

Prognostic factors in the treatment of breast carcinoma

Algirdas Jackevičius*,
Valerijus Ostapenko,
Saulius Bružas,
Juozas Kurtinaitis,
Raimondas Medžauskas,
Algimantas Mudėnas

*Institute of Oncology,
Vilnius University,
Santariškiø 1, LT-08660
Vilnius, Lithuania*

Background: According to literature, the prognostic factors such as tumor size, grade and lymph node involvement are very important in the treatment and survival of patients with breast carcinoma. We try to analyse our the study cohort patients according to these prognostic factors.

Materials and methods: At the Department of Breast Diseases of the Institute of Oncology of Vilnius University, 1269 patients with breast carcinoma were treated in 1998–2000. Most of the patients (929, 73.2%) were treated in early stages of the disease (I–IIA and IIB). In stage IIIA were 199 (15.7%) patients, in IIIB (pT4) 103 (8.1%), 38 (3.0%) were in stage IV of the disease. The most common operation was a modified mastectomy by the Madden method (in 807, 63.4%). Quadrantectomy was performed in 439 (34.6%) cases.

Results: Most of the treated patients (1197, 94.3%) received combined treatment – surgery and additional therapy (radiotherapy, chemotherapy or both, hormonal therapy). The 5-year survival (90.9%, 95% CI 59.1–78.2) was longest in patients who were treated with quadrantectomy+ chemotherapy. We received good results in patients treated with mastectomy and tamoxifen 74.8% (95% CI 63.6–82.9) of them survived for 5 years.

Conclusions: According to multivariate analysis, tumor size, lymph node involvement and histological grade are important prognostic factors of the survival of patients with breast carcinoma. Hormone receptor status in the early stages of the disease has a marginal influence on the survival of such patients. Optimization of treatment in the early stages has improved the follow-up results.

Key words: breast carcinoma, treatment, overall survival, prognostic factors

INTRODUCTION

According to literature data and our experience, the survival of patients with breast carcinoma is determined by the clinical stage of the disease, which is estimated by pathological parameters such as tumor size, grade and lymph node involvement (1, 2). However, the malignant potential is a dynamic process progressing through many intracellular molecular changes, which may be responsible for genetic alterations and overexpression of genes that normally regulate cell proliferation and differentiation, such as hormone receptors, growth factors, oncoproteins and tumor suppressor genes (3, 4). However, the prognostic significance of standard prognostic factors such as tumor size and lymph node status have remained to be very important in statistical analysis. L. Hiupière, J. Jakiè-Razumoviè, J. Bobikova et al. (5) have made a statistical analysis of traditional prognostic factors and the immunohistochemically determined expression of steroid re-

ceptors, bcl-2, p53, Ki-67, nm23 and HER-2/neu in each tumor. According to these authors, the data of ER status were associated with the patient's age ($p = 0.010$) and lymph node status ($p = 0.32$). The PgR status was clearly associated with tumor size ($p = 0.010$) and grade ($p = 0.033$). Data on the results of treatment of breast carcinoma according to classic prognostic factors such as tumor size, lymph node status and hormone receptors in Lithuanian literature are not numerous. We try to analyse the results in the patients treated at the Clinic of Surgery of the Institute of Oncology of Vilnius University.

MATERIALS AND METHODS

At the Department of Breast Diseases of the Institute of Oncology of Vilnius University, 1269 patients with breast carcinoma were treated in 1998–2000. The distribution of patients according to the stage of disease and the age of patients is shown in Table 1. Most of our patients (929, 73.2%) were treated in early stages of the disease (I–IIA and IIB). In stage

* Corresponding author. E-mail address: algirdasj@is.lt

IIIA there were 199 (15.7%) and in IIIB (pT4) 103 (8.1%) patients; 38 (3.0%) patients came for the treatment to the Clinic of Surgery in stage IV of the disease. Histological examination results of patients with breast tumor is shown in Table 2. The most common type of tumor was *carcinoma ductale* – in 770 (60.7%) cases. *Carcinoma lobulare* was detected in 196 (15.4%) patients. *Carcinoma solidum* was diagnosed in 57 (4.5%) cases, *adenocarcinoma* in 49 (3.9%). Other types of breast tumor were very rare. In our material, *carcinoma in situ* was detected only in 14 cases: 10 patients had *carcinoma intraductale in situ*, three had Paget tumor and one patient *carcinoma lobulare in situ*. Over the last years, in our Clinic of Surgery *carcinoma in situ* has been detected during operations more often in patients with breast carcinoma. Among breast tumors sarcomas are rare. They were detected only in 7 (0.6%) cases. Most patients with breast sarcomas were diagnosed in late stages of the disease: four patients had stage IIIA and one stage IV of the disease.

