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Prognostic factors in breast cancer

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Prognostic factors in breast cancer comprise those characteristics of primary tumors on the basis of which we can predict the course of disease, and thus the prognosis of breast cancer patients. The established prognostic factors are tumor size, histological type and grade of malignancy, axillary lymph node involvement, and the presence of hormone receptors in the tumor. At present the primary treatment is planned with respect to these prognostic factors. Even though adjuvant therapy is accepted as standard care in primary breast cancer neither the particular therapeutic modalities involved nor the specific subset to which it should be directed are well defined. Therefore, we look for new prognostic factors the role of which in the prediction of recurrence and survival of breast cancer patients still needs to be confirmed. These include ploidy, tumor proliferation markers, growth factors and receptors, growth suppressor and antimetastatic genes, invasion markers, tumor angiogenesis and some others.

Key words: breast neoplasms; prognosis; established prognostic factors, putative prognostic factors

Introduction

Breast cancer is the most frequent cancer of females. In the last two decades, its incidence has been increasing throughout the world.[1, 2] According to the data of the Cancer Registry of Slovenia for 1991, it represented 19 % of all female cancers in Slovenia.[3] Breast cancer is also the leading cause of cancer-related death of females in the developed countries.[4] In the last decade, mortality due to breast cancer has decreased only by few percents so that almost a half of all patients still die from this disease. In the phase of distant dissemination, the disease becomes incurable.[5] Metastatic disease cannot be treated even by a high-dose chemotherapy combined with simultaneous bone-marrow transplantation or peripheral blood stem cell support, according to the schedule which was considered very promising a few years ago.[6] Therefore, research has been focused again on the search of a more effective primary treatment of breast cancer. Adjuvant systemic therapy has been found to improve the survival of patients with operable breast cancer.[5] Adjuvant therapy with cytotoxic drugs proved effective in patients with axillary lymph node involvement, while adjuvant hormonal therapy prolonged the survival of patients with hormone dependent tumors.[7]

The question remains, how to recognize the biologically more aggressive cancer at the time of diagnoses, and which are those properties of

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the primary tumor that help us to predict an unfavourable course of the disease, and select a more suitable treatment accordingly. We already know some of the primary tumor properties, the so-called established prognostic factors for breast cancer, according to which the primary treatment is planned in every patient.[8] The established prognostic factors, are as follows: tumor size, pathohistological type and grade of malignancy, axillary lymph node involvement, and the presence of hormone receptors in the tumor (Table 1).[9, 10] Axillary lymph node involvement is considered to be the prognostic factor with the highest predictive value. Already in the 60's, adjuvant chemotherapy was introduced into the primary treatment of patients with lymph node involvement. It has considerably improved the survival of these patients.[7] Nevertheless, in almost a half of the patients with axillary lymph node involvement metastatic disease will develop within few years following completed primary therapy. Furthermore, dissemination of the disease will also occur in a third of the patients without axillary lymph node involvement at the time of surgery.[7, 11]

Table 1. Established prognostic factors.

1. Tumor size
2. Axillary nodal status
3. Histopathology
4. Steroid hormone receptors

Table 2. Putative prognostic factors.

1. DNA-ploidy
2. Tumor proliferation markers
S-phase
Ki67
cyclin D_1
3. Growth factors and receptors
EGF (EGFR)
erb-B2 (p185)
4. Growth suppressor or antimetastatic genes
p53
nm23
5. Invasion markers
cathepsin D
μPA/PAI 1
stromelysin 3
6. Tumor angiogenesis

The need to better identify breast cancer patients who are at risk to develop a reccurrence and are likely to benefit from adjuvant therapy, and to spare others from treatment related side effects is spurring researchers to look for new prognostic indicators. Since their predictive value has not been exactly determined yet, these factors are called putative prognostic factors (Table 2).[12]

Established prognostic factors

Tumor size

Primary tumor size is an independent prognostic factor of operable breast cancer. The survival of patients with small tumors is better than the survival of those with large tumors.[13] Tumor size is also an important prognostic factor in patients with negative axillary lymph nodes, whose prognosis is generally better. Thus, the disease recurs in every tenth patient with a tumor smaller than 1 cm, and in every third with a tumor measuring approximately 2 cm.[14] Therefore, only the patients with negative axillary lymph nodes and small tumors have good prognosis while the same is less favourable in those with larger tumors, even when their lymph nodes are negative.

