

THERAPY

Treatment strategy of early-stage breast cancer

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The treatment options for early stage breast cancer include local-regional and systemic therapy. Surgery and radiotherapy can minimize the risk of local recurrence, while systemic adjuvant chemotherapy and hormonal treatment is related to prolongation of survival rate. Several prognostic factors were identified. The dominant prognostic factor is lymph node involvement with cancer. The decision regarding treatment must be made according to risk versus benefit for every patient. The absolute benefit of systemic treatment is major in patients with intermediate and poor prognosis (Tab. 3, Fig. 2, Ref. 10). Key words: breast cancer, adjuvant treatment.

Breast cancer is the most common form of malignancy occurring in women. Every year more than one million women worldwide are diagnosed with early-stage breast cancer. There are an estimated 40,410 breast cancer deaths in United States in 2005. In Slovakia, 1827 new cases were diagnosed in 2001.

Breast cancer-systemic disease

According to Halstedt theory of spreading breast cancer it was thought that primary tumor first spreads locally to the skin and axillary lymph nodes, than to the supraclavicular lymph nodes and afterwards to distant organs. Local-regional lymph nodes should serve as a “filter” before systemic dissemination of cancer cells.

Today we know that carcinoma of the breast is able to metastasize to distant organs from the early beginning after penetration of the basal membrane of ducts and lobules without impairment of the regional lymph nodes. Breast cancer cells can cause any type of metastasis regardless of the size of primary tumor or lymph node involvement (Fig. 1). According to this we consider breast cancer as a systemic disease from beginning.

Local-regional treatment of breast cancer

The local-regional treatment options for patient with early stage breast cancer are surgical treatment and radiotherapy. The impact of local treatment on overall survival rate is low because of systemic character of the disease.

Within the last 20 years there has been a decrease in the radicalism of surgery from the Halstedt radical mastectomy to the modified radical mastectomy and finally to breast conserving surgery. The main difference between the Halstedt radical mastectomy and the modified operation is that modified radical mastectomy involves complete removal of the breast, the underlying pectoral fascia and some of the axillary lymph nodes, but pectoral muscle and adjunctive structures are saved. The breast conserving surgery is resection of the primary tumor with sparing of the surrounding grossly normal breast tissue. Ipsilateral axillary lymph node dissection is an obligatory part for every type of surgical treatment.

The switch to less radical surgery from radical mastectomy occurred when data demonstrated that treatment failure after breast cancer surgery is usually caused by systemic dissemination of cancer cells before surgery, rather than an inadequate operative procedure.

Breast conserving surgery is contraindicated for women with multifocal tumors located in different quadrants of the breast, diffuse malignant-appearing microcalcifications, or history of prior therapeutic irradiation to the breast that precludes full breast irradiation. Additionally, a high ratio between tumor size and breast size or large, pendulous breast are other relative contra-

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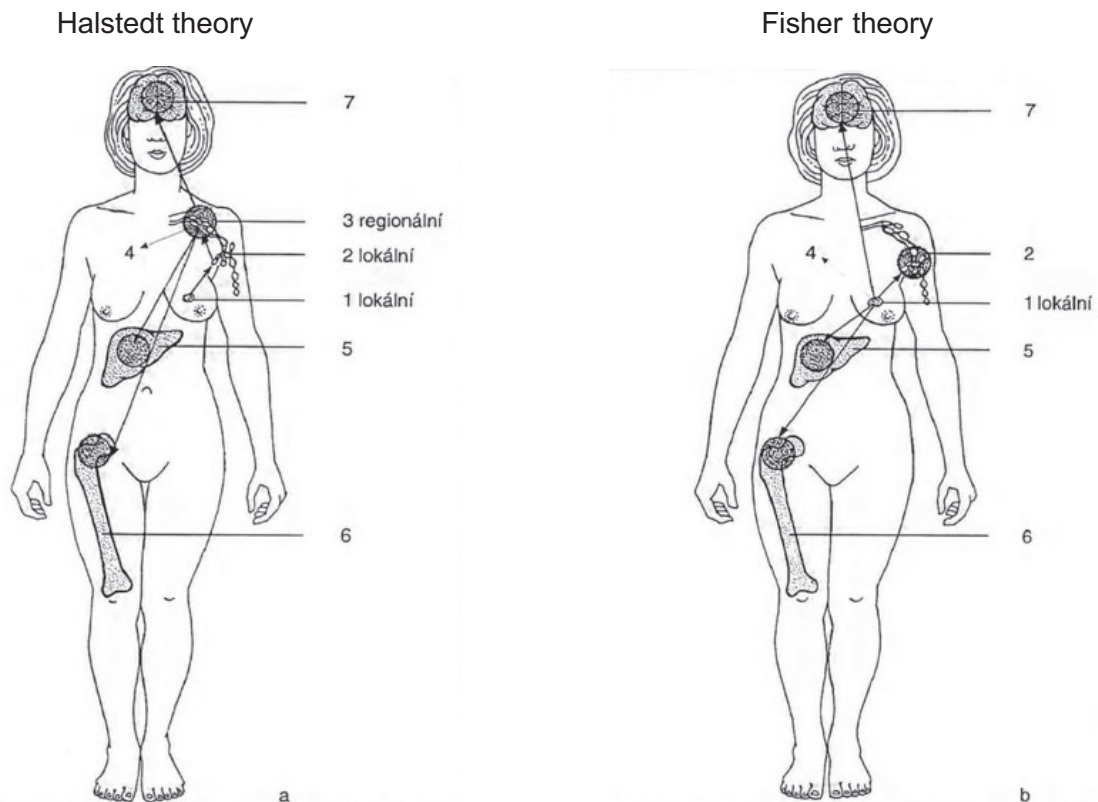


