of the first three years of follow-up in this study, we did not observe any difference

Table IV. Influence of various parameters on WHO performance status deterioration

		Without neo-adjuvant chemotherapy (N=2242)				With neo-adjuvant chemotherapy (N=1624)			
Effect		**OR**	**95% CI**		P-value	**OR**	**95% CI**		P-value
Treatment	IM-MS vs. No IM-MS	1.02	0.77	1.35	0.89	1.12	0.68	1.86	0.66
Side	left vs. right	0.98	0.75	1.30	0.92	1.15	0.69	1.91	0.60
Adjuvant hormonal therapy	Yes vs. None reported	**0.56***	**0.44**	**0.76**	**<0.0001**	0.99	0.59	1.67	0.97
Adjuvant chemotherapy	Yes vs. No	**1.26**	**0.90**	**1.75**	**0.18**	N.A.			
Age	45-<55y vs. <45y	1.34	0.82	2.19	0.48	**1.41**	**0.72**	**2.74**	**0.06**
	55-<65 vs. <45 y	1.10	0.67	1.81	(df=3)	**0.66**	**0.29**	**1.54**	**(df=3)**
	≥65 vs. <45 y	1.34	0.80	2.23		**2.13**	**0.91**	**4.99**	
Type of surgery	Breast conserving vs. Mastectomy	0.88	0.61	1.29	0.52	0.87	0.51	1.50	0.61
Tumour size (pathology)	>1cm-2cm vs. <=1 cm	0.95	0.66	1.37	0.66	1.98	0.59	6.62	0.71
	>2 cm-3cm vs. <=1 cm	1.20	0.79	1.82	(df=3)	1.70	0.49	5.89	(df=3)
	>3 cm vs. <=1 cm	108	0.60	1.94		1.98	0.55	7.17	
pN	pN+ vs. pN0	1.15	0.86	1.53	0.34	0.65	0.37	1.13	0.13
Pathological Stage	Stage IIa vs. Stage I	0.98	0.70	1.37	0.41	1.19	0.54	2.64	0.60
	Stage IIb vs. Stage I	1.33	0.89	1.97	(df=3)	0.81	0.33	1.99	(df=3)
	Stage III vs. Stage I	1.35	0.71	2.56		0.81	0.32	2.06	
Oestrogen receptor	positive vs. negative	**1.06**	**0.69**	**1.63**	**0.005**	0.89	0.50	1.58	0.79
	Unknown vs. negative	**2.22**	**1.24**	**3.99**	**(df=2)**	1.39	0.31	6.36	(df=2)
Progesterone receptor	positive vs. negative	**0.81**	**0.58**	**1.12**	**0.025**	1.10	0.64	1.92	0.77
	Unknown vs. negative	**1.38**	**0.88**	**2.15**	**(df=2)**	0.77	0.25	2.29	(df=2)
Combination of Receptors	ER+, PG-,unkn vs. ER+, PG+	1.32	0.92	1.88	0.50	0.63	0.29	1.38	0.66
	PG+, ER-,unkn vs. ER+, PG+	0.97	0.41	2.31	(df=3)	1.01	0.30	3.37	(df=2)
	ER-, PG- vs. ER+, PG+	1.09	0.67	1.77		1.07	0.57	2.02	
Menopausal status	Post-Menopausal vs. Pre-menopausal	0.95	0.70	1.29	0.74	1.02	0.61	1.71	0.94

*Significant in multivariate model

between the two randomised groups in terms of "cardiac fibrosis" or "evidence of cardiac disease". However, further follow-up is required to confirm the absence of any deleterious impact of IM-MS treatment on cardiac function because late cardiac toxicity often appears 10 or even 15 years after treatment [17–29] and because we observed already a significant detrimental impact of the presence of cardiac disease on the PS of the patients. A limitation of this study will however remain that there was no precise definition of cardiac fibrosis in the protocol and that there was no specific investigation planned.

Pulmonary fibrosis was observed in 0.9% and 2.8% of patients in respectively the standard and IM-MS treatment arm. Lung toxicity of any kind was observed in only 1.3% vs. 4.3% of patients, representing an increase of only 57 cases of lung toxicity with IMMS irradiation. These results are in line with recent reports on pulmonary toxicity of breast radiotherapy [29–33]. This increased lung toxicity with IM-MS radiation was the only

Table V. Influence of various parameters in the multivariate analysis on WHO performance status deterioration

