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Clinical and Pathohistological Factors Affecting the 5 Year Survival Rate in a Population of Croatian Women with Invasive Ductal Breast Carcinoma

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ABSTRACT

Breast carcinoma falls into a heterogeneous group of diseases which can be determined by various prognostic factors. The identification of clinical and histopathologic factors is of great value in predicting the progression of tumor growth and survival outcome. Due to a high degree of cell proliferation in breast tumors and high genetic instability of these tumors, as a consequence of defective DNA repair mechanisms, chemotherapy as a treatment option often renders very successful results. During our scientific study of the expression of genes responsible for mismatch repair of DNA in cells of invasive ductal carcinoma we also compared the patient survival rate with the major prognostic factors. This study included 108 patients who were surgically treated for invasive breast cancer at the Department of Plastic, Reconstructive and Aesthetic Surgery, University Hospital »Dubrava«. The overall survival rate was compared to factors such as initial tumor stage, regional lymph node involvement and distant metastasis. The overall five year survival rate of our patients was 78,7%. Patients without the presence of distant metastasis, a lower rate of local lymph node involvement and a lower tumor stage statistically had a longer overall survival period. It is important that physicians recognize the various clinico-pathohistological factors in patients with breast carcinoma. This study confirms that these prognostic factors determine the type of treatment required and most important, the patient overall survival period.

Key words: Breast carcinoma, overall survival rate, metastasis, tumor grade, lymph nodes, recurrence

Introduction

Breast carcinoma is a leading cause of cancer related deaths among women worldwide. Every ninth woman at some point in her lifetime will develop breast carcinoma.

Its multifactorial etiology means that there are a wide range of exogenous and endogenous factors which increase the risk of developing breast carcinoma. Despite numerous options available to the physician for the diagnosis and treatment of breast carcinoma, this disease still remains the leading cause of death in women aged 35 to 59. Women in Croatia are at a high risk of developing breast carcinoma, with an increased number of young females developing aggressive subtypes when compared to other western countries¹⁻⁶.

Breast carcinoma has been attributed to abnormal genetic and epigenetic changes specifically occurring in the

BRCA1 and BCRA2 genes^{2,7}. There are more than 40 genes that have been shown to be inactivated in breast carcinoma cells. These include the genes responsible for cycle regulation, cell signalization, cell adhesion and DNA repair⁸. DNA polymerase is responsible for base pair integration during replication and should errors occur, including incorrectly matched base pairs, they are usually repaired by the presence of the mismatch repair system (MMR). Lowered MMR protein activity can lead to a mutated phenotype with an increased degree of spontaneous mutations as the result. It has been observed in breast carcinoma that the MSH2 gene, responsible for recognizing any mismatched base pairs, can be mutated into many variants^{9,10}.

The majority of authors agree that the successful treatment of breast carcinoma is dependant on early diagnosis^{5,9,11,12}.

This research was conducted with the aim to compare the clinical and patohistological factors with the overall 5 year survival rate in a population of Croatian women with invasive ductal breast carcinoma.

Materials and Methods

This research analyzed the clinical and patohistological factors affecting the 5 year survival rate in Croatian women with invasive ductal breast carcinoma. 108 female patients who were operated at our Department between 1999 and 2002 were included in this study. The required data was collected through the available documentation which included patient history charts, clinical charts, operative charts, anesthiological charts and personal interviews. Survival and prognostic data was also taken from the Croatian Epidemiological registry of cancer patients and deaths due to malignant diseases. It was determined that the majority of the sample group, 70 patients (77.8%) were in the first two stages of disease classification. 34 patients (37.8%) were in the first stage, 36 (40%) in the second, 16 (17.8%) in the third and only 4 (4.44%) patients in the fourth. Initially, all of our patients were surgically treated which included axillary lymph node resection as well. Afterward, standardized type of adjuvant therapy was indicated and initiated. In all of our patients, information regarding tumor size, TNM stage, age, menopausal status, type of adjuvant therapy used, lymph node status, residual disease, length of disease remission and overall survival rates were collected. Only patients with complete statistical information were included in the study.

The analysis of variance between quantitative variables such as the degree of differentiation with clinical and laboratory standards was compared using the ANOVA method while qualitative variables were analyzed using the χ^2 -test.

The main ethical committee at the Clinical Hospital Dubrava in Zagreb, Croatia approved the methods and research conducted.

The data regarding the overall survival rate of our patients was collected and was compared to prognostic factors such as initial tumor stage, regional lymph node involvement and distant metastasis. With the high risk of Croatian women developing aggressive subtypes of breast carcinoma the aim of our research was to determine any significance between the overall survival rate and those prognostic factors.

