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CLINICAL INVESTIGATION **Breast**

LOCOREGIONAL TREATMENT OUTCOMES FOR BREAST CANCER PATIENTS WITH IPSILATERAL SUPRACLAVICULAR METASTASES AT DIAGNOSIS

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Purpose: To evaluate the locoregional efficacy of multimodality treatment for breast cancer patients who present with ipsilateral supraclavicular (SCV) disease without systemic metastases.

Methods: We retrospectively reviewed the data from 71 patients with ipsilateral SCV involvement at presentation. SCV involvement in 16 patients (23%) was diagnosed by ultrasound examination only, without palpable disease. All patients were treated with curative intent using neoadjuvant chemotherapy, mastectomy or breast-conserving surgery (BCT), and radiotherapy.

Results: The 5-year SCV control, locoregional control (LRC), disease-free survival, and overall survival rate was 90%, 77%, 30%, and 47%, respectively. Patients with persistent SCV disease after neoadjuvant chemotherapy by physical examination had a lower rate of LRC (64% vs. 86%, $p = 0.026$), as did those with persistent SCV disease by ultrasound examination (66% vs. 96%, $p = 0.007$). Of those with a complete response of SCV disease by physical examination after neoadjuvant chemotherapy, those with persistently abnormal ultrasound findings had significantly worse disease-free survival (0% vs. 55%, $p = 0.03$). BCT was not associated with lower rates of LRC (82% for BCT vs. 76% for mastectomy, $p = 0.80$).

Conclusion: Radiotherapy achieved excellent LRC after surgery for patients with ipsilateral SCV metastases who achieved a complete response of the SCV disease after neoadjuvant chemotherapy. For patients who achieved a complete response of the SCV disease by physical examination, ultrasonography of the SCV fossa may help assess the risk of disease recurrence. SCV involvement should not be considered a contraindication for BCT.

Supraclavicular lymphadenopathy, Radiotherapy, Breast cancer.

INTRODUCTION

The American Joint Committee on Cancer (2002) recently revised the staging of breast cancer. In the updated staging system, ipsilateral supraclavicular (SCV) nodal metastases are considered locoregional disease (N3c or Stage IIIC) rather than distant metastases (1). Historically, patients with SCV nodal involvement were considered to have a poor prognosis similar to those with Stage IV disease, and many were treated with palliative intent. However, investigators have recently reported their institutional experience using aggressive treatment that combined neoadjuvant and adjuvant chemotherapy, surgery, radiotherapy (RT), and hormonal therapy (2, 3). With the use of multimodality therapy such patients were able to achieve long-term survival rates of 30%, similar to that of patients with Stage IIIB disease. These data have demonstrated that this disease extent, although locally advanced, is potentially curable and support the revision of the staging system.

Although these data suggest that the survival rate of patients with ipsilateral SCV disease at the initial diagnosis is similar to that of other patients with locally advanced breast cancer (2, 3), little data are currently available re-

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garding the efficacy of locoregional treatment for this subset of patients. The purpose of this study was to evaluate the locoregional outcomes after multimodality therapy for breast cancer patients who presented with SCV disease without systemic metastases.

METHODS AND MATERIALS

Patient and treatment characteristics

We retrospectively analyzed the outcomes of 71 patients who presented with ipsilateral SCV nodal involvement without systemic metastases and were treated at the University of Texas M.D. Anderson Cancer Center (Houston, TX) between 1974 and 2000 for noninflammatory, nonmetastatic breast cancer. The SCV involvement of 16 patients (23%) was diagnosed by ultrasound examination only, without palpable disease (4). Because we were interested in the locoregional treatment outcomes, we only included those patients who completed curative multimodality therapy consisting of neoadjuvant chemotherapy, surgery, and postoperative RT. The patients included in this series were slightly different from those in our previously published institutional experience by Brito *et al.* (2), which consisted of 70 patients treated between 1974 and 1991. This series included patients treated more recently, between 1992 and 2000, but also excluded patients who did not complete multimodality therapy because of early development of distant disease.

All patients underwent clinical staging according to the 2002 American Joint Committee on Cancer guidelines (1). Patients were assessed at presentation using physical examination, mammography, and staging studies to exclude metastatic disease. Twenty-six patients underwent ultrasound-guided fine-needle aspiration to confirm SCV disease (4).

