PREOPERATIVE CHEMOTHERAPY IN T3N0M0 (STAGE III) BREAST CANCER AND LYMPH NODE STATUS

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Abstract: *Axillary dissection retains an essential role in breast cancer treatment. Preoperative chemotherapy has become the standard of cure for local advanced in breast cancer. The purpose of this study was to determine the effect of preoperative chemotherapy on the lymph nodes status after axillary dissection. Methods: We analysed 95 patients with stage T3N0 breast cancer treated between 2002 - 2008 and who received combined preoperative chemotherapy. 55 patients received preoperative chemotherapy and postoperative chemotherapy and 40 patients only postoperative. In definitive surgical approach, all patients were made complete axillary lymph node dissection (levels I, II, III). Results: In the group with preoperative chemotherapy (CT), the number of histologically positive N +) lymph nodes was lower (average 0 vs. 3, p <0.1) and the extranodal extension was lower (18% vs. 43 % p = 0.2). In patients with preoperative chemotherapy, the univariate analysis showed that the extranodal dissemination(p <0.1), the number of pathologically positive lymph node (N+) (metastatic) (p <0.1) was predictive for survival of specific disease, but the multivariate analysis showed that only the extension extranodal was an independent prognostic factor in these cases (p <01). The overall 5 year survival in patients with chemotherapy compared between pre and post operatively was similar (66 % vs. 57 % p = 0.4). Patients with preoperative chemotherapy with 4-9 positive lymph nodes (N +) had a lower 5-year disease-free survival rate, compared with postoperative chemotherapy beneficiary group with 4-9 lymph nodes (17 % vs. 48 % p = 0.4). Conclusion: After preoperative chemotherapy the presence of pathologically positive lymph nodes was associated with a worse prognosis than the same nodal status before chemotherapy. Axillary lymph nodes status is a prognostic marker after chemotherapy.*

INTRODUCTION

The staging of axillary lymph node invasion of breast cancer is considered to be the single most important factor.(1,2) Therefore, axillary staging is a mainstay of surgical therapy for invasive breast disease.(3,4)

In the era prior to determination of sentinel lymph node (NLS), axillary lymph dissection was performed systematically.(4,5)

Established breast cancer prognostic factors - those that determine natural history of breast cancer-, include axillary nodal status, tumour volume, histological grade, hormone receptor status, HER-2 expression and presence of lymphovascular invasion. These factors influence the decision on the application of adjuvant systemic therapy.

In contrast, predictive markers such as: estrogen receptor expression (RF), alpha, progesterone receptor (PR) and HER2 protein, are powerful tools to select the right type of therapy.

In this molecular age, it is important to reflect on the continuing importance of classic histopathology. One such feature is the identification of lympho-vascular invasion. Bags for important prognostic what was suggested in 2007 consensus conference in St. Gallen (2) where extensive lympho-vascular invasion was identified as a factor to identify women at moderate risk factor in contrast with a low relapse.

This classic histopathology analysis has been amplified by immunohistochemistry analysis (IHC).(6,7)

Preoperative chemotherapy has become the standard of cure for inoperable locally advanced breast cancer, and the role of preoperative chemotherapy for operable breast cancer evolved with three proposed theoretical advantages of preoperative chemotherapy.(8,9,10,11)

The first is preoperative tumour regression, allowing breast conservation therapy, for that category of patients which would have required mastectomy.(12,13,14,15,16)

The second is the treatment of micrometastases without delay postoperative recovery.(17,18)

The third is the ability to evaluate the response to chemotherapy administered in vivo.(19,20,21)

Several studies have consistently shown that lympho-vascular invasion is an adverse prognostic factor for recurrence and survival in node-negative patients in combination with other risk factors such as tumour grade, volume and receptor status.(22)

B. Ejlersten et al (23) reported a comprehensive analysis of the prognostic value of lympho-vascular invasion in breast tumours from 15%, 59 women registered in to the Davish Breast Cancer Group between 1996 to 2002, noting the presence of lympho-vascular invasion, in only 15% of tumours.

Intramammary lymph nodes represent a potential extraaxillary site of regional breast cancer metastasis, which are defined as lymph nodes surrounding by breast parenchyma and can be located anywhere in the breast.

PURPOSE

The purpose of this study was to determine the prognostic information gained through clear dissection of axillary lymph nodes that were altered by preoperative

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chemotherapy in patients with stage T3N0 breast cancer treated in the Ist Surgical Clinic of Sibiu between 2002 and 2008.