We tried to analyse the location of the tumor in the breast. We selected 790 patients with breast carcinoma according to localisation (sector) of the tumor in the breast and the stage of disease. These data are shown in Table 3. The most common place of tumor was the outer upper sector of the breast (451, or 57.1%). In the central sector, breast carcinoma was detected in 125 (15.3%) patients. In 23 (2.9%) cases the tumor had affected all sectors of the breast. From this group, 18 patients had pT4. The distribution of patients with breast carcinoma according to the stage of the disease and the method of treatment is shown in Table 4. Most of the patients received a combined treatment surgery and additional therapy (radiotherapy, chemotherapy or both, hormonal therapy); 72 patients received only surgical treatment: in 54 cases mastectomy and in 8 quadrantectomy was performed. Three patients were treated by simple mastectomy (without dissection of axillary lymph nodes), to eight patients only sectorectomy (quadrantectomy without dissection of axillary lymph nodes) was performed.

Table 1. Distribution of patients with breast cancer according to the stage of disease and age of patients

Stage	Age					Total
	< 35	35–49	50–64	65–74	75+	
0	1	6	4	1	2	14
I	8	75	101	48	21	253
IIA	11	114	143	86	27	381
IIB	9	86	105	53	28	281
IIIA	6	45	85	48	15	199
IIIB	0	21	33	33	16	103
IV	1	13	11	8	5	38
Total	36 (2.8%)	360 (28,4%)	482 (38,0%)	277 (21,8%)	114 (9,0%)	1269

Table 2. Histological examination of breast tumors according to the stage of disease

Histological type of tumor	S 0	TA I	GE IIA	of IIB	DI IIIA	SEA IIIB	SE IV	Total
Adenocarcinoma	0	6	10	10	14	7	3	49
Ca intraductale <i>in situ</i>	10							10
Ca lobulare <i>in situ</i>	1							1
Ca ductale	0	158	239	178	121	56	18	770
Ca ductale + lobulare	0	14	11	17	8	5	0	55
Ca lobulare	1	39	58	44	29	17	8	196
Ca medulare		7	4	2	0	0	0	13
Ca mucoides	0	2	6	1	1	2	1	13
Ca papillare	0	2	6	2	1	0	0	11
Tumor Paget	3	2	1	0	0	0	0	6
Sarcoma	0	0	1	1	4	0	1	7
Ca scirrhosum	0	1	4	1	1	1	0	8
Ca solidum	0	8	13	14	7	11	4	57
Ca tubulare	0	3	5	2	1	0	2	13
Others	0	11	23	9	12	4	1	60
Total	14	253	381	281	199	103	38	1269

Table 3. Distribution of 790 patients with breast carcinoma according to the stage, pTNM of disease and localisation (sector) of tumor

Stage of disease	pTNM	Tumor localisation						Total
		Outer upper	Inside upper	Outer inferior	Inside inferior	Central	All breast	
0	Is00	1			1	2		4
I	100	93	28	12	11	16		160
IIA	110	31	6	9	2	8		56
	200	106	26	11	9	27		179
IIB	210	97	15	13	4	20		149
	300	11	3	0	2	5	0	21
IIIA	120	8	3	1	0			12
	220	36	2	8	5	9	0	60
	310	19	1	2	0	8	1	31
IIIB	320	15	1	3	0	10	3	32
	400	5	1	0	1	3	2	12
	410	10	1	1	2	7	3	24
	420	13	4	3	0	4	5	29
IV	221	3	0	1	0	1	0	4
	301	1	0	0	0	0	0	1
	311	0	0	0	1	0	0	1
	321	0	0	1	0	1	1	3
	411	0	0	0	0	0	1	1
	421	7	1	0	0	0	7	15
Total		451	92	65	38	121	23	790
	%	57.1	11.7	8.2	4.8	15.3	2.9	

