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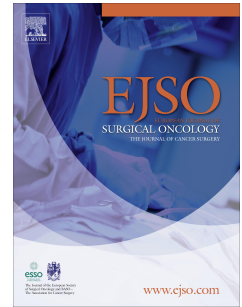
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Can we predict local recurrence in breast conserving surgery after neoadjuvant chemotherapy?

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Abstract

Background: One of the benefits of neoadjuvant chemotherapy (NAC) is its ability to convert patients ineligible for breast conservative treatment (BCT) to be candidates for this treatment, although questions have been raised regarding the effectiveness of BCT in terms of loco-regional recurrence (LRR). The objective of this study is to evaluate LRR in this group and the influence of tumor characteristics in recurrence.

Material and Methods: Between 1996 and 2007, 137 patients were treated with BCT after NAC at our Service. After completion of NAC a multidisciplinary team evaluated the cases eligible for BCT. All patients treated with BCT had negative margins and received radiation therapy. Risk factors associated with local recurrence were analysed using Kaplan Meier survival curves and long-rang test.

Results: Information was obtained in 121 patients. Median age was 54 years old (SD: 12 years). At a median follow up of 35 months (range, 18 to 87 months), 6 (4.95%) patients developed a LRR, with an accumulative incidence at 5 years of 7.3% (95% CI: 0.4%-14.1%) and at 10 years of 11.5% (95% CI: 2.8%-20.1%). Overall survival at 5 and 10 years was 94.8% (95% CI: 90.9%-98.6%) and 82.3% (95% CI: 67.3%-97.2%) respectively. Tumor size (T3) ($p < 0.001$) and pathological stage (Stage III) ($p = 0.001$) after surgery were strongly associated with LRR.

Conclusions: The results of this study confirm that BCT is an effective treatment in patients with NAC. Tumor size and pathological stage after systemic treatment influence loco-regional recurrence in patients with BCT.

Keywords: breast cancer; neoadjuvant therapy; conservative surgery; local recurrence; loco-regional recurrence

Introduction

Neoadjuvant chemotherapy (NAC) is considered to be the standard treatment for locally advanced breast cancer. One of its benefits is to reduce tumor size, so, patients with initially inoperable tumors can be eligible for surgery after NAC. Nevertheless, the results obtained during the last two decades in different studies have made NAC to be considered for early stage breast cancer, in order to increase the number of conservative surgeries [1-3].

NAC confers three important advantages: a) it shows an *in vivo* determination of tumor chemosensitivity, b) it can reduce the micrometastatic component of the disease and c) it allows breast conservative therapy (BCT) for those patients who would need a mastectomy [1,4,5].

Many reports have compared the use of NAC with adjuvant chemotherapy. The NSABP B-18 study demonstrated that there were no survival differences between groups of treatment [6]. Other studies have reported that the presence of pathologic complete response (pCR) is associated with a better prognosis in patients after NAC [4,7-11].

Despite previous information regarding NAC and BCT and although it has not shown to increase survival, questions have been raised related to BCT in terms of loco-regional recurrence (LRR). LRR rates after NAC and BCT have been reported to be about 5-10% and 22.6% at 10 years depending on different studies [9,12-15]. This disparity in results are probably due to the variability of inclusion criteria used to determine the choice of conservative treatment after chemotherapy and that the majority of the studies were including a small number of patients with complete response. Despite the fact that there are guidelines of clinical practice that allow to select those

patients who will benefit from conservative treatment after NAC, the goal is to identify the risk factors that could affect the local and distant control of the disease.

The aim of this study is to determine LRR rates and its influence in survival in patients with breast cancer treated with BCT after NAC and to analyze those factors that can influence the outcome in this group of patients.

Material and methods

Patients

From December 1996 to December 2007, charts of women diagnosed with invasive breast cancer, stage I-III, who received neoadjuvant treatment and BCT at the Breast Surgical Oncology Unit at the Hospital Universitario Vall d'Hebron, were evaluated retrospectively. Patients with occult breast cancer and axillary involvement at diagnosis (Tx, N1-2) were excluded.