MATERIALS AND METHODS

From this study, patients who received preoperative radiotherapy were excluded and the remaining 95 patients received neoadjuvant chemotherapy combined according to the protocol during the interval studied.

Fifty-five patients received both: preoperative chemotherapy (preoperative CT) and postoperative chemotherapy (postoperative CT) and 40 patients received postoperative chemotherapy only (postoperative CT).

All patients with preoperative chemotherapy, tumour biopsies were performed with surgical excision biopsy or fine needle aspiration or biopsy with cylindrical trocar.

All patients underwent staging techniques including history, physical examination, blood analysis, bilateral mammography, chest X-ray, abdominal CT or ultra-sonography.

None of these patients had distant metastastatic disease, and none of them developed distant metastasis or clinically positive lymph node during preoperative chemotherapy. The clinical response to preoperative CT was defined as partial response (> 50% reduction in the two largest dimensions of the breast mass), stable disease (breast mass reduction <50%) and complete response (complete resolution of breast mass).

During the current study, one patient has progression of her primary tumour on preoperative CT, and received preoperative radiotherapy, therefore this case is not included in the current study.

After preoperative chemotherapy and complete response, or a response >50%, and peripheral tumour, large mammary sectorectomy and axillary lymph node dissection, or modified radical mastectomy was indicated, and in all cases with response <50% the modified radical mastectomy was systematically indicated.

The follow-up time was 5 years (1-13 years).

Disease specific survival was calculated from the date of diagnosis and disease free survival was calculated from the date of surgery, using the method of Kaplan and Meier and tag-rank analysis was used for univariate comparison, multivariate regression model was applied to calculate the proportional bazard of events.

Differences between groups were considered statistically significant at p <0.5.

RESULTS

The list of patients and tumour characteristics for the pre- and postoperatively CT are shown in table no. 1.

Table no. 1. Tumour characteristics for the pre- and postoperatively CT

Date		CT preop	CT postop
Number of patients		55	40
Age (mean years)		50 (25-66)	49 (24-76)
Initial tumour volume (mean cm)		6 (5-12,5)	6 (5-10)
Family history		10(17%)	7 (16%)
Histology	cc. invasive ductal	45 (83%)	23 (58%)
	cc. invasive lobular	7 (11%)	8 (18%)
	noninvasive	3 (4%)	2 (3%)
	other	0	7 (18%)
Estrogen receptor status	negative	21 (48%)	13 (32%)
	positive	25 (45%)	21 (53%)
	not	9 (17%)	6 (16%)
Progesterone receptor status	negative	28 (51%)	10 (24%)
	positive	11 (19%)	10 (24%)
	not	16 (30%)	20 (53%)

Table no. 1 shows that there was no difference between the groups in patient characteristics or in most tumour characteristics.

Patients with preoperative CT showed the highest percentage progesterone receptor negative tumours (51% vs. 24% p = 0.3).

After preoperative CT 5 (8%) of the 55 patients had complete clinical response, 37 (68%) partial clinical response and 13 (25%) had a stable disease.

In the group with preoperative CT, 9 (15%) of patients underwent conservative breast surgery and two (3%) of the postoperative CT group underwent breast conservative surgery (p = 0.5).

The median tumour volume in the group with preoperative CT was lower (3 cm) compared with postoperative CT group (6 cm) p <0.1 (table no. 2), reflecting the primary tumour response in the preoperative CT cases.

The vascular/lymphatic invasion in preoperative CT group was lower (15%), compared to 47% of postoperative CT group (p <0.1), and the difference about extranodal extension was 19% vs. 42% (p = 0.2).

In the group with preoperative CT average number of positive lymph nodes was 0 vs. 3 (p <0.1) and in preoperative CT group 64% of the patients had pathologically lymph node, and 5% of patients from the group postoperative CT has negative lymph nodes (p = 0.3).

Table no. 2. Constants pathological cases with pre- and post-operative CT

Anat. pathological		CT preop n=55	CT postop n=40	Value p
Tumour size (cm average)		4 (1-7,5)	7 (4,12)	<0-0,1
Vaculo-lymphatic invasion		9 (15%)	19 (47%)	<0-0,1
Extranodal extension		10 (19%)	16 (42%)	0-0,2
The average number of harvested NL		11	14	0-0,5
Nr. NL +	0 N+	35 (64%)	3 (5%)	
	1-3 N+	13 (23%)	19 (47%)	
	4-9 N+	6 (6%)	10 (26%)	
	>N+	1 (2%)	8 (21%)	0-0,3

In 75% of patients with preoperative CT, there was observed the presence of residual tumour, 6% had microscopic tumour and 19% of cases had residual active tumours.

