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Clinical Investigation: Breast Cancer

Postmastectomy Hypofractionated and Accelerated Radiation Therapy With (and Without) Subcutaneous Amifostine Cytoprotection

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Summary

The feasibility and efficacy of hypofractionated/accelerated radiation therapy supported with amifostine cytoprotection (HypoARC) in the postmastectomy therapy of breast cancer patients was assessed. An excellent early and short-term late toxicity profile was recorded, and amifostine further reduced early and late radiation soft tissue and lung sequelae. Encouraging local control rates are obtained in high-risk subgroups (ie, with lack of steroid receptor expression, simple human epidermal growth factor 2 positivity, or triple negative phenotype).

Purpose: Postmastectomy radiation therapy (PMRT) provides major local control and survival benefits. More aggressive radiation therapy schemes may, however, be necessary in specific subgroups, provided they are safely administered. We report the tolerance and efficacy of a highly accelerated and hypofractionated regimen (HypoARC).

Methods and Materials: One hundred twelve high-risk patients who had undergone mastectomy received 10 consecutive fractions of 3.5 Gy in 12 days (thoracic wall and axillary/supraclavicular areas). Two consecutive additional fractions of 4 Gy were given to the surgical scar area (electrons 8-10 MeV) and 1 3.5-Gy fraction to the axilla (in cases with extensive nodal involvement). A minimum follow-up of 24 months (median, 44 months) was allowed before analysis. Of 112 patients, 21 (18.7%) refused to receive amifostine, the remaining receiving tolerance-based individualized doses (500-1000 mg/day subcutaneously).

Results: By use of a dose individualization algorithm, 68.1%, 11%, and 18.7% of patients received 1000 mg, 750 mg, and 500 mg/day of amifostine. Patchy moist skin desquamation outside and inside the booster fields was noted in 14 of 112 (12.5%) and 26 of 112 (23.2%) patients, respectively. No case of acute pneumonitis was recorded. High amifostine dose offered a significant skin protection. Within a median follow-up time of 44 months, moderate subcutaneous edema outside and within the booster thoracic area was noted in 5 of 112 (4.4%) and 8 of 112 (7.1%) cases, respectively. Intense asymptomatic radiographic findings of in field lung fibrosis were noted in 4 of 112 (3.6%) patients. Amifostine showed a significant protection against lung and soft tissue fibrosis. A 97% projected 5-year local relapse free survival and 84% 5-year disease-specific survival were recorded. Lack of steroid receptor expression, simple human epidermal growth factor 2 positivity, or triple negative phenotype defined higher metastasis rates but had no effect on local control.

Conclusions: PMRT with HypoARC showed an excellent early and short-term late toxicity profile, and amifostine further reduced early and late radiation sequelae. Encouraging local control rates are obtained in high-risk subgroups.

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Introduction

Modified radical mastectomy remains a therapeutic option for breast cancer patients with multifocal or locally advanced tumors. As reported in the American College of Radiology (ACR) Appropriateness Criteria on Postmastectomy Radiotherapy (PMRT), the latter is recommended in cases with T3/T4 stages and in T1/T2 stages with 4 or more positive nodes (1). A controversy exists concerning patients with 1 to 3 positive nodes. A systematic review by Rowell (2) suggested that apart from staging, risk factors such as young age, lymphovascular invasion, close resection margins, and high histology grade can be considered to favor PMRT, especially when 2 or more of these factors are present.

Large randomized trials and meta-analyses have clarified the role of PMRT. In the Danish trials, the 18-year probability of any breast cancer event was reduced from 73% to 59%, whereas the locoregional recurrence was reduced from 49% to 14% (3). In a meta-analysis of 78 randomized trials completed by 1995, PMRT eliminated 1 of 4 breast cancer deaths for every 4 local recurrences (4). The important role of radiation therapy on overall survival has been also confirmed in a recent meta-analysis of patients undergoing breast conserving therapy, even in node-negative cases (5). It seems that the eradication of local disease that is microresidual or micrometastatic to the nodes prevents the subsequent development of metastasis, which is presumably intensified in cases of local tumor regrowth.

