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Original article

Ipsilateral supraclavicular lymph nodes metastases from breast cancer as only site of disseminated disease. Chemotherapy alone vs. induction chemotherapy to radical radiation therapy

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Summary

Background: To define the role of radiotherapy (RT) in the treatment of ipsilateral supraclavicular lymph-nodes metastases (ISLM) from breast cancer as only site of disseminated disease, we started a prospective non-randomized clinical trial in 1989. Here we report the final results with a median follow-up of 8.75 years.

Patients and methods: Thirty-seven patients (pts), with ISLM from breast cancer, were consecutively enrolled into two arms. Arm A (18 pts): chemotherapy (CT) for six courses. Arm B (19 pts): CT for three courses followed by RT to the site of ISLM at 'radical' dose of 50–60 Gy.

Results: In arm A, a median Time to Progression (TtP) of 7 months with a median Overall Survival (OS) of 28 months was recorded. In comparison, patients in arm B had a longer median TtP with 20 months as well as a better median OS with 41 months, respectively. An actuarial five-year disease-free survival of 5.5% was obtained in arm A vs. 21% in arm B. A statistically significant difference in TtP was demonstrated between the two groups ($P = 0.01$).

Conclusions: These data demonstrate that a better event-free survival could be achieved in patients with ISLM submitted to induction CT and radical irradiation. This also translated into a longer survival although this did not achieve statistical significance. We want to stress the importance of local control by RT since it does imply that not all of these patients have micrometastases at the time of relapse in the supraclavicular fossa.

Key words: breast cancer, chemotherapy, lymph nodes, metastases, radiotherapy, supraclavicular

Introduction

Since 1988, ipsilateral supraclavicular lymph-nodes metastases (ISLM) from breast cancer are considered a metastatic disease and are codified as stage IV [1]. This classification by stage was justified by the fact that, in general, prognosis in patients (pts) with ISLM is similar to patients with metastases in other sites (i.e. bone, liver) [2] and the treatment does not seem to influence survival [3].

Up to date, to our knowledge, no standard treatment exists for an ISLM as only site of metastatic disease. This could be explained by a fairly rare occurrence of ISLM and by the frequency of supraclavicular lymph node metastasis with simultaneous distant progression. Furthermore, this lack of consensus results from the absence of a randomized trial in this issue that definitely establishes the prognosis and the optimal treatment.

The aim of this non-randomized clinical trial was to evaluate if radiotherapy (RT) at 'radical' dose can alter the outcome of patients with ISLM.

The primary end-point of this study was the evaluation of the Time to Progression (TtP); the second end-point was the observation of the Overall Survival (OS). Preliminary results had been previously published [4]. We did not estimate the patients' quality of life.

Here we report the final results with a median follow-up of 8.75 years (105 months) in 37 patients.

Patients and methods

Study design, inclusion criteria, patients and tumor characteristics (Table 1), and preliminary results, have been published previously [4]

The pretreatment evaluation included physical examination and complete blood count, postero-anterior and lateral chest X-ray, liver ultrasound and bone scan in all patients. Other investigations were performed in presence of clinically suspect signs.

Patients with cytological (7 of 37 patients) or histological (30 of 37 patients) confirmation of ISLM were alternatingly assigned to arm A or B. However, after informed consent but before start of treatment they had the possibility to change the arm of study which they were allotted to. One patient (the first one) refused the assigned treatment option of chemotherapy alone (arm A) and was enrolled in the RT arm (arm B).

Arm A, 18 patients: chemotherapy (CT) for six courses (+/− hormonotherapy); if during the CT progressive disease in the supraclavicular fossa occurred, the patients underwent palliative RT (3 pts)

and the TtP was calculated; these patients went off-study regarding overall survival, but their TtP was evaluated for this final report.

Arm B, 19 patients· CT for three courses (+/− hormonotherapy) followed by RT 'involved field' to the site of ISLM.

Fully informed, written consent was required.

The two groups of patients were homogeneous and balanced, without significant statistical differences, even in the median disease-free survival (time from breast cancer diagnosis and appearance of ISLM) of 19 months in arm A and 24 months in arm B.

The potential median follow-up for all patients was 105 months (range 66–138 months): for arm A 110 months (range· 66–137); for arm B 102 months (range 67–138).