Loco-regional treatment

Patients included in the study received neoadjuvant therapy followed by breast conservative surgery and axillary node dissection 3 to 5 weeks after finishing neoadjuvant treatment. Before starting the neoadjuvant treatment, all patients had their tumor marked by skin tattoo to identify residual tumor at the time of surgery. During the treatment, patients were assessed by clinical examination of the breast and axilla before every cycle of treatment. After finishing NAC, all patients were evaluated with mammography to assess radiological response to treatment. Additional breast ultrasound was performed in those patients with complete response by mammography to assess if there was any residual tumor by ultrasound. Response to treatment was scored as complete clinical response if there was no clinical or radiographic or sonographic evidence of disease after NAC, or partial clinical response if there was shrinkage of the tumor size of more than 50%. Eligibility criteria for conservative surgery were decided by clinical and radiological response once NAC was finished. Breast conservative surgery was performed guided by the skin tattoo and specimen was sent to Pathology. Median time between diagnosis and surgery was 6.62 months (range: 1-9 months).

All patients received radiation therapy (54Gy in 28 sessions during 5-6 weeks) on the whole breast with an additional boost radiation (10Gy) on tumor bed. Axillary and supraclavicular radiation was added in those patients with more than 4 positive nodes. Adjuvant radiation therapy started 4 to 6 weeks after surgery.

Pathologic examination

All patients had negative margins in the final pathology report (margins not touching the ink). Pathologic complete response (pCR) was defined as the absence of invasive cancer in both breast and lymph nodes. Carcinoma in situ and presence of atypical cells were considered to be pathological complete response.

Estrogen (ER) and progesterone (PR) receptors were assessed by immunohistochemistry stain (IHC). Her-2-neu tumors were considered positive if reported as 3+ by IHC and those tumors reported as 2+ that were amplified by FISH (fluorescence in situ hybridization).

Systemic treatment

Neoadjuvant treatment included: anthracyclines and taxanes in 71.9 % (87/121 patients), hormone therapy in 13.2 % (16/121 patients, 14 of which were included in the RAD-Femara protocol), epotilone plus FAC in 9.9 % (12/121 patients) and in 6 cases (5 %) other chemotherapy regimens. Tumor overexpressed Her-2-neu in 18 patients (14.9 %), a third of them (6 patients) were treated with trastuzumab.

Ninety-seven patients (80.2 %) were treated with adjuvant hormone therapy. Of these, 62 patients (63.9 %) received tamoxifen, 31 patients (31.9 %) had aromatase inhibitors and 4 patients (4.1 %) had tamoxifen for two years followed by aromatase inhibitors for three years.

Loco-regional recurrences, distant metastasis or deaths were registered as events in disease progression. Time intervals were calculated from the date at diagnosis to the date of the event. Follow-up disease free intervals were obtained taking as reference the last visit date.

Age, menopause status at diagnosis, disease stage, clinical and pathological tumor size, pathologic response to neoadjuvant treatment, lymph node involvement, margin assessment, hormonal receptor status and Her-2-neu overexpression were analyzed.

Statistical analysis

Data were analyzed by SPSS (version 15.0). Survival analysis was performed using Kaplan-Meier's curves for LRR accumulative incidence, disease free survival (DFS) and overall survival (OS).

Mantel-Cox's test (log-rank test) with univariate Cox model considering significant values $p < 0.05$ was used for association between risk factors and LRR.

Results

This study included 135 patients diagnosed with invasive breast cancer who received NAC and BCT. Only 3 patients were excluded because of occult breast cancer and lymph node metastasis at diagnosis. It was not possible to obtain any follow-up information in 11 cases (8.3%), so final sample included a total of 121 cases.

Mean age was 54 years (SD: 12 years), 113 patients (93.4%) were older than 35 years old, and 74 patients (61.2%) were menopausal at diagnosis.

In 112 patients (92.6%) the tumor was an infiltrating ductal carcinoma, 2 patients (1.7%) had an infiltrating lobular carcinoma and 7 patients (5.7%) were otherwise classified.

Mean follow-up was 50.98 months (SD: 38 months, range: 7-128 months). Patient's characteristics are explained in Table 1.

Loco-regional recurrences

Six patients (4.95%) developed LRR. All recurrences were in the ipsilateral breast, there were no regional recurrences. LRR accumulative incidence at 5 and 10 years was 7.3% (95% CI: 0.4%-14.1%) and 11.5% (95% CI: 2.8%-20.1%) respectively (Figure 1). Of these 6 patients, two also developed metastasis in the pleura and the liver.

Fourteen patients (11.6%) developed disease progression, defined as presence of metastasis or LRR during follow-up. Disease free survival (DFS) was 81.8 % (95% CI: 72.1%-91.4%) at 5 years and 77.4 % (95% CI: 66.4%-88.3%) at 10 years (Figure 2). Disease progression included 6 cases with LRR and 8 cases presented as metastatic breast cancer (5 patients developed metastasis to the bone, 2 patients to the Central Nervous System and one patient to the lung).