The 50 Gy of conventional fractionation to the chest wall and eventually a booster dose to the surgical scar, as recommended by the ACR (1), however, seem to be insufficient in some patients with steroid receptor (SR) negativity, human epidermal growth factor 2 (HER2) overexpression, and the triple negative category (6). Increased death and local relapse rates were seen despite the addition of conventional radiation therapy. It is therefore suggested that more aggressive radiation therapy schemes may be demanded in specific subgroups, as yet partially identified.

In previous studies we evaluated the concept of accelerated and hypofractionated radiation therapy with cytoprotection (HypoARC) in breast conserving strategies, providing evidence of an excellent tolerance of a very short, 2-week, radiation therapy scheme (7, 8). Acceleration of radiation therapy may prevent cancer cell growth during radiation therapy, enhancing the efficacy of radiation therapy in specific subgroups. By contrast, hypofractionation has been recently embraced as having a toxicity comparable with that of standard fractionation, given that the α/β breast cancer ratio is estimated to be 3.4 Gy, a value also shared by normal tissues (9). Amifostine, on the other hand, used as a cytoprotector, may further reduce early and late toxicities (7, 8).

In the current study, we report results from a prospective nonrandomized trial of HypoARC in high-risk patients who had undergone mastectomy, focusing on tolerance and efficacy. Analysis of the SR and HER2 status is also provided.

Methods and Materials

From March 2003 to March 2010, 112 breast cancer patients (103 treated with modified radical mastectomy and 9 with simple mastectomy) were recruited to assess the toxicity and efficacy of HypoARC as a PMRT regimen. All patients fulfilled the ACR criteria (1) and thus were of T3/T4 stages and/or had 4 or more positive nodes. A minimum follow-up time of 24 months was allowed before analysis, for patients alive at the time point of analysis. Thirteen patients (11.6%) were dead at the time of analysis, and 1 was lost to follow-up 19 months after therapy. The median follow-up time for patients who survived was 44 months (range, 24-90 months). The median follow-up time for all patients was 41 months (range, 8-90 months). Before analysis, all patients were clinically examined, recent computed tomography (CT) scans were reviewed by 2 observers, and toxicities were recorded by consensus.

All patients had a performance status of 0 (World Health Organization scale). Patients previously treated with radiation therapy or pregnant women or patients with major heart, lung, liver, renal, or psychiatric disease or hematologic malignancies were excluded from the protocol. Table 1 shows the patient, disease, and medical treatment characteristics. Written informed consent was obtained from all patients. The study was approved by the local ethics and scientific committees.

Toxicity evaluation

Acute radiation toxicity was monitored daily during therapy. Radiation toxicity was monitored once a week for a month after completion of radiation therapy, every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter. Disease status was monitored with 6-monthly CT scans of the chest and abdomen and by tumor serum markers. Mammography, ultrasonography of the contralateral breast, or both was performed yearly.

The National Cancer Institute Common Toxicity Criteria Version 2 was used to assess chemotherapy and acute radiation toxicity (10). The Late Effects of Normal Tissue—Subjective, Objective, Management, and Analytic scales (LENT-SOMA) criteria were used for the clinical assessment of late sequelae (11).

Radiation therapy technique

Radiation therapy was delivered using a 6/18-MV linear accelerator (Elekta, Stockholm, Sweden) endowed with a multileaf collimator after CT simulation and conformal radiation therapy planning (Plato, Nucletron, Stockholm, Sweden). A mixed x-ray/electron technique was applied. Radiation therapy was given to the upper thoracic wall and related axillary area by use of tangential 6-MV fields with appropriate wedges (Fig. 1a). The thickness of this upper thoracic wall area is inhomogeneous and sometimes exceeds 5 cm at the outer parts (vs 2 cm at the inner parts). Moreover, the lower axillary areas at this level must be included in the radiation fields, so electron fields are inadequate to provide a good dose distribution. By contrast, the thickness of the lower thoracic wall is rather homogeneous and is between 2 cm and 3 cm. Thus, a direct electron field was used to treat this lower thoracic wall area by use of 8- to 10-MeV electrons, with appropriate bolus.