Table 4. Distribution of patients with breast carcinoma according to the stage of disease and the method of treatment

Treatment	Stage of disease							Total
	0	I	IIA	IIB	IIIA	IIIB	IV	
Sectorectomy*	3	2	2	1				8
Sectorectomy + rad	0	2	1	3			1	7
Ablatio**			1			1	1	3
Ablatio + radiotherapy	1	1	1			3	2	8
Quadrantectomy	2	3	1			1	1	8
Quadrantectomy + radiotherapy	5	133	90	35	9			272
Che + quadrantectomy + che		12	40	23	16		1	92
Che + quadrantectomy + rad		5	21	12	7	2		47
Quadrantectomy + tamoxifen		7	8	3	1	1		20
Mastectomy		14	21	11	3	3	2	54
Mastectomy + radiotherapy		17	57	61	32	25	3	195
Radiotherapy + mastectomy			9	8	14	3		34
Mastectomy + chemotherapy		9	44	55	63	27	19	217
Mastectomy + che + rad		1	16	43	42	24	7	133
Mastectomy + tamoxifen	3	47	69	26	12	13	1	171
Total	14	253	381	281	199	103	38	1269

Explanations: Sectorectomy* – quadrantectomy without dissection of axillary lymph nodes, ablatio** – simple mastectomy without dissection of axillary lymph nodes. Rad – radiotherapy, Che – chemotherapy.

Many patients (13) who were treated with sectorectomy or simple mastectomy were in early stages of the disease. However, in 10 cases conservative surgery was performed in late stages of the disease (IIIB and IV). The state of patients' health was so poor that there was no possibility to perform mastectomy. In our material, among radical operations most com-

mon was modified mastectomy by the Madden method, in which the surgeon must preserve m. pectoralis major and minor. Small vessels and nerves were preserved during the dissection of axillary lymph nodes. Radical mastectomy by the Madden method was performed in 804 cases (63.4%): only 12 (1.5%) patients were operated on by the Halsted method. In

Table 5. Distribution of patients with breast carcinoma according to hormone receptor status and age

Age	< 35	35–49	50–64	65–74	75+	Total
Estrogen receptor						
negative		3	6	5		14
weak	2	8	12	4	3	29
moderate		14	13	4	3	34
active		9	6	2	2	19
total	2	31	36	14	7	94
Progesterone receptor						
negative		1	8	3	1	13
weak	1	13	15	8	3	40
moderate	1	9	7	4	1	22
active	2	9	5	4	2	20
total	4	34	36	21	8	97

Table 6. Distribution of patients with breast carcinoma according to hormone receptor status and the stage of disease

Stage	0	I	IIA	IIB	IIIA	IIIB	IV	Total
Estrogen receptor								
negative		4	2	3	2	3		14
weak	1	6	10	6	3	3		29
moderate	2	8	9	8	2	1	4	34
active		10	4	4	1		1	20
total	3	28	25	19	8	7	5	97
Progesterone receptor								
negative		4	2	3	2	1	1	13
weak	2	10	11	6	4	6	1	40
moderate	1	10	2	8			1	22
active		4	9	3	2		1	19
total	3	28	24	20	8	7	4	94

439 (34.6%) cases quadrantectomy was performed; 400 (91.1%) patients were treated surgically in early stages of the disease and the other 39 in the late stages of tumor. The patients with stage IIIA of the disease had been treated with neoadjuvant chemotherapy before surgery. In some cases after such treatment there was a regression of tumor and the surgeon had a possibility to perform quadrantectomy. Most of our patients to whom quadrantectomy was performed received adjuvant therapy: 319 patients after quadrantectomy were treated with radiotherapy, in 139 cases with chemotherapy; 92 patients had received neoadjuvant chemotherapy before surgery. Among these patients, 16 were in stage IIIA of the disease. After quadrantectomy the patients received adjuvant chemotherapy. Many patients (362) to whom mastectomy was performed received radiotherapy, in 217 cases after mastectomy the patients were treated with adjuvant chemotherapy; 133 patients after surgery were treated with chemotherapy and radiotherapy. A big group of patients after mastectomy were treated with hormonal therapy (tamoxifen).