Overall Survival

There were 5 deaths (4.15%) reported during the follow-up. Overall survival (OS) at 5 and 10 years was 94.8% (95% CI: 90.9%-98.6%) and 82.3% (95% CI: 67.3%-97.2%) respectively (Figure 3). Among these five cases of death, four were due to breast cancer. The fifth patient died as a consequence of a cardiac failure due to myocardiopathy induced by anthracycline toxicity.

Median time for LRR as well as for disease progression was 55 months (p25-75: 36-62 months) and 38 months (p25-75: 23-46 months) respectively. The patients who died in our study had a median time of follow-up of 53 months (p25-75: 32-91 months).

Risk factors

When analyzing the relationship between risk factors and LRR, there were no statistically significant differences for age younger than 35 years, menopause status at diagnosis, clinical stage, lymph node metastasis and surgical margins between 1-5mm. Neither statistically significant difference was found for recurrence depending on hormonal receptor status as well as for those patients who overexpressed Her-2-neu.

We did not find significant differences in LRR rates in patients who achieved pCR; even we observed lower recurrence rates in the partial pathological response group. We found statistically significant differences when comparing LRR survival curves associated with pathologic size of tumor and pathologic stage after neoadjuvant treatment (Table 2). There was also a statistical trend (p : 0.1-0.05) for risk of recurrence in patients with large tumors before NAC and in patients with lympho-vascular invasion, although these associations were not statistically significant ($p < 0.05$).

Discussion

One of the major problems concerning neoadjuvant treatments is the local control of the disease. In our study, we have found a LRR accumulated incidence of 7.5% and 11.5% at 5 and 10 years of follow-up, with an average of 50.98 months of follow-up (SD 38 months, range 7-128m). These rates are consistent with those reported in the literature (table 3).

Risk factors for LRR

The main challenge for neoadjuvant chemotherapy followed by conservative surgery is to reduce LRR. Tumor size is an independent factor that shows statistical significant differences in terms of DFS. Thus, larger tumors are at higher risk of recurrence. In a similar way, cancer stage after chemotherapy is also correlated with DFS. Tumor size assessment and stage of the disease have a great importance in order to choose if the patient is candidate for conservative or radical surgery, because the final assessment will influence the outcome of the patient.

Beriwall et al. [19] reported a study that included 153 patients with different stages of breast cancer: Stage IIA in 22% of all patients, IIB in 28%, IIIA in 39%, and IIIB in 11%. In the multivariate analysis, advanced stage before chemotherapy ($p=0.03$) and positive surgical margins ($p=0.04$) were correlated with higher LRR. Similar conclusions showed Chen et al [18] in the study that included 340 patients that received neoadjuvant chemotherapy followed by conservative surgery. The authors found statistically correlation between local recurrence and positive axillary nodes, tumor size larger than 2 cm after chemotherapy, multifocal disease after chemotherapy and lympho-vascular invasion. We did not find statistical differences between lympho-vascular invasion and LRR, although we could observe a statistic trend ($p=0.085$).

Pathologic complete response rate in our study was 23.1%. Previous published studies have reported similar pCR rates [18,20,22]. In our series there were no significant correlation between pCR and LRR, and we found similar LRR-free survival rates when compared pCR group against partial pathologic response group (table 2). Considering that the benefit in prognosis within groups depends on tumor downstaging after chemotherapy, probably better conclusions could be obtained with studies with larger number of patients.

Breast cancer in young women is relatively uncommon. In our study, only 6.5% of all cases were younger than 40. Young women tend to have breast cancer characterized by being less differentiated, more advanced disease, higher Her-2-neu overexpression, negative hormone receptors, higher rate of lympho-vascular invasion and higher extensive intraductal component [23]. In our study only six patients were diagnosed before 35 years old and none of them developed LRR. Due to the small number of patients in this group, we didn't find any significant difference in LRR rates.

When hormonal status was analyzed, there was no statistically significant differences between hormonal status and LRR. Similar survival rates between pre-menopausal (94.6%) and post-menopausal group (95.7%) were observed probably due to the small number of recurrences and its distribution between the groups.