The doxorubicin-based neoadjuvant chemotherapy regimens followed those used in prospective institutional trials during the study period. The details concerning these regimens have been described in previous reports (5–7). Most of the patients were evaluated in a multidisciplinary setting before and after completion of neoadjuvant chemotherapy. Surgery consisted of either mastectomy ($n = 60$) or breast-conserving surgery (BCT) ($n = 11$). Patients deemed eligible for BCT were carefully selected not to have diffuse calcifications, residual skin involvement after chemotherapy, or significant residual disease after chemotherapy that would preclude obtaining clear surgical margins. Residual SCV disease after neoadjuvant chemotherapy was not considered a contraindication for BCT. BCT typically involved excision of the residual primary tumor with a margin of normal tissue, without an attempt to resect the prechemotherapy tumor volume. The surgery type was determined on an individual basis according to our institutional selection criteria and the biases of the patient and her care providers. All the patients underwent at least a Level I and II axillary dissection, and the median number of nodes recovered was 12. None of the patients underwent surgery of the SCV fossa.

All patients in this series received comprehensive external beam RT to the breast or chest wall and the regional lymphatics as a component of their treatment. In general, 50 Gy was delivered in 25 fractions to the breast or chest wall using tangential fields, followed by a 10-Gy boost to the tumor bed or chest wall scar using an appositional electron field. All patients received RT targeting the SCV fossa that typically consisted of an appositional field delivering 50–66 Gy (median, 58 Gy). Higher radiation doses were given for those with gross residual SCV disease at RT; these were delivered using one or two smaller boost fields. RT targeting the internal mammary chain nodes was delivered at the discretion of the radiation oncologist, with a median dose of 50 Gy.

Adjuvant chemotherapy was also delivered in 59 patients (83%). The indications for chemotherapy varied depending on patient and physician biases, as well as the protocol open at treatment. Tamoxifen was used by 22 patients (31%). In general, tamoxifen was recommended to postmenopausal patients with estrogen receptor (ER)-positive tumors.

Statistical analysis

SCV control was defined as freedom from disease progression or recurrence in the ipsilateral SCV fossa. Locoregional control (LRC) was defined as freedom from disease recurrence in the ipsilateral breast or chest wall or in the ipsilateral axillary, SCV, infraclavicular, or internal mammary nodes. All SCV recurrences and locoregional recurrences were counted as events, regardless of whether they were the first site of failure or occurred after distant metastasis. Disease-free survival (DFS) was defined as freedom from any breast cancer recurrence. The actuarial rates of LRC, DFS, and overall survival were calculated according to the Kaplan-Meier method from the date of diagnosis, and differences among groups were compared using the log–rank test. Multivariate analyses of LRC and DFS were performed using a Cox proportional hazards model. All p values were two-sided, and $p \leq 0.05$ were considered significant (8).

RESULTS

Table 1 displays the patient and disease characteristics of the 71 patients included in this series. SCV disease was diagnosed by physical examination in 27 patients (38%) before the routine use of ultrasound examination, by ultrasound examination only without palpable disease in 16 (23%), and by both physical and ultrasound examinations in 28 (39%). The clinical complete response (CR) rate to neoadjuvant chemotherapy, including the primary and regional nodal disease, was 18%. The clinical CR rate within the SCV fossa was 49%. The pathologic CR rate (no residual disease found in the breast or axillary lymph nodes) was 10%.

The median follow-up of the surviving patients was 3.7 years (range, 1.0–24.0 years). The 5-year SCV control, LRC, DFS, and overall survival rate was 90%, 77%, 30%, and 47%, respectively (Fig. 1). Of the 15 patients who had locoregional recurrence, 7 had failure in the SCV nodes (5 had isolated SCV recurrence) and 10 had chest wall failures (6 had isolated chest wall recurrence; Table 2). All seven SCV failures recurred within the radiation field. Higher radiation doses delivered to the SCV field were not associated with greater rates of SCV control, although the higher radiation doses were associated with the presence of residual SCV disease at RT (median dose 60 Gy for those with residual disease vs. 56 Gy for those who had a CR). The extent of residual SCV disease after neoadjuvant chemotherapy was significantly associated with recurrence in the SCV fossa. Patients with residual SCV disease >1 cm had lower rates of SCV control at 5 years (54% vs. 95%, $p = 0.001$), as did those with any amount of residual SCV

