Survival in primary inoperable breast cancer patients

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Summary

Purpose of investigation: Patients described as having inoperable breast cancer comprised a heterogeneous group of patients with variable natural history and survival. Over the past 20 years combined modality therapy has been used to improve control of disease and enhance survival. However, systemic evaluation of these patients has been limited and additional clinical research is needed.

Methods: This is a retrospective review of 136 patients with primary inoperable breast cancer. Twenty-five years of experience was used to examine the effect of several prognostic variables and different treatment modalities on survival.

Results: The median survival of inoperable breast cancer patients was 46 months (2 to 220). Metastatic status at initial diagnosis was an independent prognostic factor, while neoadjuvant chemotherapy followed by surgery seems to offer a survival advantage. Also, hormonal receptor status affects the long-term survival.

Conclusion: Metastatic status, status of receptors and type of treatment provide additional prognostic information and therefore should be used as prognostic indicators for primary inoperable breast cancer.

Key words: Inoperable breast cancer; Advanced breast cancer; Treatment; Survival; Prognosis.

Introduction

Despite the availability of mammographic screening programs and the extensive campaigns promoting early diagnosis and treatment, a sufficient number of patients continue to present with primary inoperable cancer of the breast. Although criteria defining operability have been proposed [1], analyses of published data can be confusing because dissimilar subsets of patients are reported and hence results may not be comparable.

Patients with primary inoperable breast cancer are those with peri-clavicular lymph node or distant metastasis at the time of presentation (Stage IV) or, with any of the signs of local inoperability that generally meet the criteria of Stage IIIb according to the AJCC/UICC TNM 1992 staging system [2]. This is similar to Haagensen and Stout's definition of inoperability [3], which has been used historically for patient selection in some retrospective series and prospective trials [1].

The management of primary inoperable breast cancer patients has evolved substantially over the last 3 decades and various therapeutic options have been proposed [4]. It is not always obvious as to what would constitute the most appropriate form of treatment at this advanced stage of the disease. Chemotherapy, radiation therapy and surgery, all have their advocates, with multimodality therapy gaining ground over the past two decades [4, 5]. However, far fewer studies have been done on patients with more advanced stages of the disease and the optimal treatment scheme still has to be established [6]. Moreover, for patients with advanced breast cancer, the window of opportunity to perform randomized trials with local therapy only as a control arm was lost many years ago [7] and the results of phase II trials have to be compared with outcomes of historical control cases. Thus, patients with advanced breast cancer present a greater problem than the group of "early" breast cancer patients in current clinical practice.

Since survival is the best objective measure of treatment benefit [8], it was thought to be of interest to review the 25-year experience of our center and to analyze the effect on survival of several prognostic factors and treatment modalities.

Materials and Methods

A. Sample description

Historical cases of 136 patients with primary inoperable breast cancer presenting between the years 1975 and 1999 were obtained from the medical files of the Breast Cancer Division, Alexandra University Hospital and IASO Women's Health Hospital, Athens, Greece. These patients presented with either supraclavicular or distant metastasis (M1), or with any of the signs of local inoperability: cancer involving the entire breast, edema (peau d'orange) and satellite nodules, invasion of the skin causing ulceration, matted fixed axilla, edema of the arm secondary to lymphatic involvement with cancer, fixation to the wall of the chest and inflammatory breast cancer. The diagnosis of cancer was confirmed by biopsy.

The pathological diagnosis included 89 cases (65%) of ductal invasive carcinoma, 31 cases (23%) of lobular invasive carcinoma and 16 cases (12%) of epithelial invasive carcinoma of another histological type. The mean age at the time of initial diagnosis was 59 years (range 29 to 92 years, SDV 12.7 years). Almost 60% of our patients were 50 to 70 years old, while 10% were younger than 40 years. Also, 77% of our patients were postmenopausal while two-thirds of our sample (102 patients, 75%) had tumors negative for estrogen and progesterone receptors. Eighty-seven out of 135 patients (64%) had not developed metastasis (Mo) at initial diagnosis but presented with locally advanced breast cancer. Forty-eight patients (36%) were

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metastatic (M1) at presentation while the majority of our patients (79%) had tumor size T4 (Table 1). Metastatic status was missing in one patient.