The majority of complete pathological responses were initially tumour estrogen receptor negative (p = 0.2) and anaplastic (p = 0.4).

Patients in groups pre- and post-operative CT did not showed significant difference in disease-free survival or disease-specific survival (table no. 3).

Table no. 3. Difference in disease-free survival or disease-specific survival

	Preop CT	Postop CT	Value p
The percentage of disease-free survival (95% CI) for 5 years	66%	57%	0.37
Disease specific survival (95% CI) to 5 years	90%	81%	0.34

In the group with preoperative CT, by Cox regression analysis showed the presence of two predictors for both disease-free and disease-specific survival – the presence of extranodal extension (p <0.1) and the number of positive lymph nodes (N +) (p = 0.01).

In survival analysis Kaplan - Meier, for preoperative CT group the only factor predictive of disease-free survival was

the pathologic tumour response.

The axillary lymph node status confers a poor prognosis when persists after preoperative chemotherapy.

DISCUSSIONS

Axillary surgery is employed to control axillary nodal disease and to staging the tumour accurately in order to assess prognosis and possible benefit from systemic therapy .In the elderly there is little evidence of the benefit of adjuvant chemotherapy.(24,25)

Consequently, same authors believe that to stage the clinically uninvolved axilla with either a clearance or sampling may be unjustified and axillary surgery is undertaken less often in the elderly patients.(26)

However, adjuvant therapy other than chemotherapy may be based on staging information, such as administration of tarroxifen or radiotherapy.(25,27,28)

In addition omitting axillary surgery exposes the patients to a high risk of axillary recurrence if axillary disease is present.

Invasive lobular carcinoma of the breast is 4.9-15% of all invasive breast cancers, making it the most common histologic subtype after invasive ductal carcinoma, the incidence in this study was 11%.

In patients with clinically stage T3N0 carcinoma, the number of cases with N (-) of the axillary lymph node (no metastasis), was higher in cases who received both preoperative and postoperative (64%) suggesting the down staging effect of CT preoperative.

The present results are limited because the study is retrospective.

Our results show the down staging of N status at the axilla, of patients with stage T3N0.

In the study reported from Kuerer et al (21) 32% of patients with locally advanced breast cancers with clinically positive lymph node clinical at the first exams axillary tumour down staging (clinically, sonographically) after preoperative CT.

McCready et al, Schwartz et al (30.31), Singletary et al (32) also reported conversion to clinically invaded axillary lymph node to pathologically negative lymph node status in patients with locally advanced breast cancer benefit from preoperative chemotherapy. In the preoperative CT patients, with four or nine positive nodes, pathologically positive nodes invaded was associated with a worse evolution, because it is possible that this reflects the evident down staging in nodal status after preoperative CT.

In the present study, patients with preoperative CT and 4-9 positive (N+) lymph nodes may be more similar in term initial stage of the disease, cases of postoperative CT with> 10 positive node, that the cases with postoperative CT cases with 4-9 positive nodes.

In our study, the pathological examination was performed by staining with hematoxylin classic - eosin, since the number of cases with IHC, HER2 determination is currently still limited. In the study of Kuerer and Colob (33) 10% of patients with preoperative CT and evaluation of lymph node with hematoxylin based - eozina were found to have accuet nodal metastases, by step-sections and IHC staiving of their lymph node, observations presented from others to.(34,35,36)

The more aggressive tumours, were those with estrogen receptor negativity and anaplastic tumours, with a higher risk for axillary metastatic dissemination, at initial clinically examination.

Machiavelli et al (37) have also reported a correlation between residual primary tumour after preoperative CT and the number of positive lymph nodes.

Similarly observations were presented by others to.(38-39) During the last decade, our understanding of the molecular alterations involved in breast cancer, and in metastatic tumours has significantly advanced.

Many of these molecular markers have been proposed as predictors of tumour biology and tumour sensitivity to chemotherapy.(40,41,42)

The role of sentinel lymph node (NLS) technology is an alternative to axillary lymph node dissection for the assessment of nodal status in patients with preoperative chemotherapy.