		Without neo-adjuvant chemotherapy			
Effect		**OR**	**95%** CI		P-value
Neo-Adjuvant chemotherapy	Yes vs. No	**0.30**	**0.18**	**0.52**	**<0.0001**
Adjuvant hormonal therapy (if no neoadjuvant CT)	Yes vs. None reported	**0.53**	**0.38**	**0.74**	**0.0002**
Adjuvant hormonal therapy (if neoadjuvant CT)	Yes vs. None reported	**0.90**	**0.50**	**1.61**	**0.72**
Age	45-<55y vs. <45y	**1.42**	**0.90**	**2.25**	**0.087**
	55-<65 vs. <45 y	**1.20**	**0.67**	**2.16**	**(df=3)**
	≥65 vs. <45 y	**1.77**	**0.96**	**3.24**	
Pathological Stage	Stage IIa vs. Stage I	**1.22**	**0.89**	**1.68**	**0.44**
	Stage IIb vs. Stage I	**1.35**	**0.92**	**1.99**	**(df=3)**
	Stage III vs. Stage I	**1.20**	**0.71**	**2.04**	
Combination of Receptors	ER+, PG-, unkn vs. ER+, PG+	**1.16**	**0.84**	**1.61**	**0.087**
	PG+, ER-, unkn vs. ER+, PG+	**0.87**	**0.43**	**1.35**	**(df=3)**
	ER-, PG- vs. ER+, PG+	**0.87**	**0.57**	**2.25**	
Menopausal status	Post-Menopausal vs. Pre-menopausal	**0.95**	**0.62**	**1.44**	**0.79**

statistically significant difference between the toxicity of the two treatment groups. Caution is however needed in the interpretation of these results the very large sample size of this study: due to the very high statistical power, statistically significant differences may not always be clinically relevant. It is important to note that the overall rate of lung toxicity remained below 5% in both treatment arms. In order to assess the impact of this toxicity on the patient's every day living, we correlated the changes of PS to the treatment arm. Despite the observed increase of lung toxicity with IM-MS irradiation, we could not demonstrate any significant difference in the risk of decreased PS between the randomised treatments nor could we demonstrate any significant correlation between the deterioration of the PS and the risk of lung toxicity. This suggests that these lung toxicities remain mainly subclinical or disappear with follow-up as is often seen with limited to moderate radio-pneumonitis.

The other reported toxicities are all well known toxicities of breast cancer radiotherapy and were not significantly increased with IM-MS irradiation.

An unexpected observation was that patients treated with neo-adjuvant chemotherapy had a lower risk of worsening their PS. A similar risk reduction was for patients who received adjuvant hormonotherapy. It is important to recognise that the trial protocol contained no strict guidelines as to which patients were to receive these adjuvant treatments. Although we observed that neo-adjuvant chemotherapy was given more frequently to young premenopausal patients with negative hormone receptors and high disease stage, whereas hormonotherapy was given to postmenopausal older women, these patients did not all receive the adjuvant therapy. The observed effects of adjuvant therapies thus likely reflect, for specified patient subgroups, the benefit of having actually received the adjuvant therapy that would be recommended in today's practice (respectively neo-adjuvant chemotherapy in young patients and adjuvant hormonotherapy in post menopausal women). However, these protective effects can not be explained by an impact on tumour progression as the patients with early relapse were censored in this analysis. It is also important to note that the PS deteriorated in only 8.5% of the patients, mostly as a deterioration from PS 0 to PS 1.which may not be very clinical relevant.

Conclusion

From this study, we conclude that IM-MS irradiation seems well tolerated and does not significantly impair WHO PS nor induces excess toxicity within the first three years after treatment. Longer follow-up is needed to further document cardiac toxicity and the impact of IM-MS irradiation on clinical outcome.

Table VI. Correlation between toxicity and WHO performance status deterioration at three years

Deterioration by year 3	No Change/ improvement (N=3056) N (%)	Deterioration (N=285) N (%)	OR	95% CI	P-value
Any lung toxicity					
No	2972 (91.5)	276 (8.5)			
Yes	84 (90.3)	9 (9.7)	1.19	0.59-2.41	0.62
Lung Fibrosis (to year 3)					
No	2996 (91.5)	280 (8.5)			
Yes	56 (91.8)	5 (8.2)	1.02	0.40-2.59	0.96
Missing	4 (100.0)	0 (0.0)			
Cardiac Fibrosis (to year 3)					
No	3038 (91.4)	285 (8.6)			Too small
Yes	11 (100.0)	0 (0.0)			sample for
Missing	7 (100.0)	0 (0.0)			testing
Evidence of cardiac disease (to year 3)					
No	2989 (91.9)	265 (8.1)			
Yes	38 (76.0)	12 (24.0)	3.71	1.90-7.24	<0.0001
Missing	29 (78.4)	8 (21.6)			

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