We have investigated the status of hormone receptors in 97 patients with breast carcinoma. These data are shown in Tables 5 and 6. Fourteen (14.4%) patients had negative estrogen receptors. In 54 (55.7%) patients estrogen receptors (ER) were positive. Progesterone receptors (PgR) were negative in 13 (13.8%) patients, 41 (43.6%) patients had positive receptors.

RESULTS OF TREATMENT

The results of surgical treatment of patients with breast carcinoma were satisfactory: no lethal cases were among 1269 patients. But in cases pT4 the healing of wounds was not good in some cases, there was infection, the patients were treated with antibiotics. There was exudation in all cases after dissection of axillary lymph nodes. The intensity and duration of exudation in most cases was related to obesity and multiple metastases of axillary lymph nodes. The duration of exudation from the axillary place was from 5 days to two weeks and more. As a rule, we used drainage with vacuum system.

FOLLOW-UP RESULTS

The follow-up results after treatment were examined on June 1, 2004. Statistical analysis of the data was made by the Kaplan–Meier method in the course of 5 years.

The 5-year survival of patients with breast carcinoma according to the stage of disease is shown in Fig.1 and Table 7. The survival of patients was highest in early stages of the disease: in the first stage it reached 90.9% (95% CI 86.3–94.1), in the second stage 77.2 (C.I 73.6–80.32), in the third 48.7% (CI 42.4–54.1), in the fourth 26.3% (C.I 13.7–40.8). There was a difference in the survival of patients in stage II of the disease: in cases pT2N0M0 and pT1N1M0 81.7% (77.1–85.5), but in cases of pT2N1M0, pT3N0M0 71.0% (65.1–76.1) the patients lived 5 years. The log-rank test showed $p = 0.0003$. Among patients with pT3N1M0, pT1,2,3N2M0 and pT4N0M0, pT4BN1.2M0 the difference in the survival of patients was insignificant. We have analysed also the follow-up results of patients with breast carcinoma in the se-

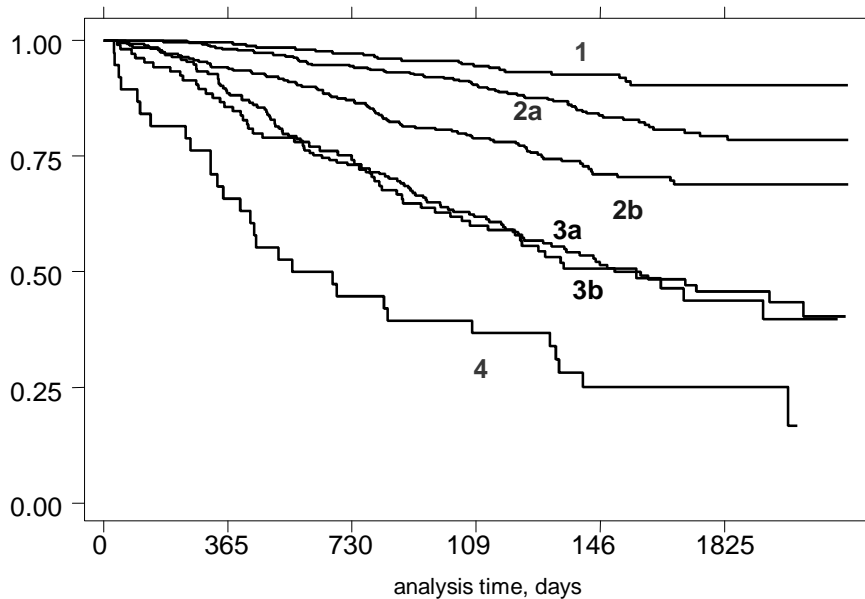


Figure. Overall survival of patients with breast carcinoma according to the stage of disease

Table 7. 5-year survival of patients with breast carcinoma according to the stage of disease