Table 1. — *Classification of patients according to tumor size and metastatic status; tumor size and metastatic status are correlated ($p < 0.001$).*

Tumor size / Metastatic status	T2 (%)	T3 (%)	T4 (%)	Total (%)
M_0 (%)	–	9 (10)	78 (90)	87 (100)
M_1 (%)	5 (10)	14 (29)	29 (61)	48 (100)
Total (%)	5 (4)	23 (17)	107 (79)	135 (100)

A statistically significant correlation by the x^2 test was observed between metastatic status and tumor size ($p < 0.001$), metastatic status and histological type ($p = 0.004$), as well as between tumor size and histological type ($p = 0.02$). Lobular histological type was more common in the M1 than in the Mo subgroup of patients (40% vs 14%). Also, the majority of T_4 tumors (76%) were ductal carcinomas, while 50% of T_3 and 80% of T_2 were lobular.

B. Therapy

Seventy-nine patients (58.5%) were treated with chemotherapy and/or hormonotherapy (conservative treatment) (Table 2). Older patients (> 75 years) and patients with major health problems received only hormonotherapy (n = 22). Chemotherapy consisted of CMF (cyclophosphamide, methotrexate and 5-flu-orouracil) prior to 1994. Since then chemotherapy has consisted of CAF (cyclophosphamide, doxorubicin and 5-flu-orouracil). Forty-four patients (32.6%) received 3-4 cycles of CMF or CAF as primary (neoadjuvant) chemotherapy followed by modified radical mastectomy (MRM), while 12 patients (8.9%) received initial radiotherapy followed by MRM. All patients who received initial chemotherapy or radiation rendered resectable underwent MRM followed by 3-4 cycles of chemotherapy with the same regiments. Also, all patients received hormonal therapy (tamoxifen 20 mg/day) as a maintenance therapy after all other treatments were completed, continuously or until progression.

The decision of treatment modality was made mainly on the basis of metastatic status ($p < 0.001$). Almost all metastatic patients (94%) were treated conservatively. In contrast, half of the non-metastatic patients received primary chemotherapy and then underwent surgery (Table 2). All T_2 tumors received conservative treatment since they were all metastatic. Between T_3 and T_4 tumors there was no statistically significant difference in treatment modality ($p = 0.09$). Although older women and women with a lobular histological type were more likely to receive conservative treatment, age and histological type were not found to influence treatment statistically significantly. Also, menopausal status and hormonal receptor status did not influence decision-making in therapy ($p > 0.05$ for all variables). Differences in treatment modality reflect the gradual changes in treatment policy over the study period.

These patients were followed-up and their length of survival and clinical status were obtained from the tumor registry. Although we believe that quality of life in these patients is an important issue, we did not calculate treatment morbidity and disease-free survival because of incomplete data.

Results

Survival and traditional prognostic variables

Seventy-one of our patients (52.2%) died during the study period. The minimum survival duration was two months; the maximum was 220 months (18.5 years), while the median survival duration was 46 months (3.8 years). Twenty-two out of 87 non-metastatic breast cancer patients (25.3%) later developed metastasis and these patients had worse survival when compared to the non-metastatic patients who did not develop later metastasis (31 vs 80 months median survival).

To examine the effect of traditional prognostic variables (age, tumor size, metastatic status, hormonal receptors status and histological type) on survival, we used the Kaplan-Meier statistical method and the log-rank test. The only variable that was found to affect survival was metastatic status ($p = 0.03$). Non-metastatic breast cancer patients experienced superior survival when compared to metastatic patients (52 vs 39 months). In multivariate analysis, using the Cox-regression model on the same variables, only metastatic status emerged as an independent prognostic factor ($p = 0.004$). The estimated risk of death for a metastatic neoplasia was double the risk of a non-metastatic one (relative risk: 2.2). Of note is that the effect of the metastatic status on survival includes the effect of treatment on survival since metastatic status and treatment modality were strongly correlated.