The upper axilla and the subclavicular and supraclavicular areas were irradiated by use of a 2 opposed field technique (18 MV), with a wedge on the anterior one, to improve the distribution of isodoses to the axilla that resides deeper in comparison with the supraclavicular area (Fig. 1b). The upper thoracic wall fields and the supraclavicular/axillary fields were designed by use of a half beam technique. No bolus was used for these photon fields. The upper borders of the electron field were placed clinically with a split zone of >0.5 cm from the lower borders of the tangential fields.

Table 1 Patient, disease, and medical treatment characteristics

No. of patients	112
Age (y)	
Median	63
Range	28-84
PS	
0	112
T, N stage	
T1	19
T2	59
T3	26
T4	8
Multifocality	15
N number	
0	14
1-3	16
>3	59
Node block	14
Unknown	9
Histology not otherwise specified	94
Lobular	13
Other	5
Grade (NOS)	
1-2	39
3	55
ER status	
Negative	29
Positive	75
Unknown	8
PgR status	
Negative	39
Positive	65
Unknown	8
HER2 status	
Negative	55
Positive	49
Unknown	8
Triple negative	
No	96
Yes	8
Unknown	8
Surgery	
Modified radical mastectomy	103
Simple mastectomy	9
Pre-radiation therapy chemotherapy	
Adjuvant*	86
Neoadjuvant	12
Hormone therapy only	14
Trastuzumab during radiation therapy	
No	72
Yes	40

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor 2; NOS = not otherwise specified; PgR = progesterone receptor; PS = performance status.

* CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in 3 of 86 patients; FEC (5-fluorouracil, epirubicin, cyclophosphamide) in 22 of 86 patients; doxorubicin+taxane in 61 of 86 patients.

The dose distribution was calculated at the maximum dose point. The isodose curve for the calculation of the dose was chosen to allow a variation of less than ±5% of the dose in areas of interest and a dose no higher than +10% in small hot spots. The angle of the tangential fields and the inner and outer limits were carefully designed to allow the least possible dose distribution to the lungs. The inner mammary nodes were not irradiated.

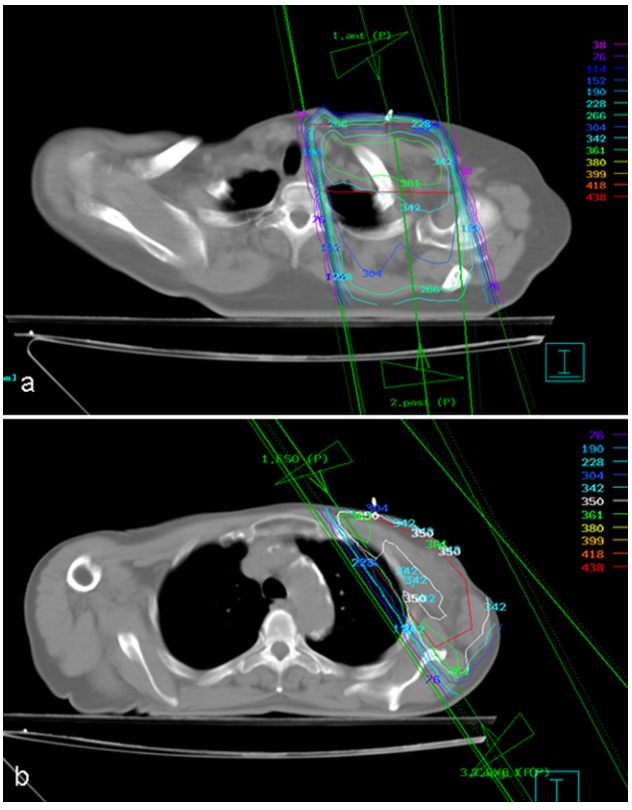

Fig. 1. Total dose per fraction distribution in the supraclavicular area (a) and in the upper thoracic wall and axillary areas (b) by use of the radiation therapy technique described.