Results

In our group of patients the average age at diagnosis was 56.1 years with 14 patients (15.6%) having a positive family history of breast carcinoma when compared to 76 patients (84.4%) who did not. All of the patients were

classified using the international TNM classification system; tumors up to 2 cm were found in 53 (58.9%) patients, tumors between 2–5 cm in 35 (38.9%) patients, and tumors larger than 5 cm in 2 patients (2.2%). It was found that the majority of our patients had carcinomas that were located in the left breast 59 (65.6%) compared with 31 (34.4%) patients who had a tumor located in the right. Lymphovascular involvement was found in only 10 patients (11.1%), compared with 88,9% of patients who lacked lymphovascular invasion at the time of initial diagnosis. While the majority of the patients (54.4%) did not have lymph node involvement at the time of diagnosis, lymph node positive cases were found in 24 patients (26.7%) who had between 1–3 positive nodes (N1 stage), 10 patients (11.1%) who had between 3–10 positive nodes (N2 stage). More than 10 positive nodes (N3 stage) were found in only 7 patients (7.8%). It was observed that the presence of distant metastases was found in 4 patients (4.4%).

All of the disease positive patients with breast carcinoma were treated with surgery, adjuvant cytostatic, hormonal and/or radiotherapy according to the stage of the disease and steroid receptor status. Out of the entire sample group, only 8 (8.9%) of our patients relapsed with disease.

In our experimental group it was determined that the overall 5 year survival rate was 78,7%. The follow up period was recorded in months, starting at the time of initial diagnosis until the death of the patient or final clinical check up. Figure 1 presents the overall survival rates in our sample group.

The analysis of the number of patients and diseases free survival period is represented in Figure 2. The 5 year disease free period in our patients was 75.4% and was recorded in months; beginning at the time of initial diagnosis.

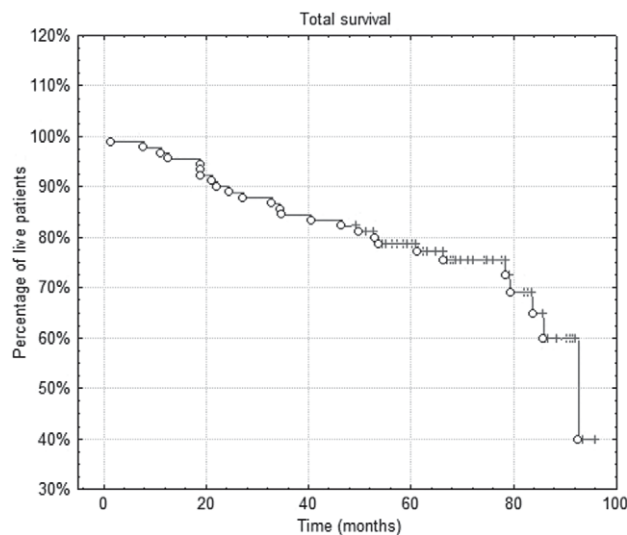


Fig. 1. Overall survival rate (in months) in Croatian women with ductal breast carcinoma.

Statistically it was proven that the overall survival rate of our patients was related to the involvement of regional lymphnode ($p=0.018$), presence of distant metastasis ($p=0.036$) and tumor stage ($p=0.001$). (Table 1)

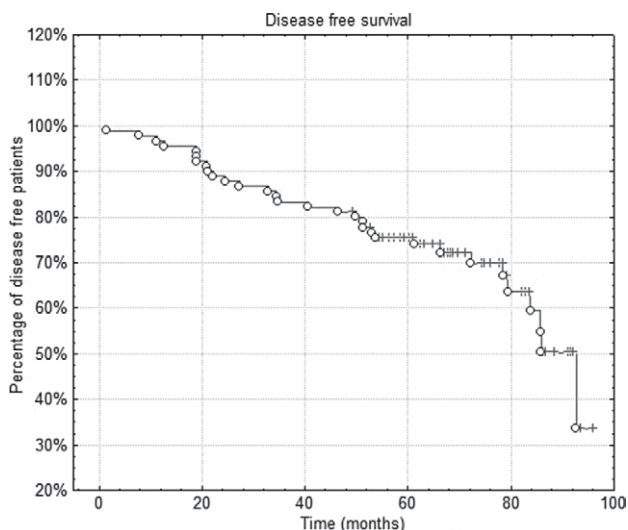


Fig. 2. Disease free survival period in months.