It has been reported that patients with M1 disease by virtue of supraclavicular adenopathy (loco-regionally advanced) may survive better than traditional M1 disease. To test this hypothesis, we examined the difference in survival curves between loco regionally advanced, inoperable locally advanced (Mo) and distant metastatic breast cancer patients. Although we found that patients

Table 2. — *Treatment modality according to metastatic status in primary inoperable breast cancer patients - metastatic status influenced therapy decision making ($p < 0.001$).*

			Therapy			Total
			Conservative	CHEM+Surgery	RAD+Surgery	
Metastasic status	Mo	Count	34	43	10	87
		% of Metastasic status	39.1	49.4%	11.5%	100.0%
	M1	Count	45	1	2	48
		% of Metastasic status	93.8%	2.1%	4..2%	100.0%
Total		Count	79	44	12	135
		% of Metastasic status	58.5%	32.6%	8.9%	100.0%

with metastatic tumors in the supraclavicular lymph nodes experienced better median survival to the other two groups of patients (64 vs 52 and 29 months, respectively) (Figure 1), there is not enough evidence to support the hypothesis that they have a different survival time than the others.

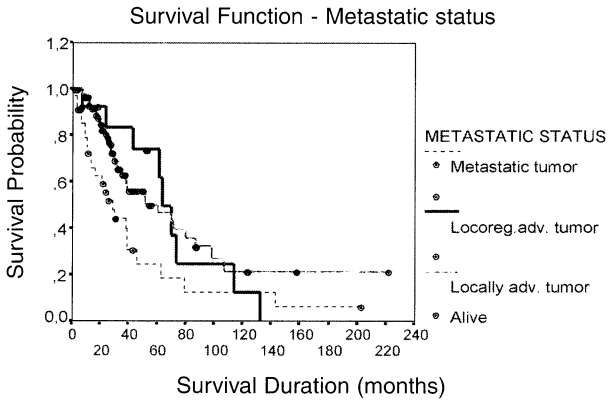

Figure 1. — Kaplan-Meier life-table analysis of primary inoperable breast cancer patients (n = 135) for overall survival by metastatic status: locally advanced (alive, 50; dead, 37; total, 87); loco regionally advanced (alive, 4; dead, 9; total, 13); metastatic (alive, 11; dead, 24; total, 35).

The effect of treatment modality on survival

To erase the effect of metastatic status on survival, we examined the effect of treatment modality on survival only in the group of non-metastatic patients (Mo, n = 87). We found that in non-metastatic inoperable breast cancer patients the treatment modality statistically significantly affected survival (p = 0.02). Patients who received chemotherapy and then underwent surgery experienced better survival when compared to the survival of the other treatment groups (99 vs 61 and 32 months median survival for the "radiotherapy + surgery" and "conservative" treatment groups, respectively), (Figure 2).

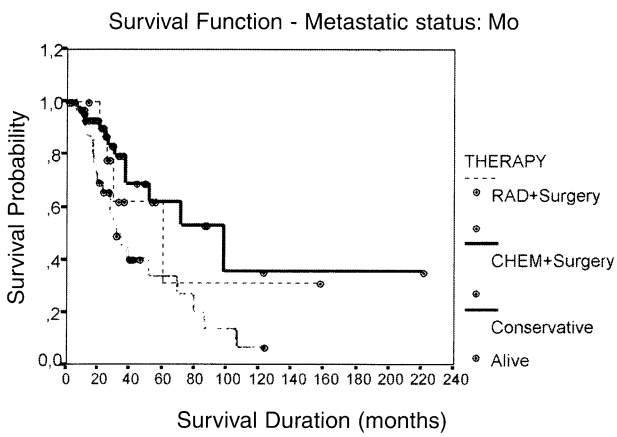

Figure 2. — Kaplan-Meier life-table analysis of primary inoperable non-metastatic breast cancer patients for overall survival by treatment modality (n = 87, p = 0.02): Conservative treatment (alive, 13; dead, 21; total, 34); CHEM+Surgery (alive, 31; dead, 12; total, 43); RAD+Surgery (alive, 6; dead, 4; total, 10).

