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**Supraclavicular recurrence after early breast cancer:
a curable condition?**

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Abstract

Purpose: The prognosis of ipsilateral supraclavicular lymph node recurrence after early breast cancer appears to be worse than for other loco-regional recurrences, but better than for distant metastases. The purpose of the present study was to investigate the relationship between different types of salvage treatment and primary patient characteristics, treatment response, and survival after supraclavicular recurrence (SR) in a large patient population.

Methods: From the Danish Breast Cancer Cooperative Group treatment database 1977-2003, 305 patients were identified with SR without distant disease as site of first recurrence. Salvage treatment types as well as other factors were related to response and survival.

Results: The median follow-up time for progression after SR was 25 months. Complete remission was 76% among patients receiving excision surgery, 67% with combined loco-regional and systemic therapy, and 48% with systemic therapy alone. Median progression-free survival (PFS) and overall survival was 18 and 29 months, respectively. The 5-year PFS probability was 15%. In univariate analysis, combination salvage therapy, negative nodal status, and low malignancy grade were related to longer PFS. In multivariate analysis, salvage therapy and malignancy grade remained independent factors for survival.

Conclusions: The prognosis of SR is generally poor. However, it appears to be a curable condition. An independent marker of improved outcome is local and systemic combination salvage treatment, which can be considered.

Key words

breast cancer, prognosis, recurrence, supraclavicular, therapy

Introduction

Loco-regional recurrence after primary early stage breast cancer occurs in up to 20% of patients. The most common locations are chest wall, breast and ipsilateral axillary lymph nodes. Recurrence in these sites is curable.

Supraclavicular recurrence (SR) is an unusual event with uncertain curability and consequently an undefined treatment approach. In general, this condition portends systemic metastases and poor survival.

Recently, a study [1] investigated the prognosis of different loco-regional recurrences among a group of patients originally enrolled in an adjuvant treatment trial by the Danish Breast Cancer Cooperative Group (DBCG): for the merged group of patients with ipsilateral infraclavicular and/or supraclavicular metastases, the authors found an intermediate prognosis, being poorer than for other loco-regional recurrence sites, but better than for distant metastases. Three studies of small patient cohorts with SR receiving multi-modality treatment have proposed a 5-year progression-free survival rate of up to 20% [2-4].

Little information exists about the influence of primary patient characteristics and of treatment modality on the prognosis of SR. The choice of treatment is controversial and primarily based on institutional preferences. Most information has been derived from retrospective studies. In case of limited local therapy the risk of progression is extremely high, and even with the addition of systemic treatment the rate of persistent tumour control remains low [5]. Few studies have investigated the outcome of radical local salvage treatment in

combination with aggressive systemic therapy [2]. More data is needed to help clarify this complex situation, in order to decide the proper treatment approach.

We have performed a retrospective study of 305 Danish patients with SR as presentation of first recurrence, relating primary patient characteristics and treatment of SR with treatment response, time to progression, and overall survival after SR.

Patients and methods

Study cohort

45854 patients with early stage breast cancer enrolled in the DBCG adjuvant treatment database [6] between January 1977 and December 2003 were considered at risk of SR. All patients had histologically proven breast cancer free of supraclavicular or distant disease at primary diagnosis and no evidence of residual disease after primary treatment. Among this population, 305 patients subsequently reported off-study with a diagnosis of SR were studied. SR was defined as first recurrence more than one month after primary diagnosis, in the ipsilateral supraclavicular lymph node region, with or without other loco-regional metastasis, but with no evidence of distant metastases within one month of recurrence. Table 1 profiles patient characteristics at primary diagnosis in the study group.

Treatment

Treatment at primary diagnosis according to national guidelines has previously been described [6]. In brief, the surgical procedure comprised a tumourectomy or modified radical mastectomy, and partial axillary dissection. Patients with a tumourectomy were offered postoperative breast radiotherapy, and for high-risk patients the postoperative treatment predominantly consisted of locoregional (including supraclavicular) megavoltage irradiation. Systemic treatment to high-risk groups predominantly consisted of chemotherapy with cyclophosphamide, 5-

fluorouacil, and methotrexate or epirubicin, and/or endocrine therapy with primarily tamoxifen (Table 1).