Chemotherapy

For both arms the chemotherapeutic regimens were employed according to the respective adjuvant treatment formerly performed Precisely:

1) Patients without precedent CT were assigned to receive CMF 1–8 (cyclophosphamide 600 mg/mq i.v 1 and 8; methotrexate, 40 mg/mq i.v. 1 and 8, fluorouracil, 600 mg/mq i.v. 1 and 8) every four weeks.
2) Patients with previous CT: if the precedent CT was without doxorubicin, patients were submitted to FEC–FAC (fluorouracil, 500 mg/mq i.v 1 and 8; doxorubicin, 50 mg/mq i.v 1, or epi-doxorubicin 60 mg/mq i.v 1; cyclophosphamide, 500 mg/mq i.v. 1) every four weeks or A (doxorubicin, 75 mg/mq i.v. 1) every three weeks; if previous CT contained doxorubicin, patients were inserted in CMF 1–8.

All patients completed the planned therapy. Table 2 shows the CT regimens administered in 37 patients.

Radiotherapy

An anterior radiation field encompassing the supraclavicular fossa, site of ISLM, was used with the gantry angle of 15° laterally to avoid irradiation of the spinal cord; the superior edge of the field was at the level of glottis, the lateral edge of the field was placed to the medial aspect of the humeral head, the median edge at the sternal notch; inferiorly the field included the apex of homolateral axilla. RT was done with a 6MV linear accelerator in supine position with the head turned toward the opposite side with respect to treated supraclavicular fossa.

The radiation dose was calculated at a depth of 3 cm and no bolus was added. When the nodes were in loco (16 pts), a total dose of 60 Gy/30 fraction/2 Gy per fraction × 5 days a week was delivered (shrinking field at 50 Gy); in patients submitted to macroscopic excision of ISLM (3 pts), the total radiation dose was 50 Gy/25 fractions/2 Gy per fraction × 5 days a week. When progression of disease at the site of ISLM was recorded during CT (3 pts, arm A), the total radiation dose was 39 Gy/13 fractions/3 Gy per fraction × 5 days a week. All patients completed the planned therapy.

End points and follow-up

The primary end-point was to evaluate the Time to Progression (TtP), the time between diagnosis of ISLM and progression disease at the site of ISLM or in distant sites, in CT alone vs. CT plus RT Breast, chest-wall, ipsilateral axillary and mammary-chain nodes relapses (local-regional failure) without simultaneous development of distant metastases, were not recorded as distant progression disease and the TtP was not calculated. In case of failure, the choice of treatment was made on an individual basis. The overall survival (OS), the time from ISLM diagnosis to death, was also evaluated.

For all patients the follow-up, until diagnosis of progressive disease, provided: physical examination and complete blood count every three months; chest X-ray, bone scan, liver ultrasound yearly; other investigations were performed if clinically advisable No patient was lost to follow-up

Table 1 Tumor and patient characteristics.

	Group A (n = 18)	Group B (n = 19)	P-value
Age (years)			
Median	58	55	$P > 0.78$
Range	32–71	39–77	
Disease free survival[a] (months)			
Median	19	24	$P > 0.15$
Range	0–96	0–216	
T Status[b]			
T1	2	1	
T2	7	11	$P > 0.19$
T3	3	3	
T4	6	4	
N Status[b]			
N0	3	4	
N1	12	13	$P > 0.98$
N2	3	2	
Receptorial status[b]			
ER+	6	5	
ER−	11	12	$P > 0.92$
Unknown	1	2	
Prior chemotherapy[c]			
Yes	15	15	
No	3	4	
Histological diagnosis of ISLM[d]	3	4	
Cytological diagnosis of ISLM[d]	15	15	
Macroscopic excision of supra-clavicular node metastases			
Yes	2	3	
No	16	16	
Synchronous local recurrence at the time of ISLM[d] diagnosis			
Yes	1	2	
No	17	17	

[a] Time from diagnosis of breast cancer and time of appearance of supraclavicular nodes metastases.
[b] Status at the time of primary diagnosis of breast cancer.
[c] Neo- or adjuvant chemotherapy at the time of primary diagnosis of breast cancer.
[d] ISLM: ipsilateral supraclavicular lymph nodes metastases.