Long-term and short-term survivors

To examine possible differences in prognostic variables between long-term and short-term survivors, patients were divided into two groups: Patients who survived less than 5-years (short-term survivors, group I, n = 55) and patients who survived more than 5-years (long-term survivors, group II, n = 24). Patients who are still alive and have survival less than 5-years were excluded from this analysis since we did not know their final outcome. This new sample of patients (groups I and II) did not differ from the initial sample (cohort of patients) in the distribution of common prognostic variables (age, menopausal status, tumor size, metastatic status, hormonal receptors status, treatment modality and histological type) or in the correlations between these variables. In univariate analysis, using the aforementioned variables, the variable that was found to statistically significantly affect the length of survival was the hormonal receptor status (x2 test: p = 0.01). Also, in multivariate analysis, using the same common variables, only the status of the receptors was found to be an independent factor that affects short and long-term survival (p = 0.002). The positive hormonal (estrogen and/or progesterone) receptor status increased the possibility of long-term survival (50% to live more than 5-years), while the opposite was observed in negative hormonal (estrogen and progesterone) receptor status; it decreased the probability of long-term survival (22% to live more than 5 years), (Figure 3).

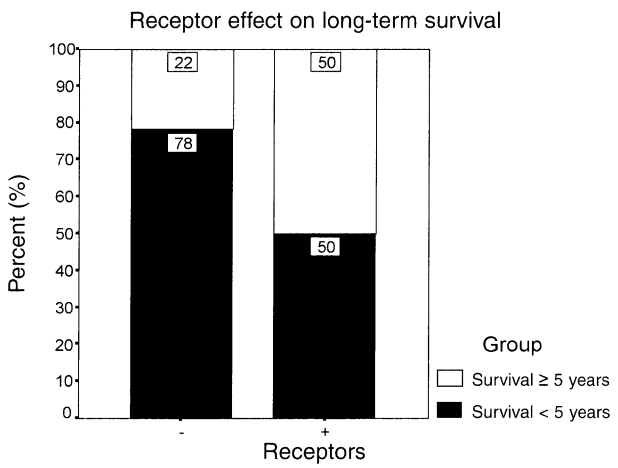

Figure 3. — Effect of hormonal receptors on long-term (≥ 5 years) and short-term (< 5 years) survival of primary inoperable breast cancer patients (n = 79, p = 0.01). Positive hormonal receptors at diagnosis increase the probability for long-term survival from 22% to 50%.

Discussion

The definition of inoperable breast cancer patients; the classification system and treatment options have changed over time

Inoperable breast cancer encompasses a heterogeneous group of patients with the common characteristic of inoperability at initial diagnosis. They have either detectable

metastasis (metastatic patients) or are likely to have undetectable micro metastasis (locally advanced patients) at presentation [6] and are generally thought to have a poor prognosis [9]. However, interpretation of published data on advanced breast cancer over the past 25 years remains difficult. The AJCC breast cancer staging system has changed several times since its inception in 1962 [10] and different staging classifications have been used.

Our patients constitute two different groups; the group of patients with inoperable locally advanced breast cancer (ILABC), which is similar to Stage IIIb, and the group of metastatic breast cancers (Stage IV). The patients in the first group were in essence unresectable based on the criteria of resectability described by Haagensen and Stouts several decades earlier [3]. Treatment of ILABC patients has changed over time from loco regional therapies to multidisciplinary management [11]. These treatment modalities have been used in various combinations and sequences of administration. Randomized trials concerning locally advanced breast carcinomas [12-18] are lacking and the optimal treatment program remains to be established [11].

Our multimodality treatment was similar to the M.D. Anderson Cancer Center 1974 multimodality treatment protocol for locally advanced breast cancer [13]. Almost half of our non-metastatic patients received primary chemotherapy followed by surgery and these patients experienced the longest overall survival. Few of the ILABC patients were treated with primary radiation followed by surgery, whereas a sizable number (39%) were treated conservatively. All patients who underwent surgery received postoperative chemotherapy for the control of potential micrometastatic disease followed by hormonal therapy. Although there are many studies supporting the positive effect of adjuvant systemic therapies on survival [19], how much they added to the outcome of our patients is uncertain.

Overall survival and the influence of metastatic status on survival

Our median survival (46 months) is similar to that reported by Hortobagyi *et al.* [13] for Stage IIIb breast cancer patients treated with multimodality therapy and superior to other reports [20, 21]. Also, the percentage of our ILABC patients who developed distant metastasis later (25.5%) is much lower than the 33-43% reported elsewhere [11, 12, 22] and the vast majority of these patients then went on to die of their disease as was expected [12, 23, 24]. However, survival comparisons between reported series of patients are very difficult because of several treatment groups and different treatment modalities.