We analyzed the relationship between hormone receptor status and Her-2- neu overexpression with prognosis and recurrences. In our series, 18 patients (14.9%) overexpressed Her-2-neu, and 6 of them (33.3%) received trastuzumab. Although there was not a significant relation between Her-2-neu overexpression and LRR rates, the small size of this group and the fact that only 1/3 of the patients received treatment with Trastuzumab may influence these results and this is one of the limits of our study.

There are very limited data regarding the relation between hormonal receptor status, Her-2-neu and LRR in the neoadjuvant setting. Huang et al [24] reported in a study that included patients treated with mastectomy and radiation therapy after NAC that ER negative tumor were an independent factor for LRR. One important bias of this study might be that more than 80% of the 542 patients were diagnosed with locally advanced (stage IIIA and IIIB) or metastatic disease (IV). In the adjuvant setting, there are studies published that show that triple negative tumors are associated with increased LRR [25] or with distant metastases [26,27]. An univariate analysis for all the variables comparing survival curves were performed and we didn't find any differences in loco-regional disease control regarding hormonal receptors status nor Her-2-neu overexpression after NAC and breast conserving surgery.

Conclusions

Some limits should be considered due to the retrospective nature of this study. Because of non-available medical records, it was not possible to obtain any follow-up data in 11 patients (8.3%). None of these missing cases were reported as deaths when we checked hospital mortality records for any reason. On the other hand, this is a retrospective study and includes treatments performed during a decade, the heterogeneity of the neoadjuvant treatments may have influence the results.

Mean follow-up is 50.9 months (SD: 38 months), but due to dispersion in follow-up times, we have preferred to use the median: 35 months (p25-75: 18-87 months). According to this, 25% of all patients have follow-up shorter than 18 months. If we consider that median interval for LRR is 55 months (p25-75: 36-62 months), we should conclude that follow-up of 50% of all patients included in the study is not long enough to present LRR. Thus, one of the main limits of our study is a follow-up too

short. With longer follow-up factors as pCR, Her-2-neu overexpression and nodal involvement that shows a trend may have shown statistical significance.

We conclude that, in our series, LRR accumulative incidence for BCT after NAC compares favourably with data reported in the literature and can be considered low. DFS and OS show the effectiveness and safety of breast conserving surgery after NAC. In this study, response to chemotherapy is an important factor that predicts the increased risk for LRR. Patients with large tumors and more advanced stages after chemotherapy are at greater risk to develop loco-regional relapse.

Breast conserving surgery after NAC is, nowadays, a safe option for breast cancer management. In selected patients it allows to obtain good cosmetic results without compromising an optimal oncologic surgery.

Conflict of interest

The authors have no actual or potential conflict of interest in relation to this article.

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Table 1. Baseline characteristics of study population (N=121)

Characteristics	number	%
<i>Clinical size</i>		
T1	6	5.0
T2	91	75.2
T3	22	18.2
T4	2	1.7
<i>Clinical stage</i>		
I	3	2.5
IIA	72	59.5
IIB	36	29.8
III	10	8.3
<i>Pathologic complete response</i>		
Yes	28	23.1
No	93	76.9
<i>Pathologic size</i>		
T1	71	58.7
T2	20	16.5
T3	2	1.7
T4	0	0.0
<i>Pathologic stage</i>		
0, I	62	51.2
IIA	35	28.9
IIB	11	9.1
III	13	10.7
<i>Lymph node metastasis</i>		
Yes	50	41.3
No	68	56.2
Unknown	3	2.5
<i>Grade of differentiation</i>		
1	7	5.8
2	79	65.3
3	35	28.9
<i>Margins</i>		
≥1mm and <5mm	54	44.6
≥5mm	52	43.0
Unknown	15	12.4
<i>ER or PR positive</i>	83	68.6
<i>HER-2 positive (3+, 2+ FISH+)</i>	18	14.9
<i>Lympho-vascular invasion</i>		
Yes	11	9.1
No	110	90.9

ER=estrogen receptor; PR=progesterone receptor

Table 2. Survival table of locoregional recurrence related to risk factors (Mantel-Cox)