Fractionation and radiobiology

The same fractionation was used for thoracic wall and axillary/supraclavicular irradiation. Patients received 10 consecutive fractions of 3.5 Gy (total dose of 35 Gy) in 12 days. An additional dose of 8 Gy (4 Gy/fraction) was given to the surgical scar (5 cm wide) by use of electrons (8-10 MeV). The number of fractions to the axillary/supraclavicular area was increased to 11, in cases with extensive nodal involvement or clinical evidence of preoperative nodal block. The overall treatment time was 16 days.

The normalized total dose (NTD) was calculated according to the formula proposed by Maciejewski et al (12): $NTD = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)]$, where D is the total physical dose, d is the dose per fraction, and α/β is the tissue-specific ratio. The NTD corrected for overall treatment time was calculated according to a previously proposed formula (7, 8): $NTD_{(T)} = D\ [(\alpha/\beta + d)/(a/b + 2)] + \lambda(Tc\text{-}To)$, where Tc is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, To is the number of days required for the delivery of the current scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation. For cancer and normal breast area tissues, an α/β ratio of 3.4 Gy was considered, as calculated by Bentzen et al (9). For cancer cells, a λ value of

0.4 Gy was considered. For normal tissues, a λ value of 0.2 Gy was adopted in radiobiologic calculations. The biologic dosimetric analysis of the regimen is presented in Table 2.

Administration of amifostine

A dose individualization algorithm was used to deliver a dose of 500 to 1000 mg amifostine per day, according to individual tolerance, as previously described (8). Briefly, oral ondasetron 8 mg/day was used to prevent nausea. Amifostine (1000 mg in 5 mL water for injection) was injected at the right and left shoulders. The dose of 1000 mg was reached gradually (first day, 500 mg; second day, 750 mg; and third day, 1000 mg) according to a previously published algorithm (8). If at any point during therapy patients showed unacceptable nausea/emesis or fatigue, dexamethasone 8 mg was administered intramuscularly before amifostine, and tolerance was reassessed. Appropriate dose reduction or permanent interruption was considered in case of intolerance.

Immunohistochemistry

Tissue samples were available from 104 of 112 cases analyzed in this study. Sections were cut at 3 μm and stained immunohistochemically with a standard streptavidin-biotin method for the detection of c-*erb*B-2 and for expression of estrogen receptor (ER) progesterone receptor (PgR) as previously reported from our group (13). The percentage of tumor cells with a strong distinct membrane c-erbB-2 staining was recorded in all optical fields, and the mean value was calculated. Tissue samples with a mean value ≥20% were considered as positive for c-*erb*B-2 (+2/+3 vs 0/+1 mark) and classified into 2 grades: tumors of high c-*erb*B-2 reactivity (20%-50% positive cells: +2); tumors of very high c-*erb*B-2 reactivity (50%-100% positive cells: +3). No routine fluorescence in situ hybridization analysis was performed for +1 cases. For ER and PgR expression, the nuclear staining was assessed, and cases with reactivity in ≥20% of cells were considered to be highly positive (+2/+3 mark).

Statistical analysis

Statistical analysis and graph presentation of survival curves were performed by use of the GraphPad Prism 5.00 version and the GraphPad Instat packages. Fisher's exact test or the unpaired 2-tailed *t* test was used to compare categoric variables, as appropriate. Survival curves were plotted by use of the Kaplan-Meier method to determine statistical differences between life tables. Curves were compared by use of the log-rank test (Mantel-Haenszel). The Gehan-Breslow-Wilcoxon method, which gives more weight to events at early time points (a feature that may be important in the analysis of progression events after therapy or death events expected to occur at a high rate early in the course of follow-up) was also used. Patient-related and treatment-related variables were analyzed in a multivariate stepwise logistic regression model to determine which ones contained independently significant information. *P* values <.05 were considered to be statistically significant.