Multiple trials have documented that sentinel lymph node biopsy (NLS) reflect the state of the axilla.(43-45)

CONCLUSIONS

Status axillary lymph nodes provide useful prognostic information in patients with breast cancer stage T3 N0, even after down staging from preoperative chemotherapy.

The presence of pathologically positive lymph nodes after preoperative chemotherapy was associated with poor prognosis.

Patients with positive lymph node after chemotherapy represent a category with relative resistance to chemotherapy.

REFERENCES

1. Kissin MW, Thompson EM, Price AB, Slavin G, Kark AE. The inadequacy of axillary sampling in breast cancer. Lancet. 1982;1:1210-12.
2. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: high-lights of the international expert consensus on the primary therapy of early breast cancer. Ann Oncol. 2007;18(7):1133-1144.Review.Erratum in: Ann Oncol. 2007 Nov;18(11):1917.
3. NIH consensus conference. Treatment of early-stage breast cancer. JAMA. 1991;265:391-5.
4. Moffat FL Jr. Lymph node staging surgery and breast cancer:patholes in the fast lane from more to less. J Surg Oncol. 2005;89:53-60.
5. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Nat Cancer Inst. 2006;98:599-609.
6. Sato Y. Molecular diagnosis of tumor angiogenesis and anti-angiogenic cancer therapy. Int J Clin Oncol. 2003;8(4) 200-206.
7. Weidner N, Semple JP, Welch WR et al. Tumor angiogenesis and metastatis correlation in invasive breast carcinoma. N Engl J. Med. 1991;324(1):1-8.
8. Braun M, Flucke U, Debald M, et al. Detection of lymphovascular invasion in early breast cancer by D2-40 (podoplain) :a clinically useful predictor for axillary lymph node metastases.Breast Cancer Res Treat. 2008;112(3)503-511.
9. Mohammed RA, Ellis IO, Elsheikh S, Paish EC, Martin SG. Lymphatic and angiogenetic characteristics in breast cancer: morphometric analysis and prognostic implications. Breast Cancer Res Treat. 2009;113(2)261-273.
10. Chicken DW, Kocjan G, Falzon M, Lee AC, Douek M, Sainsbury et al. Intraoperative touch imprint cytology for the diagnosis of sentinel lymph node metastases in breast cancer. Br J Surg. 2006;93:572-6.
11. Perez NV, Sicart S, Zanon G, Velasco M, Santamaria G, Palacin A, et al. A practical approach to intra-operative evaluation of sentinel lymph node biopsy in breast carcinoma and review of the current methods. Ann surg