Treatment for subsequent SR was carried out according to institutional preference, and included biopsy or radical surgery, involved field or loco-regional radiotherapy, anthracycline or other type chemotherapy, and aromatase or non-aromatase inhibitor endocrine therapy.

Follow-up and data collection

After primary diagnosis, patients were routinely followed minimum by history and physical examination twice yearly for five years and yearly for an additional five years [6]. After diagnosis of SR, follow-up was conducted as per the treating oncologists' discretion, typically quarterly. Follow-up continued until death or last date of hospital contact. Data registration of death was 1 October 2007. Staging procedures at time of SR typically included physical examination, chest X-ray, bone scan, and laboratory tests.

The long-term follow-up data collection source for the investigated population was the patient individual medical record. Extractions from the medical records included patient, tumour and therapy characteristics at the time of primary diagnosis, and characteristics of SR, including date, size, pathological confirmation, concomitant loco-regional disease extension, treatment, response to treatment, loco-regional progression, distant progression and death or last patient contact.

Endpoints and statistical analysis

Time to recurrence was defined as time from date of primary diagnosis to diagnosis of SR. Progression-free survival (PFS) was defined as time from SR to any localization of progression. The overall survival (OS) was calculated from SR to death of any cause. Complete remission was defined as disappearance of detectable tumour at SR. Potential prognostic factors for survival after SR were analysed as to patient individual variables before, at, and after SR. Interactions between confounding factors were analysed with the Mantel-Haenszel test. The probability of survival was estimated by the Kaplan-Meier method, and frequencies were reported. The log-rank test was used for comparison between subgroups of patients. Time proportionality of hazard ratios (HR) was evaluated by Schonfeldt analysis. All analysed univariate variables were included in a Cox regression model, and successively a stepwise backward elimination was performed. Level of significance was chosen as 5%.

Results

Survey of the SR cohort

Data was collected from a total of 305 breast cancer patients diagnosed with SR as first site of failure between 1977 and 2003. The frequency reported among patients entered into the DBCG adjuvant treatment database was as low as 1% (305/45854). A proportionally large fraction of the study group had axillary lymph node involvement (74%) and – for ductal carcinomas - high tumour malignancy grade (80%) at primary diagnosis (Table 1). The median time to recurrence was 27 months (range 2-114 months). At time of SR diagnosis, the median and mean age was 57 years (range 32-79 years). Among the cohort, 188 patients had isolated SR and 117 patients had synchronous other loco-regional disease extension, mostly with only one additional disease site (86 patients). After SR, 234 (77%) events of progression had been observed and 267 (88%) patients were dead at the time of analysis. The median follow-up time after SR was 25 months (range 1-136 months) for progression and 43 months for death (range 2-275 months).

158 (52%) patients had reported local symptoms prior to verification of SR. Median supraclavicular tumour size was 14 mm (range 4-70 mm). 96% of the patients had biopsy verification of their recurrence; in the remaining select cases, the recurrence was verified by ultrasound, X-ray and/or physical examination. Additional staging procedures comprised physical examination, chest X-ray/CT, skeletal X-ray/CT or bone scan, and laboratory tests for $\geq 95\%$ of

the patients; liver ultrasound or CT was performed in 35% of the cases. Table 2 profiles patient characteristics at SR.

Treatment of SR

Most of the patients with SR received systemic salvage treatment, whereas a smaller fraction had loco-regional treatment, either as radiotherapy alone or in combination with surgery (Table 3).

19% of the patients were surgically treated with at least removal of the macroscopic tumour. 103 (33%) patients received radiotherapy with curative intent at least to the involved field with megavoltage to 48-50 Gy in 22-25 fractions. A boost of 10-20 Gy was applied in 56 of these cases. Only 10% of the patients had combined surgery and radiotherapy.