Results

Amifostine tolerance

Of 112 patients, 21 (18.7%) refused to receive amifostine after the known hazards from amifostine side effects and the potential, yet unknown, benefits had been explained to them; still they agreed to participate as a control group. By use of the dose individualization algorithm, 62 of 91 (68.1%) patients received 1000 mg amifostine; 10 of 91 (11.0%) received 750 mg, and 17 of 91 (18.7%) received 500 mg. Another 2 of 91 (2.2%) patients did not tolerate the dose of 500 mg (unacceptable fatigue, vomiting, or both), and amifostine was interrupted. Fever, rash, or both appeared in 15 of 91 (16.5%) patients (6 of 32 and 9 of 58 patients receiving 500-750 mg and 1000 mg, respectively; $P=.77$). For these patients, amifostine administration was interrupted. Symptoms appeared within a median of 6 days of therapy (range, 3-10 days). No case of necrolytic syndrome, clinical hypotension, or hypoglycemia was noted. At the individualized dose established, patients had an excellent tolerance.

The total doses of amifostine received at the 500-, 750-, and 1000-mg dose levels during the 12 days of therapy were 6000 mg, 8750 mg, and 11,250 mg, respectively. In the 15 patients with fever, rash, or both in whom amifostine was interrupted, the received total dose was reduced. To assess the protective efficacy of amifostine according to the dose delivered, patients were regrouped according to the total dose received, as follows: 0 mg, 21 patients; ≤6000 mg, 25 patients; 6500 to 8750 mg, 12 patients; and 9000 to 11,250 mg, 54 patients.

Acute radiation toxicity

During the 16-day therapy, increased sensitivity of the irradiated area was occasionally reported. The toxicity peaked 7 days after the completion of radiation therapy and regressed completely within 1 to 2 weeks (Table 3).

Dry and patchy moist skin desquamation outside the booster fields was noted in 62 (55.4%) and 14 (12.5%) patients, respectively. The later was mainly located in the axillary area. In the

Table 2 Radiation therapy schedule, physical dose, normalized total dose, and normalized total dose with time correction delivered to normal tissues and cancer

Location	(Gy/fraction) × (No. of fractions)	Physical dose (Gy)	NTD (n,c) (Gy)	Treatment d	Accel. d	NTD-T (n) (Gy)	NTD-T (c) (Gy)
Thoracic wall	3.5 × 10	35	43.90	12	18	47.50	51.10
Tumor bed	+4 × 2	43	54.80	16	21	59.00	63.20
Axilla/Scl	3.5 × 11	38.5	49.10	16	20	53.10	57.10

Abbreviations: Accel = days of acceleration of radiation therapy; NTD-T (c) = normalized total dose corrected for time delivered to cancer calculated for λ = 0.4 Gy; NTD-T (n) = normalized total dose corrected for time delivered to normal tissues calculated λ = 0.2 Gy; NTD (n,c) = normalized total dose to normal and cancer tissues calculated for α/β = 4 Gy; Scl = supraclavicular area.

Table 3 Early toxicity in 112 patients, assessed with the National Cancer Institute Common Toxicity Criteria version 2 scale