In our patients, the presence of metastatic status was by far the most prognostic factor and other prognostic factors would not be expected to be more significant than metastatic disease. Our metastatic breast cancer patients have double the risk of dying of the disease. This is not surprising and is in line with most articles in the literature demonstrating that metastatic patients have a poorer prognosis [4, 9, 25]; however, we report a better median survival (39 months) of metastatic breast cancer patients to other studies. The metastatic breast cancer group had a heterogeneous natural history with some patients demonstrating rapid dissemination and death within a few months, while others followed a very indolent course and stability for many years. Furthermore, different doses and combinations of systemic therapy probably affected the survival rates. Systemic treatments had a predominant role in the management of metastatic breast cancer, while surgery and palliative radiotherapy offered limited but important contributions to the therapy of specific localized problems in a very few patients.

Since 1992, ipsilateral supraclavicular or infraclavicular lymph node involvement has been considered Stage IV disease instead of Stage IIIb. However, most clinical research studies to date have been based on earlier staging schemes [26] and some researchers [11, 12] include periclavicular lymph node involvement in locally advanced breast cancer. Hortobagyi *et al.* [27] found that in loco regionally advanced breast cancer patients median disease-free survival was statistically better in patients who had supraclavicular nodal disease, while Kantarjian *et al.* [28] reported that supraclavicular lymphadenopathy had no effect on prognosis. In our group, despite the observed trend, the statistical analysis does not support better survival and the number of patients is too small to draw significant conclusions.

Treatment outcome

Since almost all metastatic patients were treated conservatively (chemotherapy and/or hormonotherapy) and metastatic status was found to influence treatment modality, we examined the effect of treatment only in the group of non-metastatic ILABC patients. The present study provides evidence that the combination of local and systemic treatment in ILABC patients results in better local control of disease and prolonged survival, as many authors have reported [4, 11, 12, 29]. Patients who received primary chemotherapy or radiation followed by surgery experienced better survival suggesting that the combination of primary chemotherapy or radiation plus surgery results in improved survival as has been previously demonstrated by others [14]. Our therapeutic results compare favorably with a summary of published results of combined modality therapy showing that 20-63% of patients remain alive 5-years after initial diagnosis [6, 12, 20]. Since all patients had at least a partial clinical response and were rendered operable, primary systemic therapy has proved to be an effective way of achieving significant tumor regression and to transform ILABCs into clearly operable tumors allowing surgery to offer a satisfactory local/regional control of disease. Furthermore, most patients with ILABCs have subclinical micrometastases, a problem in that primary chemotherapy attacks from the very beginning without any delay of local therapies which do not alter the course of micrometastases [19]. This probably reflects on the better survival of patients treated with neoadjuvant chemotherapy. Although these

observations are not novel, our study, with a long-term follow-up, provides additional information concerning advanced breast cancer treatment and outcome.

Long-term and short-term survivors; do they differ in any of the known prognostic variables?

In advanced breast cancer many prognostic factors have been described including clinicopathological [6, 8, 9] as well as biological characteristics [1, 6, 30]. However, they are not highly predictive or generally applicable and their real meaning in the context of breast cancer as a disease is obscure [31]. The traditional way of analyzing survival by prognostic factors has been to divide patients into subgroups by, for example metastatic status. These forms of presentation of results, while clinically valuable, tell us little about the nature of the disease. An alternative interpretation is that the biological nature of the disease in patients who survive for a long time (≥ 5 years, given the poor survival of inoperable patients) differs from the disease in patients with short-term survival (< 5 years) [32].

We examined possible prognostic factors and found that these two groups of survivors (long-term and short-term) differ statistically significantly only in hormonal receptor status. This means that inoperable patients with tumors positive for estrogen and/or progesterone receptors at diagnosis have a possibility of 50% to survive more than five years independently of the treatment that will follow, whereas when the tumor is negative, the probability for long-term survival is just 22%. Of note is that the status of the receptors was not correlated to any of the examined prognostic variables.

There are many studies in the literature demonstrating the biological significance of hormonal receptors in breast cancer [1, 30, 33]. However, we report that hormonal receptors is a major biological prognostic factor at presentation of primary inoperable breast cancer exerting its influence on the disease long after it has been measured in the primary tumor. How much this factor reflects the natural history of the disease and how much it can predict response to therapy needs to be established.