Endocrine treatment was used for 123 (40%) of the patients, predominantly as tamoxifen (107 cases) and rarely as letrozol or megestrole acetate (16 cases). Virtually all of these patients (120) had a steroid hormone receptor positive tumour or unknown receptor status. Endocrine treatment was combined with loco-regional therapy in 52 cases. Chemotherapy was used for 136 (45%) of the patients. Anthracycline based regimens were administered in 99 of these cases, whereas taxanes were used in only 4 cases. Chemotherapy was combined with loco-regional therapy in only 37 cases.

Overall, 78 (26%) patients had combined loco-regional (surgery and/or radiation) and systemic (endocrine and/or chemo) therapy.

Since type of treatment at SR was not randomly assigned, but carried out according to institutional preference, the study group was further analysed for

interactions between confounding factors and salvage treatment: patients with negative lymph node status at primary diagnosis received combination therapy at SR more often than patients with node positive primary diagnosis (42% versus 20%) ($P=0.01$). Explanatory, patients without adjuvant primary radiotherapy – prevalently node negative cases – received local or combination salvage therapy more often than patients with adjuvant primary radiotherapy ($P=0.03$). Also, an interaction between tumour size at SR and systemic or combination therapy was observed ($P=0.0005$). No interactions were observed for tumour size or grade at primary diagnosis, age or disease extension at recurrence, or recurrence-free interval.

Response to treatment

Overall, complete remission rate was 48%, partial remission 23%, stable disease 9%, and early progressive disease during salvage treatment 20%. Complete remission rates depended on type of treatment, and the highest frequency was seen in patients given loco-regional therapy; among patients receiving excision surgery complete remission rate was 76% - significantly higher than for patients not given surgery (43%) ($P<0.0001$) - and for curative radiotherapy the rate was 62%. A small group of 15 patients receiving only surgery plus radiotherapy experienced a very high remission rate of 87%. For patients receiving systemic therapy, the complete remission rate was lower, 58% for chemotherapy and only 42% for endocrine treatment. Combining loco-regional and systemic therapy resulted in a proportionally higher rate of remission by 67%, as compared to loco-

regional therapy only (64%) or – in particular – systemic therapy only (40%) ($P<0.0001$).

Analysis for interactions between confounding factors and salvage treatment response revealed a positive correlation between decreasing tumour size at SR and rate of complete remission ($P=0.03$). However, there was no interaction with response for primary tumour size, grade, lymph node status, age, recurrence-free interval, or whether SR had synchronous other loco-regional disease extensions or not.

Prognosis after SR

After treatment of SR, follow-up was conducted between 2 and 6 times yearly for 93% of the patients. Thus, treatment induced persistent tumour control could be assessed. 66 (22%) patients remained free of evidence of disease during the entire follow-up period, whereas 138 ultimately progressed locally and 96 progressed with distant metastases. At time of analysis 31 (10%) patients still remained alive and free of progression. Figure 1 shows the Kaplan-Meier estimates of PFS and OS after SR. The median PFS and OS was 18 and 29 months, respectively. The 5-year PFS and OS probability was 15 and 24%, respectively (Table 4). Survival in relation to prognostic parameters is also shown in Table 4.

In univariate analysis, the following parameters were related to prognosis of SR: response to salvage treatment, where progression after SR was related to salvage treatment response – i.e. complete remission was related to good prognosis, whereas partial or no response predicted poor survival ($P<0.0001$);

type of salvage treatment, where systemic treatment resulted in prolonged progression-free survival ($P=0.003$) - in particular the risk of disease progression was significantly reduced when combined with loco-regional treatment as demonstrated in Figure 2 ($P=0.01$); negative nodal status ($P=0.02$) and low tumour grade ($P=0.03$) at primary diagnosis were related to good SR prognosis. There was a longer OS for patients experiencing SR after >2 years ($P=0.004$). Multivariate Cox analysis included 280 patients with 233 events regarding PFS and 305 patients with 267 events regarding OS. The analysis demonstrated that salvage treatment assignment was an independent parameter for PFS (Table 5); for loco-regional versus combination treatment the hazard ratio was 1.8 (95% confidence interval: 1.2-2.8) ($P=0.006$). Also, negative lymph node status and low tumour malignancy grade at primary diagnosis remained independent parameters ($P=0.03$). For OS, salvage treatment ($P=0.04$) and malignancy grade ($P=0.02$) were the only independent parameters.