Characteristics	Total number	Recurrence cases	Survivors	%	p
<i>Age</i>					
≤35	8	0	8	100	
>35	113	6	107	94.7	0.469
<i>Menopause</i>					
Yes	74	4	70	94.6	
No	47	2	45	95.7	0.615
<i>Clinical size</i>					
T1	6	0	6	100	
T2	91	3	88	96.7	
T3	22	3	19	86.4	
T3	2	0	2	100	0.059
<i>Clinical stage</i>					
I	3	0	3	100	
IIA	72	2	70	97.2	
IIB	36	3	33	91.7	
IIIA, IIIB, IIIC	10	1	9	90.0	0.187
<i>Pathological size</i>					
Unknown	4	0	4	100	
0	24	0	24	100	
T1	71	2	69	97.2	
T2	20	3	17	85.0	
T3	2	1	1	50.0	<0.001
<i>Pathological stage</i>					
0, I	62	3	59	95.2	
IIA	35	0	35	100	
IIB	11	1	10	90.9	
IIIA, IIIB, IIIC	13	2	11	84.6	0.001
<i>Complete pathologic response</i>					
Yes	28	2	26	92.9	
No	93	4	89	95.7	0.954
<i>Margins</i>					
≥1mm and <5mm	54	4	50	92.6	
≥5mm	52	2	50	96.2	
Unknown	15	0	15	100	0.420
<i>Lymph node metastasis</i>					
Yes	50	3	47	94.0	
No	68	3	65	95.6	
Unknown	3	0	3	100	0.637
<i>Lympho-vascular invasion</i>					
Yes	11	1	10	90.9	
No	110	5	105	95.5	0.085
<i>Immunohistochemistry classification</i>					
ER&PR positive	80	4	76	95.0	
Triple negative	20	0	20	100	
HER-2 positive	11	1	10	90.9	
Unknown	10	1	9	90.0	0.235
<i>HER-2 positive</i>					
Yes	18	1	17	94.4	
No	93	4	91	95.7	
Unknown	10	1	9	90.0	0.783

ER=estrogen receptor; PR=progesterone receptor

Table 3. Comparative table for recurrence rates in breast conserving surgery after neoadjuvant chemotherapy.

<i>Study</i>	<i>n</i>	<i>LRR (n)</i>	<i>LRR rate (%)</i>	<i>Median follow-up (months)</i>	<i>LRR incidence at 5 years</i>	<i>LRR incidence at 10 years</i>	<i>DFS at 5 years</i>	<i>DFS at 10 years</i>	<i>OS at 5 years</i>	<i>OS at 10 years</i>
Mauri et al. [16]‡	3946	520	13.1	76	NA	NA	NA	NA	NA	NA
NSABP-B18 [17]	751	104	13.8	192	NA	16%†	67%	55%†	80%	69%†
NSABP-B27 [17]	2344	217	9.2	102	26.4%	31.4%‡	69.6%	61%‡	82.3%	74.3%‡
Chen et al. [18]	340	29	8.5	60	9%	NA	NA	NA	89%	NA
Beriwal et al. [19]	153	8	5.23	55	7%	NA	70%	58%	NA	NA
Peitinger et al. [20]◇	109	3	2.7	79.2	1.9%	3.5%	NA	NA	96%	92%
Tiezzi et al. [21]	88	7	7.9	61.3‡	NA	NA	NA	NA	NA	NA
Present study Cebrecos et al.	121	6	4.9	50.9‡	7.3%	11.5%	81.8 %	77.4 %	94.8%	82.3%

LRR = loco-regional recurrence; DFS = disease free survival; OS = overall survival; NA = not available

‡ Meta-analysis of 9 randomized trials that compare neoadjuvant chemotherapy vs. adjuvant therapy regardless surgery and/or radiation treatment. Median follow-up of all studies.

† LRR incidence, DFS and OS at 9 years

‡ LRR incidence, DFS and OS at 8 years. In NSABP-B27 data has been calculated by mean values among three groups of neoadjuvant therapy.