Axillary lymph node involvement

Axillary lymph node involvement is presently the most important prognostic factor for breast cancer. Within the first ten years after surgery the disease recurs in as many as 3/4 of patients with positive axillary lymph nodes, and in only 1/4 of those with negative axillary lymph nodes.[11, 13] The extent of lymph node involvement is important as well. The greater the number of affected lymph nodes, the worse is the survival of patients. While the 10-year survival of patients with 1–3 positive axillary lymph nodes is 60 %, the 10-year survival of those with more than 10 positive axillary lymph nodes is only about 20 %.[15]

Histological type and grade of malignancy

Invasive cancer is the most frequent type of

breast cancer. There are a few different histological types of invasive breast cancer. Prognostically most favourable among them are pure mucinous, tubullar, and papillary invasive breast cancer. Five-year survival of patients with these cancer types is over 80%. Lobular and medullary invasive breast cancers are considered somewhat less favourable, while ductal invasive breast cancer is prognostically the least favourable of all invasive breast cancers.[16] The latter type represents approximately 70% of all invasive cancers and is thus the most frequent breast cancer.

According to the grade of malignancy (G), ductal cancer is classified into three subgroups; the higher the grade of malignancy, the worse is the survival of patients. While 10-year survival rate of patients with tumors of low-grade malignancy (G1) is 56%, the relevant rate of those with high-grade malignancy (G3) is only 33%.[17] Also in patients with negative axillary lymph nodes the grade of malignancy is found to be an independent prognostic factor.[18] The predictive value of this factor is adversely affected by the subjectivity of assessment, and by differences in the methodology of sample processing. Nowadays, malignancy grade is most frequently assessed according to Scarf-Bloom-Richardson (SBR) system which is based on nuclear pleomorphism, mitotic activity and tubular formation in the tumor.[19]

Steroid hormone receptors

The presence of estrogen (ER) or progesterone (PR) receptors in the tumor tissue greatly influences the prognosis of breast cancer patients. Hormonal receptors can be found in approximately half of the primary tumors. They are present at a slightly higher percentage in postmenopausal women. The patients with hormone positive tumors have better prognosis.[13] Patients with axillary lymph node involvement are known to have worse prognosis than those with negative lymph nodes. However, there is no difference between the survival of the patients with axillary lymph node involvement and positive hormone receptors and the patients without axillary lymph node involvement and negative hormone receptors.[8] The presence of hormone receptors is not only a prognostic factor of survival, but it is also an predictor of the effectiveness of hormonal therapy. Patients with positive hormone receptors, both premenopausal and postmenopausal, respond to hormonal therapy at a much higher percentage than patients with negative hormone receptors.[8]

Putative prognostic factors

DNA-ploidy and the percentage of cells in S-phase

Flow-cytometry is a new method for quantitative determination of biological, chemical and physical cell properties.[20] The method makes possible the determination of tumor DNA-ploidy and the percentage of cells in S-phase. DNA-ploidy expresses the DNA content in tumor cells. Normal non-dividing cells contain an euploid quantity of DNA. Changes in tumor cell genome, however, can result in a changed, aneuploid DNA content. The rate of cells in S-phase is an indicator of the tumor's proliferative activity. Different authors have reported from 53 to 73% of aneuploid tumors among the breast cancers studied.[21] DNA-ploidy was found to be a relevant prognostic factor of survival by the majority of univariate analyses, whereas its predictive value as independent prognostic factor failed to be confirmed by most of the multivariate analyses.[22, 23, 24, 25, 26] Likewise, our study of 230 operable breast cancer patients did not confirm DNA ploidy to be an independent prognostic factor.[27] On the other hand, the percentage of cells in S-phase was undoubtedly found to be an independent prognostic factor.[26, 28, 29] The greater the rate of cells in S-phase, the worse is the patient's prognosis, regardless other prognostic factors. The prognostic value of DNA-ploidy and of the rate of cells in S-phase is increased when both these factors are considered together.[26, 29] Thus, patients with diploid as well as those with aneuploid tumors have worse prognosis in the case of higher percentage of cells in S-phase. Particularly in diploid tumors, the rate of cells

in S-phase significantly influences the patient's prognosis. Five-year disease-free survival of patients with diploid tumors and a low rate of cells in S-phase is 90 % whereas in the case that the same tumors are associated with a high percentage of cells in S-phase, the survival is 70 %.[26]

The percentage of cells in S-phase is also a predictive factor of the effectiveness of chemotherapy. In patients with a high percentage of tumor cells in S-phase chemotherapy is more effective than in those with a low percentage of tumor cells in S-phase.[30]

Cyclin D1

Cyclins are cell proteins which play an important role in controlling the speed of cell division. The most known among these is cyclin D1 which controls the transition of cells into the S-phase of the cell-cycle. Increased expression of cyclin D1 was established in a half of all breast cancer patients. Its prognostic value is still subject to extensive research.[12]

Growth factors and growth-factor receptors

Growth factors accelerate the growth of tumor cells. Several growth factors and their receptors have been detected in breast cancer tissue. One of the most important and widely studied ones is the epidermal growth factor receptor (EGFR). The presence of EGFR in breast tissue is associated with worse prognosis.[31] EGFR is a trans-membrane glycoprotein coded by erb-B1 gene. It is present in breast tissue in approximately 40 % of cases.[32] Different growth factors released either by tumor cells or other cells in the organism, which accelerate tumor growth, are bound to this receptor.