Table 1. Patient characteristics

Characteristic	*n*	%
Method of N3c diagnosis		
Physical examination only	27	38
Physical examination + ultrasonography	28	39
Ultrasonography only (nonpalpable)	16	23
Age (y)*		
<50	36	51
≥50	35	49
T stage		
T1	3	4
T2	18	25
T3	9	13
T4	41	58
Response to neoadjuvant chemotherapy		
Complete	13	18
Partial	40	57
Minimal	13	18
No change	2	3
Progression	3	4
Pathologic tumor size (cm)		
0–2.0	37	52
2.1–5.0	18	25
>5	16	23
Positive axillary nodes *(n)*		
0	14	20
1–3	17	24
≥4	37	52
Unknown	3	4
Estrogen receptor status		
Positive	32	45
Negative	26	37
Unknown	13	18

* Median 49 y.

disease (82% vs. 97%, $p = 0.047$). Having ER-negative disease was also associated with worse SCV control (81% vs. 97%, $p = 0.023$).

The clinical and pathologic factors associated with LRC are shown in Table 3. Patients with palpable SCV lymphadenopathy at presentation had a lower rate of LRC than

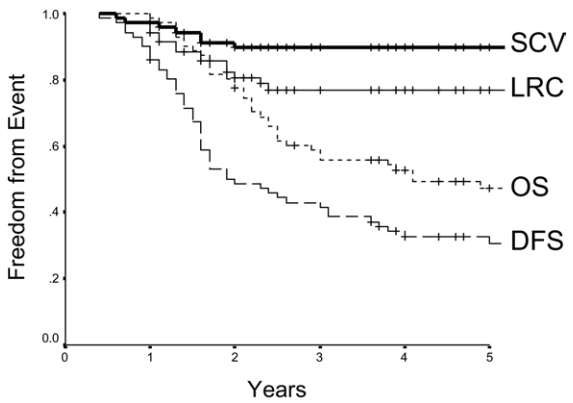

Fig. 1. Supraclavicular (SCV) control (7 events), locoregional control (LRC, 15 events), disease-free survival (DFS, 48 events), and overall survival (OS, 36 events) rate for all patients with Stage IIIC disease ($n = 71$).

Table 2. Sites of locoregional recurrence

Site	*n**	%
Chest wall or breast	10	14
Supraclavicular nodes	7	10
Infraclavicular nodes	1	1
Axilla	1	1
Internal mammary chain	0	0

* Of 71 patients, 15 had locoregional recurrence (crude rate 21%), with some having multiple recurrence sites.

those with nonpalpable SCV disease detected only by ultrasound examination (69% vs. 100%, $p = 0.017$). The extent of SCV disease after neoadjuvant chemotherapy was also associated with worse outcomes. Patients with residual SCV disease by physical examination had a lower rate of LRC (64% vs. 86%, $p = 0.026$), as did those with residual SCV disease by ultrasound examination (66% vs. 96%, $p = 0.007$). Other factors significantly associated with lower rates of LRC included having clinical Stage T4 disease, ER-negative disease, axillary dissection of <10 lymph nodes, and not having a CR of the primary tumor after chemotherapy. The use of BCT was not associated with a lower rate of LRC (82% for BCT vs. 76% for mastectomy, $p = 0.80$; Fig. 2a).

The clinical and pathologic factors associated with DFS are also shown in Table 3. Similar to the analysis of LRC, patients with palpable SCV lymphadenopathy at presentation and patients with residual SCV disease by either physical examination or ultrasound examination had lower DFS rates. Of the patients who had a CR of the SCV disease by physical examination, those with persistently abnormal ultrasound findings after chemotherapy had significantly worse DFS (0% for CR on physical examination with residual disease on ultrasound examination vs. 55% for CR on physical examination with normal ultrasound findings, $p = 0.030$; Fig. 3). Other factors that were significantly associated with lower rates of DFS included not having a clinical CR of the primary tumor after chemotherapy, not having a pathologic CR to chemotherapy, four or more positive axillary nodes after neoadjuvant chemotherapy, and axillary dissection of <10 lymph nodes. The use of BCT was not associated with lower rates of DFS (44% for BCT vs. 28% for mastectomy, $p = 0.34$; Fig. 2b).