TABLE 1
ANALYSIS OF CLINICAL AND PATHOHISTOLOGICAL FACTORS AND THE OVERALL SURVIVAL RATE OF CROATIAN WOMEN WITH INVASIVE DUCTAL BREAST CARCINOMA

Observed Factor	Beta*	χ^2	p
Tumor Stage (I, II, III, IV)	0,726	10,985	0,001
Nodal involvement (0,1,2,3)	0,429	5,078	0,018
Distant Metastasis (0,1)	1,393	3,274	0,036

* Regression coefficient. Negative results signify an inversely proportional relationship

When comparing tumor stage and overall survival rates of our patients it was statistically proven that a large variation in survival rates exists between the various tumor stages ($p=0.001$). Overall survival rates was 90% in the first stage, while only 25% in the fourth stage. It is important to emphasize that the majority of patients with stage 4 disease die within 20 months of initial diagnosis (Figure 3). It was observed a statistically significant correlation to overall survival rates and the presence of local lymph node involvement ($p=0.018$). (Figure 4)

There was a statistically significant correlation to overall survival rates and the presence of distant metastasis at the initial time of diagnosis ($p=0.036$). It was concluded that patients with the presence of distant metastasis have a significantly lower survival rate when compared to patients without any distant metastasis (Figure 5).

In the sample group, the overall 5 year survival rate was 78.7%, with 75% of these patients without any relapse of disease. It has been found that the overall sur-

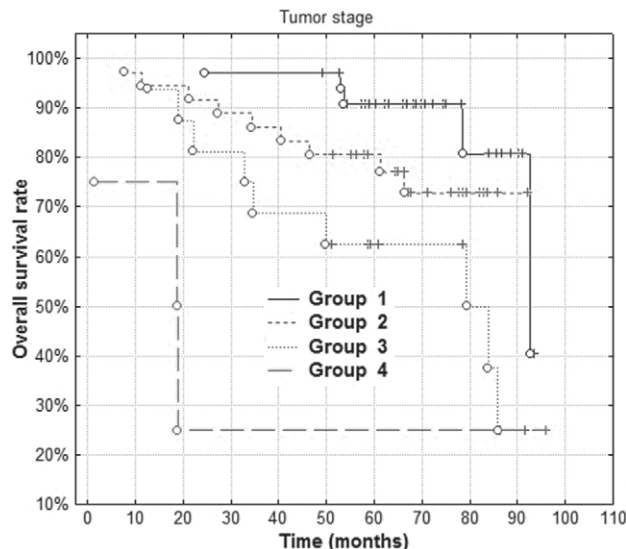


Fig. 3. Tumor stage and the overall survival rate of Croatian women with invasive ductal breast carcinoma. (Group 1,2,3,4) relates to the subsequent stage of disease at the time of initial diagnosis.

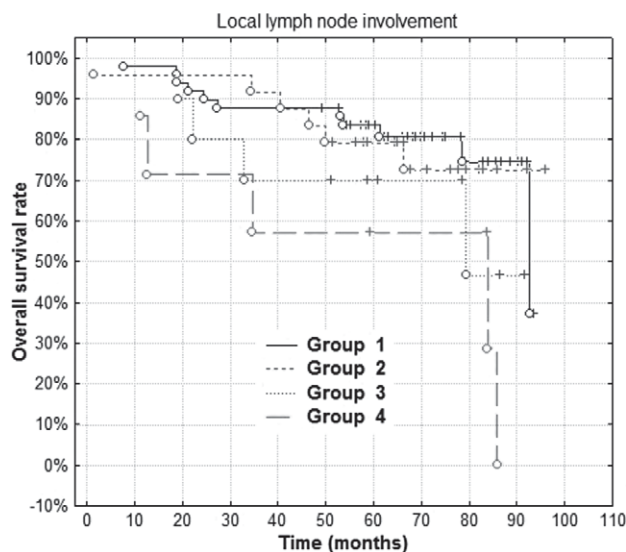


Fig. 4. Stage of local lymph node involvement and the overall patient survival rate. (Group 1,2,3,4) relates to the degree of regional lymph node involvement.

vival rate is statistically related to the involvement of axillary lymph nodes ($p=0.018$), the presence of distant metastasis ($p=0.036$) and the stage of disease ($p=0.001$).