Stage	5-year survival (%)	95% confidence interval	Log-rank test for equality of survivor functions
I	90.9	86.3–94.1	
IIA + IIB	77.2	73.6–80.3	
II A	81.7	77.1–85.5	IIA–IIB p = 0.0003
II B	71.0	65.1–76.1	
IIIA + IIIB	48.4	42.4–54.1	IIIA–IIIB p = 0.7131
III A	48.7	41.3–55.8	
III B	47.6	37.3–57.3	
IV	26.3	13.7–40.8	

cond stage of the disease according to the methods of treatment. The data related to the various methods of treatment are shown in Table 8. The 5-year survival was best in patients with stage IIA breast carcinoma who were treated with quadrantectomy + chemotherapy: 90.9% (95% CI.79.2–96.2) patients survived over this period. After quadrantectomy + radiotherapy, 5-year survival was shorter: 79.1% (CI.69.7–85.9) of treated patients were alive. The survival of patients after mastectomy+ chemotherapy was worse: only 69.8% (CI.59.1–78.2) of patients remained alive. We received good results of treated patients with mastectomy and tamoxifen: 74.8% (CI. 63.6–82.9) of patients lived 5-years.

We have analysed the survival of patients in the second stage of the disease according to hormone receptor status. These data are presented in Table 9.

There is a tendency that patients who have active hormone receptors live longer than patients with ne-

gative hormone receptors. The patients in stage IIIA of the disease with active hormone receptors had also a longer survival – 75.0% (95% C.I 12.8–96.1) while with negative estrogen receptors 48.8% (C.I. 42.7–54.5) (Table 9).

We have analysed the 5-year survival of patients with breast carcinoma in stage II of the disease according to the histological type of tumor. These data are presented in Table 10. The survival was best in patients who had *carcinoma solidum*: 88.3% (95% CI.68.4–96.1) patients survived the period of 5 years. Patients with the most common histological type of *carcinoma inductuale* were alive in 76.3% (CI. 71.6–80.3).

It is difficult to say from our data which histological type of tumor is predictive of a better survival of patients. There are also other factors such as the histological grade of tumor and oncogenes that influence the survival of patients with breast carcinoma (6). We have analysed a 4-year survival of patients with intraductal carcinoma according to the histological grade of tumor. These data are shown in Table 11.

The patients that had malignant cells of low differentiation (G3) lived shorter than those who had tumor G 1; the 4-year survival of patients was longer in stages II and III of the disease.

DISCUSSION

Our analysis of surgically treated 1269 patients with breast carcinoma shows that tumor size, lymph node involvement, histological grade of tumor were statistically significant for the survival of patients. According to some authors, the histological tumor grade and hormone receptor status had a marginal influence on the survival of patients (5). Our data on the effect of hormone receptor status on the survival of patients are not numerous, and further investigations are required on a larger number of patients. We have no follow-up results of treatment after investigation of HER-2/neu in patients with breast carcinoma. At the Department of Breast Diseases of Institute of

Table 8. The 5-year survival of patients with stage II breast carcinoma according to the method of treatment

Method of treatment	5-year survival of patients (%)	95% Confidence	Interval
Quadrantectomy + radiotherapy	79.1	69.7	85.9
Chemotherapy + quadrantectomy	90.9	68.3	97.6
Chemotherapy + quadrantectomy + chemotherapy	90.9	79.2	96.2
Chemotherapy + quadrantectomy + radiotherapy + chemotherapy	81.5	44.8	94.9
Quadrantectomy + hormonotherapy	75.0	40.8	91.2
Mastectomy	75.0	56.2	86.6
Mastectomy + radiotherapy	75.5	65.5	82.9
Radiotherapy + mastectomy	63.2	37.9	80.4
Chemotherapy + mastectomy + radiotherapy + chemotherapy	77.2	64.0	86.1
Chemotherapy + mastectomy + chemotherapy	69.8	59.1	78.2
Mastectomy + hormonal therapy	74.8	63.6	82.9

Table 9. 5-year survival of patients with stage II breast carcinoma according to hormone receptor status

Estrogen receptor status	Survival of patients (%)	95% confidence	interval
negative	76.4	72.6	79.8
weak	72.4	52.3	85.1
moderate	96.0	74.8	99.4
active	89.6	64.1	97.3
Progesterone receptor status			
negative	76.4	72.6	79.8
weak	78.8	60.6	89.3
moderate	100.0		
active	77.8	51.1	91.0

Table 10. 5-year survival of patients with stage II breast carcinoma according to the histological type of tumor

Histological type of tumor	5-year survival of patients (%)	95% confidence	interval
Adenocarcinoma	63.2	37.9	80.4
Ca solidum	88.5	68.4	96.1
Ca intraductale	76.3	71.6	80.3
Ca lobulare	74.2	63.0	82.4
Ca medullare	83.3	27.3	97.5
Ca ductale+lobulare	77.1	55.8	89.1
Ca papillare	87.5	38.7	98.1