Multivariate analysis of LRC was performed with a Cox proportional hazards model to assess the significance of each of the factors regarding the extent of SCV disease (Table 4). Each of the SCV disease factors was added one at a time to a model that incorporated the other factors significantly associated with lower LRC rates (Stage T4 disease, ER-negative disease, dissection of <10 nodes, and no clinical CR of primary tumor). Using this model, the presence of residual SCV disease after chemotherapy detected by ultrasound examination was significantly associated with worse LRC (hazard ratio 10.2, 95% confidence interval 1.2–85.1, $p = 0.031$). A similar multivariate analysis was performed to assess for factors associated with

Table 3. Actuarial rates of locoregional control and disease-free survival

Variable	LRC		DFS	
	5-y Rate (%)	*p*	5-y Rate (%)	*p*
Clinical T stage		0.009		NS
T1-T3	92		33	
T4	65		25	
SCV disease at presentation		0.017		<0.001
US detectable only	100		75	
Palpable	69		19	
SCV disease after chemotherapy by PE		0.026		0.002
Complete response	86		39	
Residual disease	64		12	
SCV disease after chemotherapy by US		0.007		0.002
Complete response	96		55	
Residual disease	66		0	
SCV disease after chemotherapy with a complete response by PE		NS		0.030
Complete response by US	96		55	
Residual disease by US	83		0	
Primary response to chemotherapy		0.040		0.057
Complete response	100		53	
Partial or less response	71		23	
Pathologic response to chemotherapy		NS		0.041
Complete response	86		71	
Residual disease	76		26	
Pathologic tumor size (cm)		NS		NS
0–2.0	76		35	
2.1–5.0	69		28	
>5	87		27	
Positive axillary nodes *(n)*		NS		0.005
0–3	83		67	
≥4	71		21	
Axillary nodes dissected *(n)*		0.051		0.005
0–9	61		11	
≥10	83		39	
ER status		0.056		NS
Positive	85		30	
Negative	68		31	
Surgery		NS		NS
Breast-conserving surgery	82		44	
Mastectomy	76		28	
Radiation dose to SCV (Gy)		NS		NS
<60	78		30	
≥60	78		25	

Abbreviations: LRC = locoregional control; DFS = disease-free survival; NS = not significant ($p > 0.05$); SCV = supraclavicular; US = ultrasonography; PE = physical examination; ER = estrogen receptor.

DFS. Each of the SCV disease factors was added one at a time to a model incorporating the other factors significantly associated with lower rates of DFS (four or more positive nodes, dissection of <10 nodes, no clinical CR of primary tumor, and no pathologic CR after chemotherapy). All four of the SCV disease factors were significantly associated with worse DFS: palpable SCV disease at presentation, residual SCV disease after chemotherapy by physical examination, residual SCV disease after chemotherapy by ultrasound examination, and residual SCV disease after chemotherapy by ultrasound examination despite a CR by physical examination (Table 4). A multivariate analysis of SCV control was not performed because the low number of events ($n = 7$) precluded an analysis of adequate power.

DISCUSSION

This report presents our institutional experience of 71 patients with ipsilateral SCV involvement at presentation who completed multimodality treatment using neoadjuvant chemotherapy, surgery, and RT. Before the routine use of systemic therapy, patients with SCV involvement were treated with local therapy alone using either RT or surgery. In such patients, the local control rates were <50% and almost all patients developed distant metastases within 1 year, with almost no survivors at 5 years (9, 10). However, in the era of multimodality therapy, these patients are potentially curable. In our series, the 5-year survival rate of patients who were able to complete neoadjuvant chemother-