Discussion

Breast carcinoma is one of the most frequent carcinomas found in women world wide. This is also the case for the Croatian population. There have been several clinical and pathohistological factors that have been recognized and are used as prognostic determinants in breast cancer

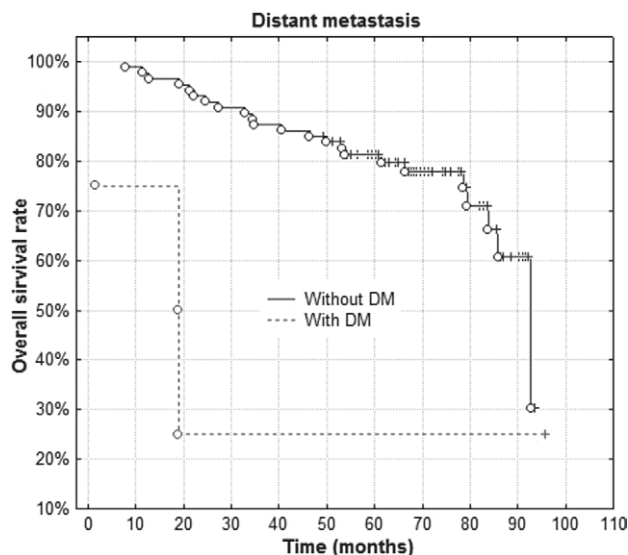


Fig. 5. The presence of distant metastasis and the overall survival period (in months).

patients including tumor size, histologic type, tumor grade, lymphovascular invasion, and hormone receptor status^{13–16}. The relationship between microscopic grade and the degree of tumor malignancy was observed by von Hansemann towards the end of the 19th century¹⁷. Presently, the Nottingham method^{18,19} is most often used in order to define the histological grade of a tumor. Literature states that patients with well differentiated tumors have a 10 year survival rate of up to 85% after diagnosis in contrast to patients who have poorly differentiated tumors and a 10 year survival rate of about 45%. Bloom²⁰, Elston and Le Dousal²¹ found that there was a direct correlation between the tumor grade and the overall survival rate. It has been shown that the tumor stage at the initial point of diagnosis is a strong predictor of breast cancer survival rate^{22,23}. It was observed by Laurens Holmes JR et al. that there is a monotonic increase in breast cancer mortality with advancing tumor stage at the time of initial diagnosis²⁴. If primary breast cancer is diagnosed when tumors are small (<1 cm) and without any presence of metastasis to regional lymph nodes, the overall 5-year survival rate has been shown to be to exceed 90%. This emphasizes the importance of early disease detection. Unfortunately, larger (>5 cm) breast cancers with regional nodal metastasis have a 5-year survival which has been found to be as low as 40%. 24740 patients were analyzed by Carter et al who found that their patients who had a tumor size smaller than 1 cm had a 99% 5 year survival period while patients with a tumor between 1 and 3 cm, had only a 89% 5 year survival rate²⁵.

Biological hormonal receptor status has been observed to be an important factor in the determination of therapy success. Kyoung-Mu Lee et al.²⁶ in 544 patients determined that patients who were without tumor based hormone receptors, overall had a worse prognosis and that the presence of hormone receptors is an important factor when determining the type of therapy required.

Similar findings by Colditz²⁷ were found. A study conducted by Soudes Karray-Chouayekh²⁸ showed that estrogen receptor negative carcinomas had a higher malignant degree. Our results also correlate with Layfield²⁹, Braum³⁰ and Scawn³¹ who displayed a relationship with positive hormone receptors and a lower tumor grade with a longer survival rate.

Fisher B and Carter CL concluded that the presence of axillary lymph node metastasis is the most important prognostic factor for predicting breast cancer patient survival³². Lymph node involvement has also been found to be an important prognostic factor since patients with lymph node metastasis had a lower overall survival rate which concurs with multiple foreign studies. One such study has found that patients after 9 years who didn't have lymph node metastasis had a 74% chance of survival as compared with 47% who had metastasis. Therefore, it is important for the physician to recognize these findings as one of the most important prognostic factors for their patients^{25,33,34}. Our research concluded that patients who were axillary lymph node negative, had a survival rate of 81.1% as opposed to 65% in node positive patients.

Perhaps one of the most important factors influencing the overall survival rate of patients with breast cancer is the presence of distant metastasis as this factor represents the main cause of death in women with breast cancer^{35,36}. Lamerato L et al. in their retrospective cohort study showed that the median time to all-cause mortality is significantly longer in women with loco-regional recurrence than in those who presented with distant metastasis (6.4 versus 3.4 years, respectively)³⁷. Similar research conducted by Lê MG et al. found that the 10-year survival rate in women with local recurrence was 56% when compared with 9% in those with distant disease³⁸.