Table 2. Chemotherapeutic regimens employed in 37 patients.

Regimen	Arm A (CT alone) n = 18 (100%)	Arm B (CT + RT) n = 19 (100%)
A	4 (22.3)	5 (26.3)
FAC/FEC	9 (50)	4 (21.1)
CMF	5 (27 7)	10 (52.6)

Tamoxifen, 20 mg/day, was used twice in arm A and once in arm B after the completion of chemotherapy.
Abbreviations. A – doxorubicin, C – cyclophosphamide; E – epi-doxorubicin; F – fluorouracil; M – methotrexate.

Statistical analysis

The trial was started in 1989 and closed in 1994 after 37 patients had been included in the study. Results were analyzed 66 months after the completion of patients enrollment, on 6/30/2000, and interim analyses were published [4]. Both patients in arm A and in arm B were

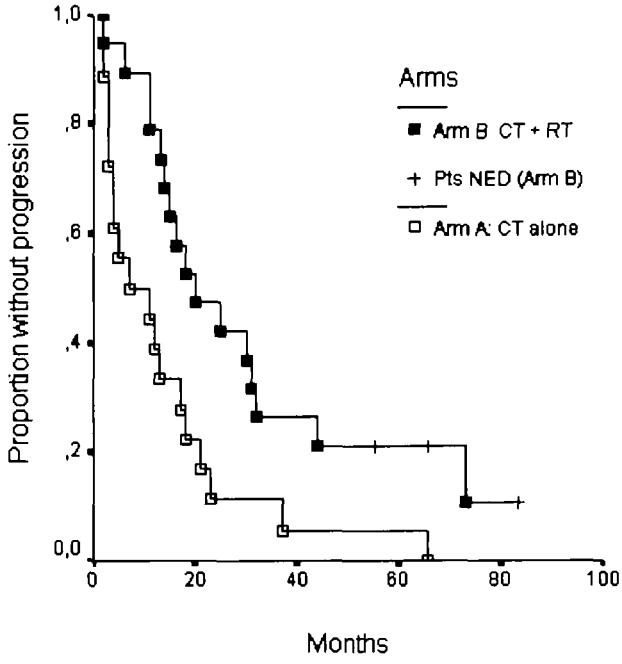

Figure 1. Life tables showing time to progression of chemotherapy alone group (arm A) and chemotherapy plus radiotherapy group (arm B). CT – chemotherapy; NED – not evidence of disease; RT – radiotherapy.

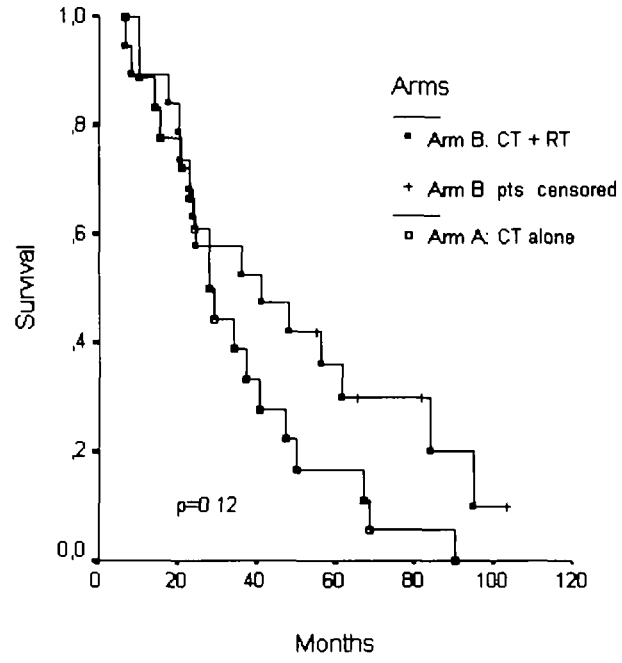

Figure 2. Life tables showing the survival of chemotherapy alone group (arm A) and chemotherapy plus radiotherapy group (arm B). CT – chemotherapy; RT – radiotherapy

investigated for homogeneity (age, DFS months, etc) by means of student *t*-test or Wilcoxon rank sum test and no statistical differences were found. TtP was the primary end-point of the study.