◇ Study performed only in patients who achieved pCR after NAC and BCT

‡ Mean follow-up

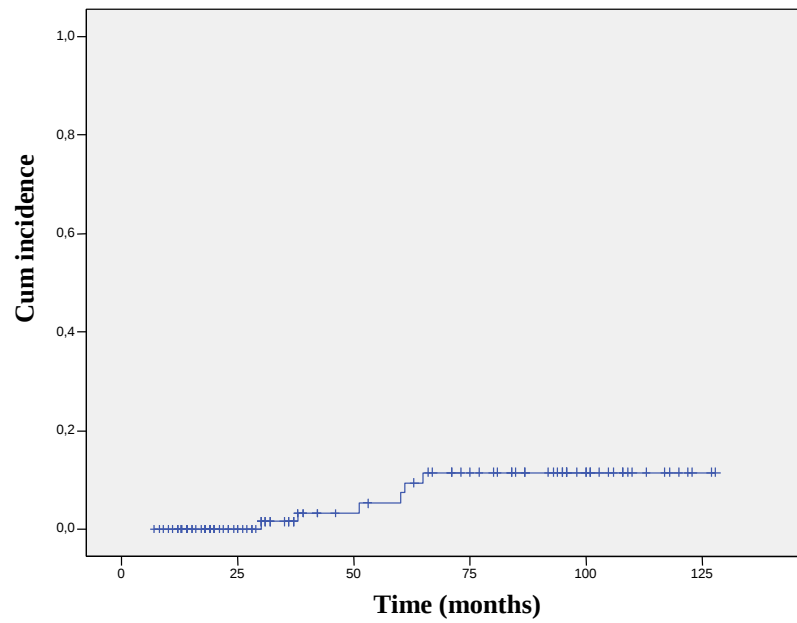


Figure 1. Kaplan-Meier loco-regional recurrence incidence curve

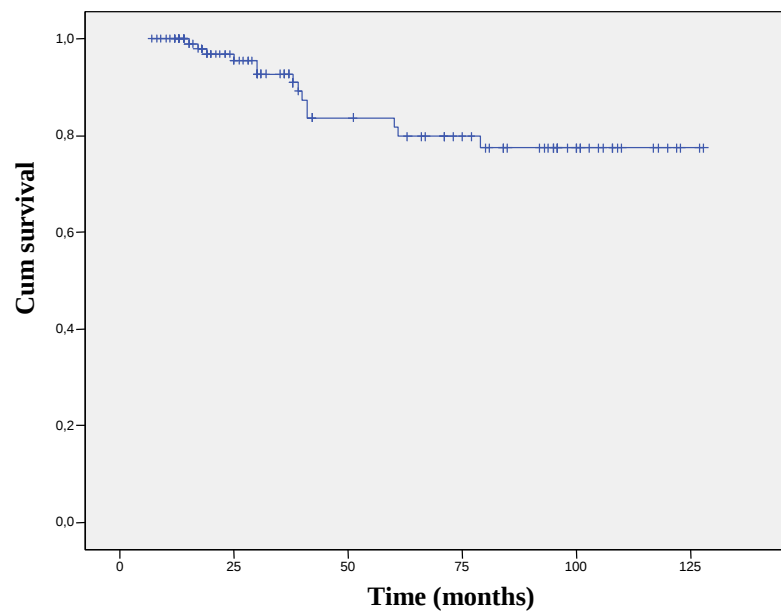


Figure 2. Kaplan-Meier free disease survival curve

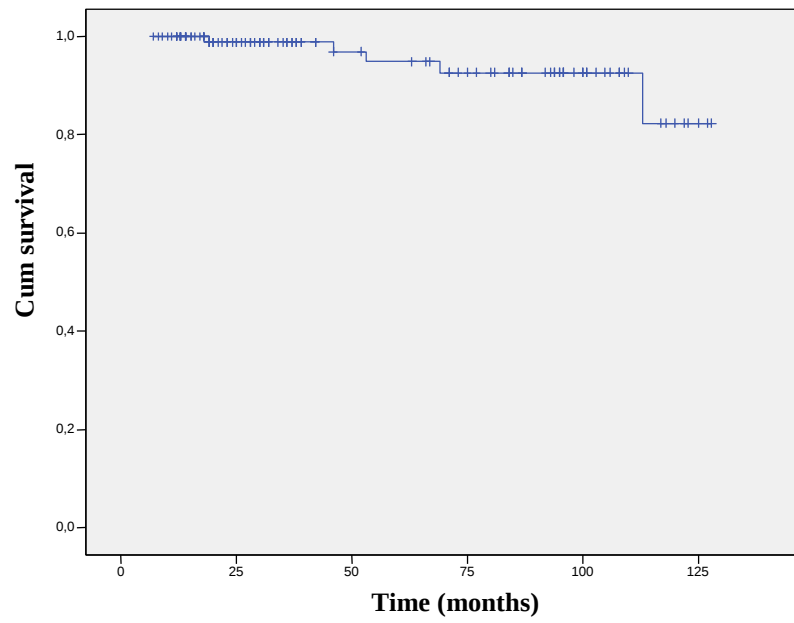


Figure 3. Kaplan-Meier overall survival curve

Conflict of interest

The authors have no actual or potential conflict of interest in relation to this article.