Subgroup analysis of 225 patients with positive lymph node status

A separate exploratory analysis of the unique group of 225 patients with the high risk factor of positive lymph node status at primary diagnosis was performed, with the understanding that salvage treatment assignment and PFS was significantly different from the group with negative nodal status. After SR, 171 events of progression and 196 deaths had been observed. In univariate analysis, combination salvage treatment remained significantly associated with prolonged time to progression, indicating its robustness as a prognostic marker for PFS. Multivariate analysis confirmed salvage treatment assignment as an independent

parameter for PFS with a hazard ratio of 1.5 (95% confidence interval: 1.03-2)
($P=0.04$) in favour of combination therapy.

Discussion

In this study we have presented data on salvage treatment, response and prognosis of SR for the, to our knowledge, largest cohort so far published. However, due to the non-randomised retrospective nature of the study, type of treatment at SR was not randomly assigned, but individually selected according to institutional preference. Inevitable bias in the selection of treatment therefore limits the interpretation of the therapeutic options.

Basically, the risk of SR is low [7-9], as also indicated by the frequency reported among patients entered into the DBCG adjuvant treatment database of only 1% among unselected consecutive patients treated for early breast cancer. The completeness of the registration of SR as site of first recurrence in the DBCG database is unknown and some misclassification may have found place. Thus, the reported number is a minimum estimate. The risk of SR may be dependent on patient characteristics and primary treatment. Although our study did not aim at identifying risk factors for supraclavicular failure, it appears from the patient characteristics at primary diagnosis that an expectedly large fraction of the study group presented with the high-risk parameters of axillary lymph node positive disease and high tumour malignancy grade as compared to the general patient population [6], in agreement with previous findings [9]. The median time to recurrence of 27 months did not differ significantly from other reports on loco-regional recurrence [1, 2]. The diagnostic set-up at time of SR of the presented cohort verified the recurrence as truly not disseminated. However, only a minority of the patients had CT, and newer modalities such as MR and PET were not

included. It should be appreciated that consistent use of such modalities might have induced stage migration. Thus, in one study as many as 50% of patients with loco-regional failure had additional disease after thoracic CT [10].

Recurrences in the residual breast, surgical scar or ipsilateral axilla are usually aggressively approached with both local and systemic salvage therapy, whereas SR traditionally has been offered systemic therapy only. This policy has been under change recently, based on small studies demonstrating long-term survival after multi-modality salvage therapy of SR [2-4]. In our study, the far majority of the patients received systemic salvage treatment (75%), whereas a smaller fraction had curative loco-regional treatment, either as radiotherapy alone or in combination with surgery. The use of radiotherapy was restricted to patients not previously irradiated supraclavicularly. In this study loco-regional treatment resulted in a high complete remission rate. Severe morbidity associated with uncontrolled supraclavicular recurrence was thereby perhaps prevented. The addition of endocrine treatment after radical surgery and/or radiotherapy of a loco-regional recurrence prolongs PFS [11], and should be considered for patients with hormone sensitive tumours. Little information exists for the benefit of chemotherapy for loco-regional recurrence [12]. The present results are biased with respect to choice of salvage treatment since the choice could be influenced by other conditions such as age and comorbidity. Also, patients were not treated according to modern standards, i.e aromatase inhibitors, taxanes and newer targeted therapies were rarely used as salvage treatment. Furthermore, our study showed that patients with negative lymph node status at primary diagnosis received combination therapy at SR more often than patients with node positive

primary diagnosis (42% versus 20%), indicative of node positive patients already having received supraclavicular radiotherapy prior to SR. Also, an interaction between tumour size at SR and salvage therapy was observed: patients with small size tumours were more often offered local therapy only, indicative of suboptimal treatment resulting in high but not lasting rates of remission.