The Kaplan–Meier method [5] was used to estimate distribution of TtP and OS. Differences in time distribution were evaluated using the log-rank test.

Results

At the last follow-up (6/30/2000), a total of 34 events contributing to the end-point TtP had been observed. With a median follow-up duration of 8.75 years, the local-regional failure was 8% (2 pts in arm A, 1 pt in arm B). All the patients in arm A died of disease progression; the median TtP was seven months (range 2–65) with a median survival of 28 months (range 10–90). In arm B the median TtP was 20 months (range 2.5–77) with a median survival of 41 months (range 6.5–106.5). The Kaplan–Meier curve of TtP for both arms is shown in Figure 1.

An actuarial five-year disease free survival of 5.5% was obtained in arm A vs. 21% in arm B; the actuarial five-year overall survival was 17% in arm A vs. 36% in arm B.

The statistical analysis showed a significant difference between the two arms regarding the TtP ($P = 0.01$); for the overall survival, a P-value of 0.12 demonstrated a lack of statistical significance (Figure 2).

Up to date four patients in arm B are alive, three of them without evidence of disease.

Table 3 resumes the results on local and disseminated progression disease and reports both the number of patients with no evidence of disease, including their characteristics, and patients alive at the last follow-up. Local-regional relapses were diagnosed in two arm A patients (one breast and one axilla) and one patient arm B (chest wall).

A long local control (at the site of ISLM) was obtained in 31 of 37 patients (83.8%); local progressive disease was recorded in 6 of 37 patients (one in group B, 2.7% and five in group A, 13.5%). Three of them (all in arm A, 3 of 18, 16.6%) showed first disease progression at the site of supraclavicular lymph nodes and were submitted to RT. The other three (one patient from arm A, two of arm B) suffered from progression at this site subsequent to distant failure.

No patient (0 of 37) showed significant painful and distressing symptoms because of ISLM; precisely, no patient suffered from disabling lymphoedema, uncontrolled shoulder-arm pain or severe sensory motor changes.

Discussion

In patients with metastatic breast cancer the maintenance of a long-term acceptable quality of life is the first aim of therapy. Radiotherapy plays a palliative role in both the symptom control (i.e., pain from bone and neurologic involvement) and the treatment of oncologic emergencies (i.e., superior vena cava syndrome, spinal cord compression). In these instances a short course of therapy with daily fractions of 2.5–3 Gy and a total radiation dose of 30–40 Gy is generally delivered.

ISLM is a rare but important occurrence in breast

Table 3. Site of first failure after treatment of ISLM (see text) and initial characteristic of NED patients.

	Local M	LRR	Distant M	NED	Alive
Arm A (CT)	3	2	15	0	0
Arm B (CT + RT)	0	1	16	3	4

Initial characteristics of NED patients in arm B

Age	T status	N status	Receptorial status	DFS (months)	Macroscopic excision of ISLM
50	T2	N1	ER+	61	No
66	T2	N2	ER−	13	Yes
67	T2	N1	ER−	24	No

Abbreviations. DFS – disease free survival (time from breast cancer diagnosis to occurrence of ipsilateral supraclavicular lymph nodes metastases, ISLM – ipsilateral supraclavicular lymph node metastases; Local M – metastases (supraclavicular lymph node progression), LRR – loco-regional relapse; NED – not evidence of disease at the time of last follow-up.

cancer, representing in fact a clinical manifestation of advanced disease with some chance of cure. For this reason, higher doses than 30–40 Gy are delivered [9]; therefore in ISLM the radio-therapeutic approach is different with respect to other metastatic sites.

Although a standard therapy doesn't exist for ISLM, a surgical approach whenever feasible and RT to the supraclavicular fossa are frequently used [9, 10]. However, no prospective studies have been reported demonstrating the benefit of this therapeutic approach.

The lack of oriented studies on ISLM could be justified by the rare occurrence of this clinical picture, both in radical mastectomy and conservative treatment. Recht et al. [11], reported eight supraclavicular failures in 467 patients affected by breast cancer with zero to three positive nodes and treated with conservative surgery and RT to the breast only. Fentiman et al. [12]) reported 35 patients with supraclavicular recurrence after mastectomy as primary treatment. Table 4 shows the number of patients with ISLM observed retrospectively by some authors [10, 12–15].