Table 11. 4-year survival of patients with breast intraductal carcinoma according to histological grade of tumor

Stage of disease	Histological grade of tumor					
	G 1	95% CI	G 2	95% CI	G 3	95% CI
II	93.8%	63.2–99.1	82.1%	69.4–90.0	65.2%	42.4–80.4
III	66.7%	54.1–94.5	57.9%	33.2–76.3	38.5%	14.1–62.8

Explanation: G 1 – cells of tumor of good differentiation; G 2 – intermediate differentiation; G 3 – low differentiation.

Oncology Vilnius University, investigation of HER-2/ neu has been started in 2004.

Analysis of 5-year survival of patients with breast carcinoma according to the method of treatment confirmed that optimization of therapy improved the follow-up results. Patients in stage II of the disease who after quadrantectomy received chemotherapy showed the highest survival – 90.9% (95% CI 68.3–97.6). Other authors who were treated with neoadjuvant chemotherapy in the same stage II of the disease also received good follow-up results after quadrantectomy (11). The results of this treatment were better than in the cases when the patients were treated after quadrantectomy with radiotherapy: 5-year survival was shown by 79.1% (95% CI 69.7–85.9). Hormonal therapy with tamoxifen improved the follow-up results after mastectomy: 5-year survival was 74.8% (95% CI 63.6–82.9); 69.8% (95% CI 63.6–82.9) of patients treated after mastectomy with chemotherapy survived this period. We agree with other authors that other factors, such as oncogenes, also influence the survival of patients with breast carcinoma, but the classic prognostic factors (tumor size, lymph node status, histological grade) are of a great value in the treatment and survival of patients.

CONCLUSIONS

1. Tumor size, lymph node involvement and the histological grade of tumor are important prognostic factors in the survival of breast carcinoma patients.
2. Hormone receptor status has a marginal influence on survival in breast carcinoma.
3. The optimization of treatment in the early stage of breast carcinoma improves the follow-up results.

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Algirdas Jackevičius, Valerijus Ostapenko, Saulius Bružas, Juozas Kurtinaitis, Raimondas Meškauskas, Algimantas Mudėnas

PROGNOSTINIAI VEIKSNIAI GYDANT KRŪTIES VĖPĄ

Santrauka

Šiame straipsnyje pateikti duomenys apie 1269 ligonius, gydytus 1998–2000 metais nuo krūties vėžio Vilniaus universiteto Onkologijos instituto Krūtų ligų ir onkologijos skyriuje. Dauguma ligonių (929, arba 73,2%) sirgo I–IIA ir IIB ligos stadija, IIIA – 199 (15,7%), IIIB (pT4) – 103 (8,1%), IV ligos stadiją turėjo 38 (3%) ligoniai. Dažniausiai buvo daroma modifikuota mastektomija Madden metodu – 807 (63,4%) ligoniams, kvadrantektomija – 439 (34,6%). 1197 (94,3%) atvejais buvo taikomas kombinuotas gydymas: operacija ir pagalbinis gydymas (spindulių terapija, chemoterapija arba abu gydymo metodai, hormonų terapija). Geriausi gydymo rezultatai buvo ligonių, sirgusių II stadijos krūties vėžiu, kurioms buvo taikoma kvadrantektomija ir chemoterapija – 5 metus išgyveno 90,9% (95% CI 59,1–78,2) gydytų ligonių. Geri rezultatai buvo gauti gydant ligones hormonų terapija (paskyrus tamoksifeną) po mastektomij: 5 metus išgyveno 74,8% (95% CI 63,6–82,9) pacienė. Gydytų ligonių statistinė analizė patvirtino faktą, kad klasikiniai prognostiniai veiksniai, tokie kaip naviko dydis, jo gradacija ir limfmazgių būklė, yra svarbūs gydant krūties vėžį, taip pat ligonių gyvenimo trukmei. Gydymo optimizacija pagerino gydymo rezultatus sergant antrąja ligos stadija.

Raktažodžiai: krūties vėžys, gydymas, gyvenimo trukmė, prognostiniai veiksniai