Despite the treatment inadequacies of SR, complete remission was achieved in half of the cases, and early progression only occurred for 1 of 5 patients. The present study indicates that excision surgery or loco-regional megavoltage radiotherapy could improve local control; especially when combined radical radiotherapy and surgery was employed a high control rate was achieved.

Ultimately, in the present study the median survival after SR was short (29 months), but a remarkable proportion of the patients (22%) remained free of evidence of disease during the entire follow-up period. Furthermore, a larger fraction of the patients escaped distant progression (45%). Several factors, primary tumour as well as recurrence related, were found to be prognostic for survival. In the multivariate analysis, first of all systemic combination salvage treatment was an independent prognostic marker of prolonged PFS and OS, indicative of a higher efficiency than monotherapy. Also, nodal status and tumour grade at primary diagnosis were related to SR prognosis, indicating inherent aggressive tumour factors less sensitive to treatment. Conversely, there was a longer survival for patients experiencing late SR from slowly growing tumours which may respond longer to salvage treatment. Interpretation of this data must be performed with the understanding of the inherent bias in selection of patients for different strategies of salvage treatment.

The prognosis of SR is generally poor: It has been shown that patients with SR have a 5-year survival ranging from anywhere between 5 and 35% [13-15], far different from the cure rate of 35-50% for an axillary recurrence [16-18]. Nielsen et al. [1] investigated the prognosis of different loco-regional sites as first recurrence among patients originally enrolled in an adjuvant treatment trial by the DBCG: for the merged group of patients with infraclavicular and/or supraclavicular metastases, the authors proposed an intermediate prognosis, being poorer than for other loco-regional recurrence sites, but better than for distant metastases. The three small studies using aggressive multi-modality treatment have demonstrated a 5-year disease-free survival rate of approximately 20% [2-4]. A recently published prospective study including supraclavicular recurrence +/- other loco-regional manifestations demonstrated a similar survival rate [19].

Fewer patients with the high risk factor of positive lymph node status at primary diagnosis received local or combination salvage therapy than node negative patients – reflecting that salvage radiotherapy in this group was rarely an option due to prior primary adjuvant irradiation. Nevertheless, the prognostic power of salvage treatment type for survival after SR was also confirmed in this unique group of 225 node positive patients: combination treatment remained significantly associated with prolonged time to progression, indicating its robustness as a prognostic marker for PFS.

In this retrospective cohort study of SR without distant disease, combined loco-regional and systemic therapy was related to longer PFS and OS compared to systemic or loco-regional therapy alone. Radical surgery and/or high-dose

radiotherapy seemed to be a mandatory part of the treatment in order to enhance persistent tumour control and systemic therapy in order to prevent distant metastases. However, the non-randomised nature of the study limits the interpretation of the therapeutic options; in the absence of randomised evidence and in spite of not up-to-date systemic treatments used in the study, a combined treatment approach could be considered in supraclavicular recurrent breast cancer. Thus, this rare site of recurrence is not inevitably a nidus for dissemination, and appears to be an occasionally curable condition.