Another possible explanation is that ISLM is often associated with other metastatic sites [4]. In addition, it is difficult to compare the results of several clinical studies [13, 14, 16] in order to extract from them the data of patients with ISLM alone because they are put together with other patients with loco-regional sites of disease.

Despite the limitation of our study, the series of 37 patients with ISLM, prospectively treated with CT alone or CT plus RT, represent the first oriented study in this issue.

The prognosis in ISLM is rather dismal as supraclavicular nodes are mostly the prelude to new metastases and both disease-free and overall survival are similar to patients with metastatic disease in other sites than ISLM [2].

An argument against radical RT in ISLM could be based on the view that distant disease is the major problem and that increasing local control is a hollow victory. Our data show that the disease-free survival can be improved by increasing local control because uncontrolled ISLM could act as a source for new distant metastases ('secondary' dissemination) and subsequent mortality. This may determine a better quality of life, at least from a psychological point of view, for patients without evidence of disease. Furthermore, although the CT regimen used together with radical RT does not lead to a statistically significant increase in overall survival the availability of new and more active cytotoxic drugs could improve even survival.

Table 4 Literature data about ISLM according to both the number of patients retrospectively observed and the years reviewed.

Author	No. of patients	Years reviewed	Treatment
Toonkel [13]	14	12	RT +/− CT
Halverson [10]	54	22	RT alone
Schwaibold [14]	22	19	RT alone
Hirn-Stadler [15]	39	9	RT alone
Fentiman [12]	35	25	

Abbreviations: CT – chemotherapy; ISLM – ipsilateral supraclavicular lymph-node metastases; RT – radiation therapy.

In a recent report, Abraham et al. [17] observed a median progression-free survival of 32 months in 20 consecutive patients with isolated supraclavicular node metastases treated according to a regimen of high-dose chemotherapy. In 11 of 20 patients consolidation RT was delivered to the supraclavicular fossa affected by metastases and, despite the use of high dose chemotherapy, a statistically significant ($P = 0.02$) better disease-free survival was reported for additionally irradiated patients.

Our study has shown that the TtP of patients with ISLM is improved when RT is employed for definite control of the disease on supraclavicular nodes and confirm the results reported by Abraham et al. [17].

We observed a long local control to ISLM and no patient showed significant painful and distressing symptoms at the site of ISLM. These results are in conflict with the data reported by both Hirn-Stadler [15] who observed pain or arm edema in 38% of patients (15 of 39) with ISLM, and McKinna et al. [18].

In metastatic breast cancer the median survival after the appearance of metastases is about three years in most reported series [6]. We observed a median OS of 3.5 years in arm B and 2.3 years in arm A. Although this did not reach statistical significance, the magnitude of the difference suggests that the improvement in overall survival could be clinically important.

The patients treated with RT (arm B) may have a better outcome because of local consolidation therapy rather than CT itself. This is confirmed by the fact that it is not logical to suggest that three cycles of chemotherapy would be more efficient than six cycles. According to Greenberg et al. [19], we think that probably a long-term disease-free status can be obtained in patients which achieve an initial complete remission after treatment for metastatic breast cancer. Another hypothesis could be that in some patients the presence of overt ISLM is not a marker for occult disease at other sites. This assumption would justify the importance of local control by RT at the time of relapse in the supraclavicular fossa. In fact, our patients who underwent RT, had a lower risk of progressive disease, despite having a less efficient CT (three cycles vs. six cycles), an observation that has not been made previously. Currently we are holding ongoing chemo-RT clinical trials in ISLM, in which data being collected should provide further information on the observation made in this study.

As a result we believe, in accordance with other authors [20, 21], that increased 'local metastatic' tumor control in disseminated breast cancer would be likely to result in improved survival.

Nevertheless, a longer TtP should be viewed as a goal in itself since patients generally consider the presence of cancer to be a highly distressing condition.

In conclusion we suggest that the administration of RT as radical treatment after induction chemotherapy in ISLM reduces the risk of failure in this site and appears to have a favorable impact on the event-free survival; in addition, according to Brito et al. [20], there is a possibility of curative treatment for some patients with ISLM. Further trials, combining RT with new chemotherapeutic agents, may give better results and may also have an impact on overall survival.

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