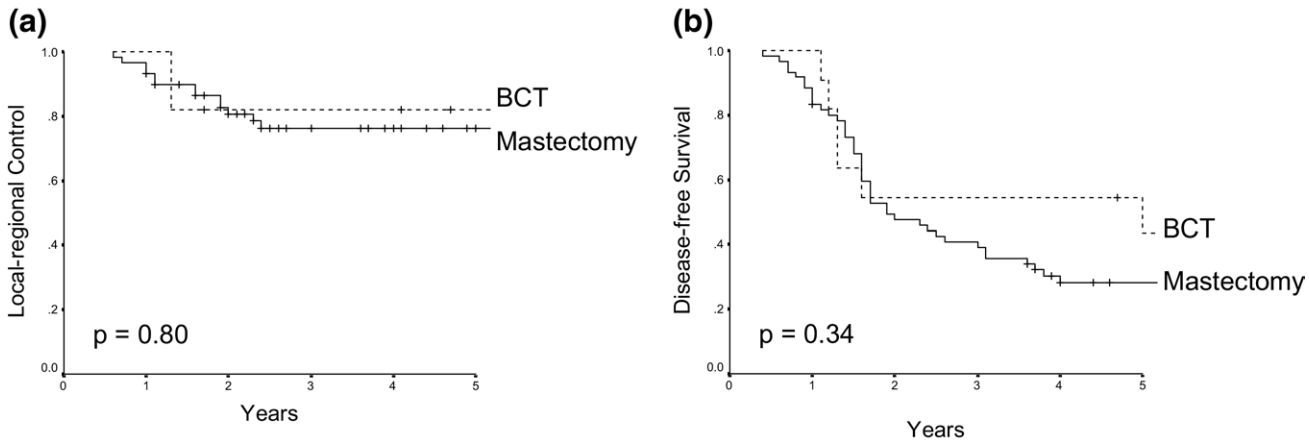

Fig. 2. (a) Locoregional control rate for patients treated with mastectomy (n = 60, 13 events) or breast-conserving surgery (BCT) (n = 11, 2 events). (b) Disease-free survival rate for patients treated with mastectomy (n = 60, 42 events) or breast-conserving surgery (BCT) (n = 11, 6 events).

apy, surgery, and RT was 47%, comparable to that of other series reported by Brito *et al.* (2) and Olivotto *et al.* (3) that reported a survival rate of 41% and 30%, respectively.

Our report is the first to provide the locoregional outcomes of patients who presented with SCV disease. With a combination of chemotherapy, surgery, and RT, the LRC rate was 77% at 5 years, similar to selected categories of patients with locally advanced disease. One of the interesting findings from our analysis was that the surgery type did not appear to significantly affect the rate of LRC (5-year rate 82% for BCT vs. 76% for mastectomy, p = 0.80). However, there are two caveats to this observation. First, the number of patients treated with BCT was relatively small, with only 11 patients and two locoregional recurrences. Second, BCT was only offered to a highly select group of patients in a well-coordinated multidisciplinary team setting. At our institution, the standard eligibility criteria for BCT include the absence of diffuse calcifications, the absence of residual skin changes after neoadjuvant chemotherapy, nonmulticentric disease, the ability to achieve negative margins with acceptable cosmesis, and the ability to undergo RT (11, 12). Despite these caveats, our results suggest that, for appropriately selected patients, SCV involvement should not be considered a contraindication for BCT.

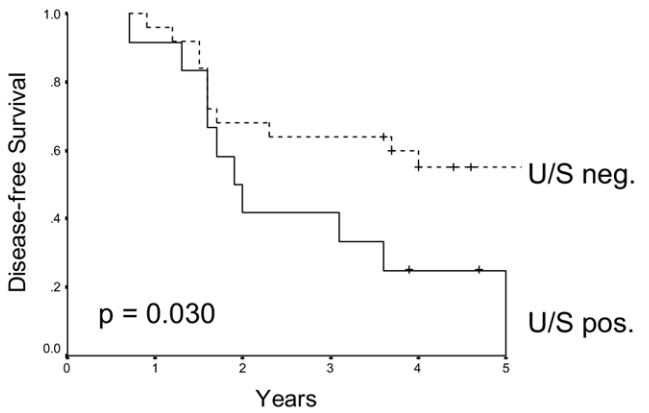

Fig. 3. Disease-free survival rate for patients who achieved a complete response by physical examination after chemotherapy, but had positive ultrasound (U/S pos.) findings of residual supraclavicular disease (n = 12, 10 events) vs. those with ultrasound-negative (U/S neg.) findings (n = 25, 11 events).