In the Early Breast Cancer Trialists' Collaborative Group meta-analysis of local therapy (39), it was found that for every four local recurrences that were prevented at 5 years, there was about one less death from breast cancer at 15 years. This finding suggests that in about 25% of local recurrences, the cancer cells in the recurrent tumor have acquired the ability or have the opportunity to spread distantly. This subsequently leads to an increased risk of death from metastatic disease. An increase in distant metastases after the diagnosis of local recurrence has been documented in both the breast-conservation and post-mastectomy patients^{39–42}.

The majority of authors agree that the successful treatment of breast carcinoma is dependent on early diagnosis^{5,8,11,12}. Tumors smaller than 1 cm in the majority of cases are considered curable. Many authors exist who believe that breast carcinoma is a systemic disease⁴³ and support of this theory can be seen with the variable biological behavior found in breast cancer cells. This holds especially true for the invasive ductal carcinoma which is also the most frequently seen. Due to this variability there is a great degree of difficulty when attempting to treat this disease. As a result and due to the uncertainty and behavior of this common disease, invasive ductal carcinoma is therefore the focus of numerous studies^{44,45}.

With the development of new medications such as cytostatics, the treatment of breast cancer is becoming more successful; although there are still numerous associated side effects^{46–49}. It is imperative that the physician recognizes the wide range of treatment options and which patients will have the greatest benefit from pharmacologic therapy. It is also important that the physician maximizes the effort to reduce the possible side effects as much as possible^{50,51}. A certain degree of disease progression can be foreseen by observing the previously known signs and symptoms at the time of initial diagnosis; this includes tumor size, axillary lymph node involvement and the hormonal receptor status^{52,53}. These factors directly influence the therapy options and the right choice of breast reconstruction method^{54–57}.

The majority of medical literature states the importance of histological tumor grading since this is an important prognostic factor. It also influences and determines for the need for adjuvant therapy in patients without lymph node involvement who initially present with a smaller tumor²⁵.

Lymph node involvement has been shown to be an important prognostic factor since patients with lymph node metastasis tend to have a lower survival rate. Our research showed that a relationship exists between lymph node involvement and overall survival rate ($p=0.018$).

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This discussion signifies the importance for physicians to recognize the various clinico-pathohistological signs and symptoms in patients with breast carcinoma. These factors influence the type of treatment required and most importantly, the overall prognosis of the patient.

Conclusion

In patients who did not have distant metastasis, had a lower rate of local lymph node involvement and had a lower initial tumor stage statistically had a longer overall survival period.

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KLINIČKI I PATOHISTOLOŠKI ČIMBENICI KOJI UTJEČU NA PETOGODIŠNJU STOPU PREŽIVLJAVANJA U POPULACIJI ŽENA S INVAZIVNIM DUKTALNIM KARCINOMOM DOJKE U HRVATSKOJ

SAŽETAK

Karcinom dojke spada u heterogenu grupu bolesti na koju utječu mnogi prognostički čimbenici. Identifikacija kliničkih i patohistoloških čimbenika je od velike važnosti u predviđanju progresije tumorskog rasta i stope preživljena pacijentica. Zbog visokog stupnja proliferacije stanica tumora dojke i genetske nestabilnosti tih tumora, kao posljedice nepravilnog mehanizma za popravak oštećenja DNA, kemoterapija kao terapijska opcija daje vrlo dobre rezultate. U sklopu istraživanja ekspresije gena odgovornih za popravak krivo sparenih baza u molekuli DNA u stanicama invazivnog duktalnog karcinoma, provedena je i usporedba stope preživljenja i glavnih prognostičkih čimbenika. U ovo istraživanje uključeno je 108 pacijentica koje su kirurški liječene zbog invazivnog karcinoma dojke na Klinici za plastičnu, rekonstruktivnu i estetsku kirurgiju, KB »Dubrava«. Ukupna stopa preživljenja promatrana je u odnosu na početni stadij tumora, prisutnost regionalnih metastaza u limfnim čvorovima i udaljenih metastaza. Ukupna petogodišnja stopa preživljenja naših pacijenata bila je 78,7%. Pacijentice bez prisutnosti udaljenih metastaza, manjim stupnjem zahvaćenosti limfnih čvorova i nižim stadijem tumora statistički su imale bolju stopu preživljenja. Ova studija potvrđuje da navedeni prognostički čimbenici određuju način liječenja i najvažnije, utječu na preživljenje pacijentica.