Toxicity	No. (%)
Radiation dermatitis (outside boost field)	
0. None	36 (32.1)
1. Dry desquamation	62 (55.4)
2. Patchy moist desquamation	14 (12.5)
3. Confluent moist desquamation	0 (0)
4. Skin necrosis	0 (0)
Radiation dermatitis (within boost field)	
0. None	34 (30.4)
1. Dry desquamation	52 (46.4)
2. Patchy moist desquamation	26 (23.2)
3. Confluent moist desquamation	0 (0)
Erythema/calor (modified by authors)	
0. None	104 (92.8)
1. Faint erythema	8 (7.2)
2. Brisk erythema	0 (0.0)
Subcutaneous edema (modified by authors)	
0. None	108 (96.4)
1. Barely palpable/asymptomatic	4 (3.6)
2. Moderate/tolerable	0 (0.0)
3. Severe/requiring therapy	0 (0.0)
Pain (chest wall)	
0. None	105 (93.7)
1. Mild	7 (6.3)
2. Moderate	0 (0.0)
3. Severe	0 (0.0)
Pneumonitis	
0. None	112 (100)
1. Radiographic changes/asymptomatic	0 (0)
2. Radiographic changes/symptomatic/steroids	0 (0)
3. Radiographic changes/symptomatic/oxygen	0 (0)
4. Assisted ventilation demanded	0 (0)

booster dose area, the moist skin desquamation was increased in 26 of 112 patients (23.2%), but this was patchy and in no case confluent. One month after therapy, faint to mild increase of skin pigmentation was a common finding. Mild erythema, palpable subcutaneous edema grade 1, and mild pain were noted in 7 (7.2%), 4 (3.6%), and 7 (6.3%) patients, respectively. No case of acute pneumonitis was recorded.

Analysis according to the total dose of amifostine showed that a dose $\geq$9500 mg offered significantly better skin protection. Grade 2 acute toxicity in the area outside the booster dose was noted in 3 of 54 (5.5%) patients who received a high amifostine dose, compared with 11 of 58 (18.9%) patients receiving a lower amifostine dose ($P = .04$). Protection within the booster field against grade 2 skin desquamation was evident, but the difference did not reach significance (9 of 54 patients vs 17 of 58 patients; $P = .12$). No erythema was noted in 66 patients receiving amifostine dose $\geq$6500 mg, compared with erythema in 6 of the remaining 46 patients ($P = .002$).

Late radiation toxicity

Table 4 shows the late toxicities recorded within a median follow-up time of 44 months (range, 24-90 months). Moderate

Table 4 Late toxicity in 112 patients, assessed with a LENT-SOMA/NCI simplified grading system

Toxicity	No. (%)
Subcutaneous edema (modified by authors)	
0. None	89 (79.5)
1. Barely palpable/ asymptomatic	18 (16.1)
2. Moderate/tolerable	5 (4.4)
3. Severe/requiring therapy	0 (0)
Skin fibrosis (booster area)	
0. None	84 (75.0)
1. Barely palpable	20 (17.9)
2. Definite firmness	8 (7.1)
3. Very marked firmness/ fixation	0 (0)
Skin telangiectasia (booster area)	
0. None	15 (13.4)
1. Sporadic	76 (67.9)
2. Intense	21 (18.7)
Circumferential arm lymphedema	
0. None	99 (88.4)
1. 2-4 cm	11 (9.8)
2. 4-6 cm	2 (1.8)
3. >6 cm	0 (0)
4. Useless arm	0 (0)
Pain (chest wall)	
0. None	99 (88.4)
1. Mild	11 (9.8)
2. Moderate	2 (1.8)
3. Severe	0 (0)
Pain (brachial plexopathy)*	
0. None	110 (98.2)
1. Minimal	2 (1.8)
2. Intermittent/tolerable	0 (0.0)
3. Intense	0 (0.0)
Lung fibrosis (modified by authors)	
0. None	84 (75.0)
1. Barely evident CT changes/ asymptomatic	24 (21.4)
2. Evident CT changes/ asymptomatic	4 (3.6)
3. CT changes/symptomatic	0 (0)

Abbreviations: CT = computed tomography; LENT-SOMA = Late Effects of Normal Tissue—Subjective, Objective, Management, and Analytic scales; NCI = National Cancer Institute.