Oncol. 2005;12:313-21.
12. Danforth DN, Zujewski J, O'Shaughnessy J, et al. Selection of local therapy after neadjuvant chemotherapy in patients with stage III A,B, breast cancer. Ann Surg Oncol. 1998;5:150.
13. Dookeran KA, Zaren HA. Sentinel lymph node biopsy in breast cancer patients treated with neoadjuvant chemotherapy. Proc Am Soc Clin Oncol. 1999;18:72.
14. Carlson GW, Losken A, Moore B, Thornton J, Elliott M, Bolitho G et al. Results of immediate breast reconstruction after skin-sparing mastectomy. Ann Plast Surg. 2001;46:222-8.
15. Peyser PM, Abel JA, Straker VF, Hall VL, Rainsbury RM. Ultra-conservative skin-sparing "keyhole" mastectomy and immediate breast and areola reconstruction. Ann R Coll Surg Engl. 2000;82:227-35.
16. Spear DL, Onyewu C. Staged breast reconstruction with saline-filled implants in the irradiated breast: recent trends and therapeutic implications. Plast Reconstr Surg. 2000;105:930-42.
17. Fennessy M, Bats T, Macrae K, Riley D, Houghton J, Baum T. Late follow-up of a randomized trial of surgery plus tamoxifen versus taroxifen alone in women aged over 70 years with operable breast cancer. Br J Surg; 2004.
18. Veronesi U, Gatti G, Luini A, Intra M, Ciocca M, Sanchez M, et al. Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery-Arch Surg. 2003;138:1253-1256.
19. Park J. Fey IV, Naik AM, et al. A declining rate of completion axillary dissection in sentinel lymph node-positive breast cancer patiens in associated with the use of a multivariate nomogram.Ann Surg. 2007;245:462-8.
20. Nassar A, Cohen C, Cotsonis G, et al. Significance of intramammary lymph nodes in the staging of breast cancer: correlation with tumour characteristics and outcome. Breast J. 2008;14:147-52.
21. McLaughlin SA, Wright MY, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements, J Clin Oncol. 2008;26:5220-6.
22. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. Breast cancer res treat. 2008;107(3)309-330.
23. Ejlersten B, Jensen MB, Rank et al. Population-based study of peritumoral lymphovascular invasion and outcome among patients whit operable breast cancer. J Natl Cancer Inst. 2009;101(10):729-735.
24. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet. 1998;352:930-942.
25. DiFronzo LA, Hansen NM, Stern SL, Brennan MB, Guiliano AE. Does sentinel lymphadenectomy improve staging and alter therapy in elderly women with breast cancer? Ann Surg Oncol. 2000;7:406-410.
26. Yancik R., Ries LG, Yates JW. Breast cancer in ageing women. A population-based study of contrast in stage, surgery and survival. Cancer. 1989;63:976-981.
27. Miller D, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J. Med. 2007;356(26):2666-2076.
28. Dellapasqua S, Bertolini F, Bagnardi V, et al. Metronomie cyclophosphamide and capecitabine, combined with bevacizumab in advanced breast cancer. J Oncol. 2008;26(30):4988-4905.
29. Mansfield CM, Komarnicky LT, Schwartz GF, et al. Ten-year results in1070 patients with stages I and II breast cancer treated by conservative surgery and radiation therapy. Cancer. 1995;75:2328-2336.
30. Veronesi U, Salvadori B, Luini A, et al. Conservative treatment of early breast cancer. Long-term results of 1232 cases treated with quadrantectomy, axillary dissection and radiotherapy. Ann Surg. 1990;221:250-259.
31. Schwartz GF, Cantor RI, Biermann WA. Neoadjuvant chemotherapy before definitive treatment for stage III carcinoma of the breast. Arch Surg. 1987;122:1430-4.
32. Singletary SE, Connolly JL. Breast cancer staging: working with the sixth edition of the AJCC Cancer staging manual.CA Cancer J Clin. 2006;56:37-47.
33. Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg. 1999;230:72-8.
34. Cody HS III. Sentinel lymph node biopsy for breast cancer: indications, contraindications and new directions, J Surg Oncol. 2007;95:440-2.
35. Shen J, Hunt KK, Mirza NQ, et al. Intramammary lymph node metastases are an independent predictor of poor outcome in patients with breast carcinoma. Cancer. 2004;101:1330-7.
36. Gill G. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy versus axillary clearance (SNAC): a randomized controlled surgical trial. Ann Surg Oncol. 2009;16:266-75.
37. Machavelli MR, Romero AO, Perez JE, et al. Prognostic significance of pathological response of primary tumour and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am. 1998;4:125-31.
38. Julian TB, Blumencranz P, Deck K, Whitworth P, Berry DA, Berrry SM, et al. Novel intraoperative molecular test for sentinel lymph node metastases in patients with early-stage breast cancer. J Clin Oncol. 2008;26-3338-45.
39. Pugliese MS, Kohr JR, Allison KH, Wang NP, Tickman RJ, Beatty JD. Accuracy of intraoperative imprint cytology of sentinel lymph nodes in patients whit breast cancer. Am J Surg. 2006;192:516-9.
40. El-Gohary YM, Saad RS, Robinson MJ, Mesko T, Poppiti RJ. Prognostic significance of intratumoral and peritumoral lymphatic density and blood vessel density in invasive breast carcinomas. Am J Clin Pathol. 2008:129(4):578-586.
41. Weider N, Folkman J, Pozza F, et al. Tumour angiogenesis a new significant and independent prognostic indicator in early-stage breast carcinoma. J Natl Cancer Last. 1992;84(24):1875-1887.
42. Arnaout-Alkatain A, Narod SA, Sun PA, Marks AN. Significance of lymph vessel invasion identified by the endothelial lymphatic marker D2-40 in node negative breast cancer. Mod Pathol. 2007;20(2):183-191.
43. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994;220:391-9.
44. Albertini JJ, Lyman GH, Cox C, Yeatman T, Balduccci L, Ku N et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA. 1996;276:1818-22.
45. Kelley MC, Hansen N, McMasters KM. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Am J Surg. 2004;188:49-61.