Conclusion

Our analysis provides insight into the nature of the various prognostic factors of primary inoperable breast cancer patients. We have demonstrated that metastatic status, type of treatment and status of hormonal receptors are prognostic indicators. There may be more important prognostic factors in inoperable breast cancer patients which have not, as yet, been identified and whose relationship with the factors we have analyzed is at most indirect. Since there are patients with a long-term and patients with a short-term survival that do not differ in common clinicopathological characteristics, we consider that an unknown factor related to the natural history of the disease may exist which directly affects survival.

References

[1] Dorr A.F., Bader J., Friedman M.A.: "Locally advanced breast cancer current status and future directions". *Int. J. Radiation Oncol. Biol. Phys.*, 1989, *16* (3), 775.

[2] Beahrs O.H., Henson D.E., Hutter R.V.P., Kennedy B.J.: "Handbook for staging of cancer". In manual for staging on cancer, edition 4, Philadelphia, Lippincott, 1993, 161.

[3] Haagensen C.D., Stout A.P.: "Carcinoma of the breast. II. Criteria of inoperability". *Ann. Surg.,* 1943, *118,* 859.

[4] Hortobagyi G.N.: "Multidisciplinary management of advanced primary and metastatic breast cancer". Cancer, 1994 (suppl.), *74* (1), 416.

[5] Pearlman N.W., Guerra O., Fracchia A.A.: "Primary inoperable cancer of the breast". *Surg. Gynecol. Obstet.,* 1976, *143* (6), 909.

[6] Honkoop A.H., Wagstaff J., Pinedo H.M.: "Management of Stage III breast cancer". *Oncology,* 1998, *55* (3), 218.

[7] Valero V., Buzdar A.U., Hortobagyi G.N. "Locally advanced breast cancer". *Oncologist,* 1996, *1* (4), 278.

[8] Falkson G., Gelman R.S., Leone L., Falkson C.I.: "Survival of premenopausal women with metastatic breast cancer. Long-term follow-up of Eastern Cooperative Group and Cancer and Leukemia Group B studies". *Cancer,* 1990, *66* (7), 1621.

[9] Bradburn M.J., Altman D.G., Smith P., Fentiman I.S., Rubens R.D.: "Time trends in breast cancer survival: experience in a single center, 1975-89". *Br. J. Cancer,* 1998, *77* (11), 1944.

[10] Chittoor S.R., Swain S.M.: "Locally advanced breast cancer: role of medical oncology". In: K.I. Bland and E.M. Copeland, III (eds.). The Breast: Comprehensive Management of Benign and Malignant diseases. Philadelphia, Saunders, 1998, 1260.

[11] Hortobagyi G.N., Buzdar A.U., Strom E.A., Ames F.C., Singletary S.E.: "Primary chemotherapy for early and advanced breast cancer". *Cancer Lett.,* 1995, *90* (1), 103.

[12] Morrell L.E., Lee Y.J., Hurley J., Arias M., Mies C., Richman S.P. *et al.*: "A Phase II trial of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin in the treatment of patients with locally advanced breast carcinoma". *Cancer,* 1998, *82* (3), 503.

[13] Hortobagyi G.N., Ames F.C., Buzdar A.U., Kau S.W., McNeese M.D., Paulus D. *et al.*: "Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy". *Cancer,* 1988, *62* (12), 2507.

[14] Jacquillat C., Weil M., Baillet F., Borel C., Auclerc G., de Maublanc M.A. *et al.*: "Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer". *Cancer,* 1990, *66* (1), 119.

[15] Abdel-Wahab M., Wolfson A., Raub W., Mies C., Brandon A., Morrell L. *et al.*: "The importance of postoperative radiation therapy in multimodality management of locally advanced breast cancer: a phase II trial of neoadjuvant MVAC, surgery, and radiation". *Int. J. Radiat. Oncol. Biol. Phys.,* 1998, *40* (4), 875.

[16] Blumenschein G.R., DiStefano A., Caderao J., Fristenberg B., Adams J., Schweichler L.H. *et al.*: "Multimodality therapy for locally advanced and limited Stage IV breast cancer: the impact of effective non-cross-resistance late-consolidation chemotherapy". *Clin. Cancer Res.*, 1997, *3* (12 pt 2), 2633.