* No case of weakness or paresthesia was recorded.

subcutaneous edema outside and within the booster thoracic area was noted in 5 of 112 (4.4%) and 8 of 112 (7.1%) patients, respectively. Skin telangiectasia was frequent within the booster area, and it was intense in 21 of 112 (18.7%) patients. Grade 1 and 2 increase of the circumferential arm edema was recorded in 11 of 112 (9.8%) and 2 of 112 (1.8%) patients. Mild and moderate pain of the thoracic wall or axillary area was reported by 11 of 112 (9.8%) and 2 of 112 (1.8%) patients. Minor pain attributed to brachial plexopathy was recorded in 2 of 112 (1.8%) patients. No rib fractures were recorded. Lung fibrosis, as assessed by CT, was barely evident in 24 of 112 (21.4%) patients, and intense but asymptomatic radiographic findings were noted in 4 of 112 (3.6%) patients.

Analysis according to the amifostine dose delivered showed a significant protection of dose levels ≥6500 mg against grade 1 to 2 lung fibrosis (11 of 66 patients vs 17 of 46 patients; $P = .02$). Grade 1 to 2 fibrosis of the subcutaneous tissue within the booster dose was also significantly reduced for doses ≥9500 mg (9 of 54 patients vs 19 of 58 patients; $P = .05$).

Survival analysis

At the time of the analysis, 3 of 112 (2.7%) patients had experienced relapse within the radiation fields, 2 of them expressing concurrently distant metastasis. Eighteen patients (16.1%) experienced distant metastasis (bone in 8 of 18 patients, brain in 4 of 18 patients, lung in 3 of 18 patients, liver in 4 of 18 patients, and soft tissue in 3 of 18 patients), which was also the cause of death in 10 of 18 patients, at the time of analysis. These data define a 97% projected 5-year local relapse free survival, 78% 5-year distant metastasis free survival, and 84% 5-year disease specific survival.

Because of the low numbers of locoregional relapse (3 of 112 patients), it was not feasible to perform analysis according to histologic and immunohistochemical variables. Kaplan-Meier metastasis free survival (MFS) (Fig. 2) revealed a significant association of lack of PgR expression with worse MFS ($P = .03$, hazard ratio [HR] 2.8). Lack of ER expression revealed a short-term ominous effect ($P = .05$). Triple negative and simple HER2+ cases (SR−) had an overall poorer MFS in comparison with the rest of the cases ($P = .009$, HR3.1). In multivariate analysis, expression of PgR was the only factor linked with better metastasis free events ($P = .04$; HR 0.3; range, 0.1-0.9).