Another interesting finding from our analysis was the relationship between the SCV disease extent and patient outcome, suggesting that the burden of residual disease after neoadjuvant chemotherapy is a prognostic factor for LRC, as well as for DFS. For patients who had residual SCV disease after chemotherapy, the LRC rate was <70% and the DFS rate was <25%. For patients who achieved a CR in the SCV fossa by physical examination, an ultrasound examination helped to further assess their likelihood of DFS. In our series, every patient who had residual disease on ultrasound examination of the SCV fossa developed breast cancer recurrence within 5 years. To better evaluate the regional nodal basins, our institution began incorporating ultrasonography and ultrasound-guided fine-needle aspiration biopsy into routine clinical practice for staging and evaluation of the response to therapy in the early 1990s. Previous work has demonstrated that ultrasonography can detect lymph node metastases as small as 5 mm using diagnostic criteria such as a rounded shape, hilar compression, and cortical thickening or hypoechogenicity (13–16).

Because of the high risk of recurrence, patients with residual SCV disease after neoadjuvant chemotherapy may benefit from new treatment strategies in a protocol setting. One of the unique aspects of this group of patients is that SCV disease is the only site in the definitive treatment of breast cancer in which gross disease is not surgically removed. This residual nidus could be a source of tumor cell dissemination, resulting in distant metastases, as well as locoregional recurrence, or, it could be a surrogate indicator of early micrometastatic disease that was already present at diagnosis. Whether patients with residual SCV disease may benefit from limited SCV dissection or lymphadenectomy remains to be studied. Although surgical treatment of this

Table 4. Multivariate analysis of locoregional control and disease-free survival

Variable	LRC			DFS		
	Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	*p*
Palpable SCV disease at presentation			NS	5.8	2.1–16.4	0.001
Residual SCV disease after chemotherapy on PE			NS	3.0	1.5–6.0	0.002
Residual SCV disease after chemotherapy on US	10.2	1.2–85.1	0.031	3.1	1.4–6.7	0.004
Residual SCV disease after chemotherapy by US despite CR on PE			NS	2.5	1.1–6.0	0.040

Abbreviations: CI = confidence interval; CR = complete response; other abbreviations as in Table 3.

region may reduce the likelihood of recurrence developing in the SCV fossa, our experience suggests that this potential benefit may be outweighed by the competing risk of distant metastases. Of the 7 patients with failure in the SCV fossa, 6 developed distant metastases before or simultaneously with the SCV recurrence. The seventh patient developed distant metastases 1 year after her SCV recurrence. Some clinicians have also considered whether SCV surgery might provide more benefit for a subset of patients with >1 cm of residual SCV disease after neoadjuvant chemotherapy. Of the 7 patients who fit this criterion in our series, 3 had SCV recurrences, but 6 developed distant metastases (that occurred before or simultaneously with the SCV recurrence in all 3 patients).

Other strategies that should be explored involve optimizing the locoregional treatment approach. The high risk of locoregional and SCV recurrences within the radiation field suggest that room for improvement exists in this area, possibly by combining RT with radiosensitizing agents. In addition, CT-based treatment planning should be used to ensure that an adequate dose is delivered to the depth required to reach the SCV nodal bed. Historically, this region may have been underdosed, because most patients in our series were treated with anterior oblique fields of 6-MV photons or cobalt RT prescribed to 3 cm or the maximal depth, especially because the maximal depth of the SCV nodes is highly variable (range, 2–10 cm) (17).

It is important to recognize the limitations of this study. Foremost, this was a retrospective study with a small number of patients. This was evident in the relatively wide confidence intervals in the multivariate analyses. Second, because our purpose was to study the locoregional outcomes for these patients, we only reviewed those who were able to complete trimodality treatment and excluded those who developed distant disease during the treatment course and were switched to more palliative approaches. Therefore, the overall survival rate of 47% in our series likely reflected this selection bias.

CONCLUSION

Radiotherapy resulted in excellent LRC for patients with ipsilateral SCV metastases who had a CR of the SCV disease after neoadjuvant chemotherapy. However, LRC remained a persistent problem despite multimodality therapy for those with residual SCV disease after chemotherapy. For patients who achieved a CR of the SCV disease by physical examination, ultrasound evaluation of the SCV fossa may help to further assess their risk of disease recurrence. In properly selected patients, SCV involvement should not be considered a contraindication for BCT.

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