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Tables

Table 1 Patient characteristics and treatment at primary diagnosis

Parameter	Frequency
All patients	305 (100%)
Tumour size	
≤ 20 mm	118 (39%)
> 20 mm	177 (58%)
Unknown	10 (3%)
Positive lymph nodes	
0	79 (26%)
1-3	84 (28%)
> 3	141 (46%)
Unknown	1
Histology	
Ductal carcinoma	276 (90%)
Non-ductal carcinoma	29 (10%)
Malignancy grade (ductal only)	
I	44 (16%)
II	145 (53%)
III	76 (27%)

Unknown	11 (4%)
Hormone receptor status	
Negative	94 (31%)
Positive	140 (46%)
Unknown	71 (23%)
Chemotherapy	
No/unknown	151 (50%)
Yes	154 (50%)
Hormonal therapy	
No/unknown	189 (62%)
Yes	116 (38%)
Radiotherapy	
No/unknown	235 (77%)
Yes	70 (23%)

Table 2 Patient characteristics at supraclavicular recurrence

Parameter	Frequency
All patients	305 (100%)
Age	
≤50 years	85 (28%)
51-60 years	91 (30%)
>60 years	129 (42%)
Supraclavicular tumour size	
≤10 mm	90 (30%)
11-20 mm	103 (34%)
>20 mm	59 (19%)
Unknown	53 (17%)
Synchronous sites	
No	188 (62%)
Yes	117 (38%)
Symptoms	
No	146 (48%)
Yes	158 (52%)
Unknown	1
Verification	
Histology	82 (28%)
Cytology	190 (65%)

Other	12 (4%)
Time to recurrence	
≤2 years	132 (43%)
>2 years	173 (57%)

Table 3 Treatment of supraclavicular recurrence

Modality	Frequency
Excision surgery	19%
Curative radiotherapy	33%
Surgery+radiotherapy	10%
Endocrine therapy	40%
Chemotherapy	45%
Endocrine+chemotherapy	11%
No systemic therapy	25%
Systemic therapy only	49%
Local+systemic therapy	26%

Table 4 Five-year progression-free and overall survival probabilities after supraclavicular recurrence

Parameter	<u>Progression-free survival</u>		<u>Overall survival</u>	
	Probability	P-value	Probability	P-value
All patients	15		24	
Age		0.89		0.97
≤50 years	15		24	
51-60 years	15		23	
>60 years	15		24	
Primary tumour size		0.31		0.91
≤20 mm	15		23	
>20 mm	13		25	
Malignancy grade		0.03		0.004
I	13		29	
II	15		30	
III	7		12	
Positive lymph nodes		0.02		0.03
0	17		29	
1-3	9		22	
>3	11		23	
Time to recurrence		0.21		0.004
≤2 years	15		19	

>2 years	13	37	
Supraclavicular tumour size	0.64		0.91
≤10 mm	8	21	
11-20 mm	14	24	
>20 mm	14	28	
Synchronous sites	0.67		0.88
No	15	26	
Yes	13	23	
Local salvage treatment	0.9		0.35
No	10	20	
Yes	10	29	
Systemic salvage treatment	0.003		0.04
No	7	18	
Yes	12	26	
Combination salvage treatment	0.01		0.04
Local + systemic	20	33	
Systemic only	11	21	
Local only	7	18	

Table 5 Independent parameters for survival after supraclavicular recurrence

Parameter	Progression-free survival		Overall survival	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Salvage treatment	0.006		0.04	
Local + systemic		1.0		1.0
Systemic only		1.3 (0.9-1.8)		1.2 (0.9-1.7)
Local only		1.8 (1.2-2.8)		1.5 (1.1-2.3)
Malignancy grade	0.03		0.02	
I		1.0		1.0
II		1.0 (0.8-1.4)		1.1 (0.8-1.5)
III		1.6 (1.1-2.3)		1.6 (1.1-2.2)
Lymph node status	0.03			
0		1.0		
1		1.5 (1.0-2.2)		
>3		1.5 (1.1-2.2)		

HR: Hazard Ratio; CI: Confidence Interval

Figure Captions

Fig. 1 Progression-free (a) and overall survival (b) after supraclavicular recurrence

Fig. 2 Progression-free survival by combination of salvage treatment after supraclavicular recurrence. Note that in this non-randomised retrospective cohort study type of treatment was not randomly assigned, but individually selected according to institutional preference! Syst+loc: combined systemic and local therapy; Syst: systemic therapy alone; No syst: no systemic therapy