[17] Glinski B., Pawlicki M., Reinfuss M., Skolyszewski J., Brandys A., Krzemieniecki K. *et al.*: "Multimodality treatment of noninflammatory Stage IIIb breast cancer". *J. Surg. Oncol.,* 1997, *66* (3), 179.

[18] Bartelink H., Rubens R.D., van der Schueren E., Sylvester R.: "Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized Phase III Trial". *J. Clin. Oncol.*, 1997, *15* (1), 207.

[19] Hortobagyi G.N.: "Comprehensive management of locally advanced breast cancer". *Cancer,* 1990, *66* (suppl. 6), 1387.

[20] Armstrong D.K., Fetting J.H., Davidson N.E., Gordon G.B., Huelskamp A.M., Abeloff M.D.: "Sixteen week dose intense chemotherapy for inoperable, locally advanced breast cancer". *Breast Cancer Res. Treat.,* 1993, *28* (3), 277.

[21] Luboinski G., Nagadowska M., Pienkowski T.: "Preoperative chemotherapy in primarily inoperable cancer of the breast". *Eur. J. Surg. Oncol.*, 1991, *17* (6), 603.

[22] Hunt K.K., Ames F.C., Singletary S.E., Buzdar A.U., Hortobagyi G.N.: "Locally advanced noninflammatory breast cancer". *Surg. Clin. North Am.*, 1996, *76* (2), 393.
[23] Billgren A.M., Rutqvist L.E., Tani E., Wilking N., Fornander T., Skoog L.: "Proliferating fraction during neoadjuvant chemotherapy of primary breast cancer in relation to objective local response and relapse-free survival". *Acta Oncol.*, 1999; *38* (5), 597.
[24] Hortobagyi G.N., Blumenschein G.R., Spanos W., Montague E.D., Buzdar A.U., Yap H.Y. *et al.*: "Multimodal treatment of locoregionally advanced breast cancer". *Cancer,* 1983, *51* (5), 763.
[25] Dunphy F.R., Spitzer G., Fornoff J.E., Yau J.C., Huan S.D., Dicke K.A *et al.*: "Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support". *Cancer,* 1994, *73* (8), 2157.
[26] Hunt K.K., Kroll S.S., Pollock R.E.: "Surgical procedures for advanced local and regional malignancies of the breast". In: K.I. Bland and E.M. Copeland, III (eds.). The Breast: Comprehensive Management of Benign and Malignant Diseases. Philadelphia, Saunders, 1998, 1234.
[27] Hortobagyi G.N., Spanos W., Montague E.D., Buzdar A.U., Yap H.Y., Blumenschein G.R.: "Treatment of locoregionally advanced breast cancer with surgery, radiotherapy, and combination chemoimmunotherapy". *Int. J. Radiat. Oncol. Biol. Phys.*, 1983, *9* (5), 643.
[28] Kantarjian H.M., Hortobagyi G.N., Smith T.L., Blumenschein G.R., Montague E., Buzdar A.U. et al.: "The management of locally advanced breast cancer: a combined modality approach". *Eur. J. Cancer Clin. Oncol.,* 1984, *20* (11), 1353.
[29] Smith I.E.: "Patients benefit from new treatment options and schedules for breast cancer". *Semin. Oncol.,* 1997, *24* (4) (suppl. 10), 10.
[30] Paterson A.H., Zuck V.P., Szafran O., Lees A.W., Hanson J.: "Influence and significance of certain prognostic factors on survival in breast cancer". *Eur. J. Cancer Clin. Oncol.,* 1982, *18* (10), 937.
[31] Reichman B.S., Osborne M.P.: "Detection of occult micrometastatic disease". In: K.I. Bland and E.M. Copeland, III (eds.). The Breast: Comprehensive Management of Benign and Malignant Diseases. Philadelphia, Saunders, 1998, 1299.
[32] Vincent M.D., Powles T.J., Skeet R., Ashley S., Coombes R.C., Gibb J. *et al.*: "An analysis of possible prognostic features of long term and short term survivors of metastatic breast cancer". *Eur. J. Cancer Clin. Oncol.,* 1986, *22* (9), 1059.
[33] Nomura Y., Tashiro H., Osaki A.: "Long term survival and the prognostic factors of advanced breast cancer patients treated with adreno-oophorectomy". *Breast Cancer Res. Treat.*, 1995, *33* (1), 47.

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