The group of epidermal growth factors also includes p-185 protein coded by erb-B2 gene, also known as neu or her-2. Increased expression of this gene was established in 20–25 % of breast cancer patients, particularly in those with tumors of high-grade malignancy and negative hormonal receptors.[12] It has not been confirmed yet whether an increased expression of this gene is an independent prognostic factor for breast cancer.[12]

Increased expression of both erb-B1 and erb-B2 in the primary tumor tissue is associated with a higher susceptibility to chemotherapy, and can thus be considered a prognostic factor of treatment response.

Suppressor genes

Suppressor genes prevent uncontrollable cell division. The most thoroughly studied one is p53-gene which controls cell division. Mutations of this gene, which cause uncontrollable cell division, are found in approximately a half of all breast cancer patients. Patients with tumors exhibiting p53-gene mutations have worse prognosis.[12, 33] Worse prognosis is also associated with lower expression of the antimetastatic gene nm23 in breast cancer tissue.[12]

Invasion markers

Tumor-cell invasion depends on the content of proteolytic enzymes in the tumor. These enzymes dissolve the basal membrane and extracellular matrix, thus accelerating local growth and metastasizing of the tumor. The proteolytic enzymes undoubtedly associated with greater invasiveness of breast cancer are as follows: cathepsins, metaloproteinases and serum proteinases. The most thoroughly studied among cathepsins is cathepsin D. Normal breast tissue contains little cathepsin D while its content in cancer tissue is increased.[34] Higher quantities of cathepsin D can be found in the tumor tissue of patients with positive axillary lymph nodes, although particularly in these patients the level of the enzyme is not found to be an independent prognostic factor. In contrast to that, the cathepsin D content in the tumor tissue of patients with negative axillary lymph nodes is lower but prognostically relevant for course of the disease.[18] The influence of other cathepsins such as cathepsins B, H and L, on the prognosis of breast cancer patients is under study.[35]

Recently, the presence of urokinase plasminogen activator (μPA) and plasminogen activator inhibitor type 1 (PAI 1) in breast tissue was found to be highly relevant. Urokinase plasminogen activator is involved in the transformation of plasminogen into the proteolytic enzyme

plasmin. An elevated level of μPA in breast cancer tissue is associated with a higher metastatic potential of particular cancer, and thus believed to greatly influence the prognosis of breast cancer patients. While the 10-year survival of patients with low μPA levels exceeds 60%, the survival of those with high levels of μPA is hardly over 20%. Elevated μPA levels in breast cancer tissue are generally accompanied by high PAI 1 values. PAI 1 is an inhibitor of plasminogen activator, and its increased content in the tissue is supposed to protect tumor cells against self-destruction. The presence of μPA and PAI 1 in breast cancer tissue is presently the most promising new prognostic factor for breast cancer.[12]

Metaloproteinase stromelysin 3 is also proteolytic enzyme. While stromelysin 3 is rarely present in benign tumors of the breast, it can be often found in breast cancer. In non-invasive breast cancers the presence of stromelysin 3 indicates the possibility of later invasive cancer development.[31] The prognostic value of stromelysin 3 in invasive breast cancer however has not been established yet. The proven correlation with other known prognostic factors, as well as the results of studies performed so far point out that it may play an important role.[37, 38]

Tumor angiogenesis

Weidener and co-workers[39] were the first to call attention to the prognostic value of tumor vascularization. He has proved that vascularization of the primary tumor is an independent prognostic factor for breast cancer. Breast cancer metastases were also found to grow faster when provided with rich blood supply. By inhibiting the proteins that stimulate endothelial cell growth, such as integrins, it is possible to slow-down angiogenesis in the tumor and thus inhibit its growth.

Conclusion

A number of primary tumor characteristics which indisputably influence the prognosis of breast cancer patients are known at present. These well established prognostic factors serve as a basis for primary treatment planning. Nevertheless new biological characteristics of primary tumors are being detected and studied in order to better predict the course of the disease. These studies are both difficult and time consuming since assessment of the reliability of prognostic factors requires long-term follow up of a large group of patients with comparable tumors and identical primary treatment. There is also a problem of the subjectivity of evaluation methods and their standardisation, as well as the cut-off values of new prognostic factors that should be taken into account. Daily determination of all prognostic factors is technically demanding and expensive. Therefore, identifying the most relevant ones among these factors is of utmost importance. Equally important is also the simplification and unification of the methods used. At this time only the established prognostic factors are routinely determined. Nevertheless, it seems that the determination of DNA ploidy, percentage of cells in S-phase, as well as of some proteolytic enzymes and oncogenes in breast cancer tissue, may soon become part of daily practice. It seems that at least some of these tumor characteristics may also predict the response to systemic treatment in individual patient.

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