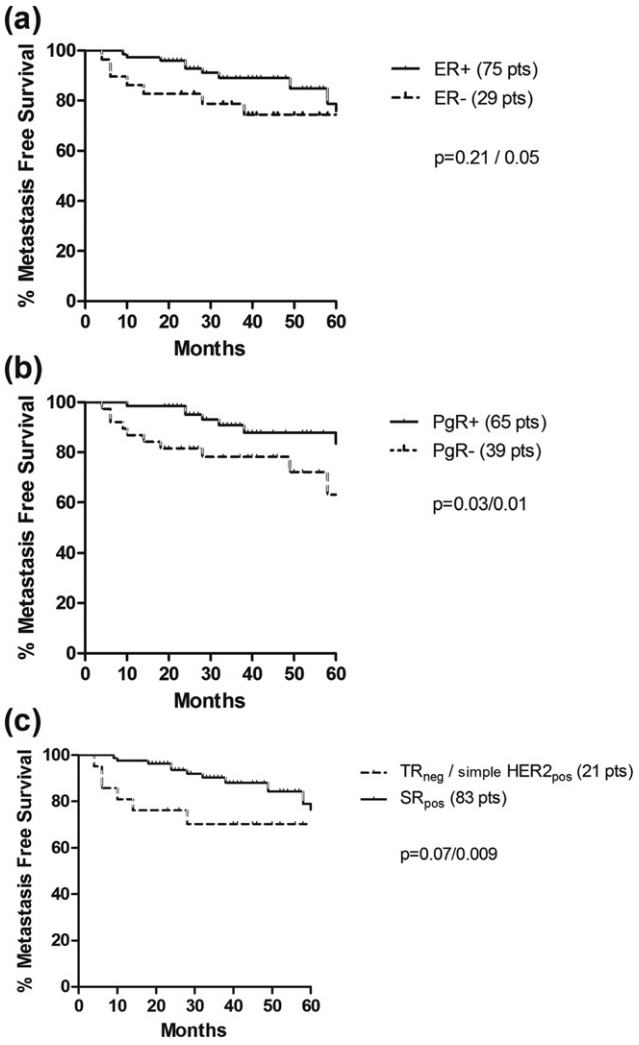

Fig. 2. Kaplan-Meier metastasis-free survival curves, stratified for estrogen receptor (ER) expression (a), progesterone receptor (PgR) expression (b), and combined steroid receptor (SR) and human epidermal growth factor 2 (HER2) expression (triple negative and simple HER2+ cases vs ER and/or PgR receptor expressing cases) (c).

Discussion

The important role of PMRT in the local control of cancer and the overall survival of cancer patients has been established during the current decade (3−5, 13). It seems, however, that specific subgroups of breast carcinomas are relatively radioresistant to conventional radiation therapy schemes. In the Danish analysis (6), for example, the locoregional relapse rate after PMRT was as low as 3% in SR+ patients but increased to 15% and 21% in the triple negative and HER2+/SR− subgroups, respectively. Impressively, PMRT was ineffective in showing any significant benefit over mastectomy alone in the latter subgroup. In 2 recent studies, the addition of PMRT significantly reduced locoregional recurrence in patients with triple negative status (13, 14), suggesting that radiation therapy is, in any case, essential for the treatment of this aggressive breast cancer subtype. Another putative subgroup of patients with radioresistant breast tumors is the group overexpressing hypoxia inducible proteins, angiogenic factors, or both. Overexpression of hypoxia-regulated genes such as carbonic anhydrase IX and the vascular endothelial growth factor gene defines higher recurrence rates, despite the addition of radiation therapy (15, 16).

Whether altered fractionation and acceleration of radiation therapy can improve the efficacy of PMRT in such relatively radioresistant breast tumors deserves thorough evaluation. On the other hand, the safety of such schedules should be also tested before randomized trials are scheduled. The current study provides an interim analysis with adequate follow-up time to enable conclusions about the safety of a highly accelerated scheme (16 days). The safety and efficacy of the hypofractionation applied has a strong biologic rational provided by clinical data pointing to a 3.4-Gy α/β ratio for breast cancer, which is similar to normal tissues. Thus, by delivering a tolerable dose through hypofractionation, the damage to cancer cells is not reduced. This is highly convenient in clinical practice, especially in overloaded departments. Moreover, the 3-week acceleration of HypoARC allows the treatment of a double number of patients.

The early and late toxicities recorded were low. The addition of high amifostine doses further reduced erythema, edema, and moist skin desquamation. Even without amifostine, the schedule had an excellent tolerance. Radiation-induced arm edema, pain, and lung toxicity were rare and, when they occurred, without important impact on the quality of life of patients. Although a longer follow-up time should be allowed to enable safe conclusions, the 4-year median time available is certainly encouraging. Two years is the time frame when the majority of late toxicities occur (17).

The efficacy was better than those reported in trials with standard fractionation. The projected 97% 5-year local control rate

was independent of HER2 or triple negative status. Although a longer follow-up time is demanded, these results compare favorably with the 15% to 20% local relapse rates of HER2+ and triple negative cases (6). In the current study, the ominous impact of SR and HER2 status was restricted to the increased rate of distant metastasis.

It is concluded that postmastectomy HypoARC is a convenient regimen for patients and overloaded radiation therapy departments and has a more than acceptable early and short-term late toxicity profile. Although this applies even when HypoARC is delivered without amifostine, the daily administration of high doses resulted in further reduction of early and late radiation sequelae. In terms of efficacy, encouraging results are obtained in high-risk subgroups. Randomized PMRT trials in such subgroups are encouraged whether or not the HypoARC regimen includes amifostine.

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