Fig. 1. Breast cancer. 1 – primary tumor, 2 – axillary lymph nodes, 3 – supraclavicular lymph nodes, 4 – lung, 5 – liver, 6 – bones, 7 – brain (J. Abrahamova et al. Atlas nádorů prsu. Praha, Grada Publishing 2000).

indications of breast conserving surgery because of cosmetic outcome. Axillary dissection is principally a prognostic procedure.

Radiotherapy is considered as a compulsory part of local-regional treatment if the patient did not undergo modified radical mastectomy. Results of many studies confirm similar rates of regional recurrence in patients treated with breast conserving surgery and radiotherapy versus mastectomy alone.

Postmastectomy irradiation reduces the local-regional recurrence about two-thirds, but has no improvement on survival. Although it reduces the risk of cancer death, it leads to elevated cardiovascular mortality. After 20 years there is no survival benefit from postmastectomy irradiation. Radiation after mastectomy is obligatory for patients with stage III disease. For this group of patients the benefit exceeds the risk. Administration of systemic chemotherapy does not substantially lower the recurrence rate of local-regional relapse after mastectomy when radiation is not given.

Recurrence

The probability of breast cancer relapse can be predicted by prognostic factors.

A *prognostic factor* is defined as a biological or clinical measurement that is associated with disease-free or overall survival in the absence of adjuvant systemic therapy.

A *predictive factor* is any measurement associated with response or lack of response to a particular therapy.

The most important prognostic factor for recurrence is the involvement of axillary lymph nodes with cancer based on at least a level I or II axillary dissection at the time of primary diagnosis. This is because axillary lymph node involvement reflects the ability of cancer to create metastasis. Lymph node status at the time of surgery directly reflects the probability of ten year survival (Tab. 1). Untreated patients with at least one positive lymph node have the probability of 10-year survival of 70 %, and only approximately 20 % of patients with 10 and more positive lymph nodes would survive at the end of 10 years without therapy. Because the prognosis of the patient is related to the number of positive axil-

Tab. 1. EBCTCG (according to Lancet, 1988).

10 year survival after chemotherapy	Positive prognostic factors
LN - + positive prognostic factors >90%	LN - histopathologic type pT <1-2 cm Grade I ER+, PR+ age older than 35 years
LN - 1-3 LN+	70-90%
4-10 LN+	50-70%
>10 LN+	25-50%
	<20%

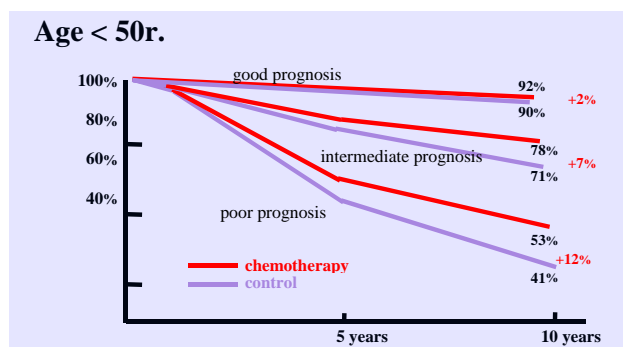


Fig. 2. EBCTCG (according to Lancet, 1998).

lary lymph nodes, the exenterating of 10 and more axillary lymph nodes is considered adequate to estimate the prognosis of patient. Many prognostic factors have been evaluated in patients with lymph node negative status. Only some of them are generally accepted for clinical use (Tab. 1). Patients with negative lymph nodes and favorable histopathology (other than invasive ductal carcinoma), pathological stage pT<1–2 cm, grade 1, estrogen/progesterone receptor positive, age older than 35 years are the group of patients with a good prognosis with a probability of 10-year survival greater than 90 %. According to prognostic criteria it is possible to divide patients with early breast cancer into 3 prognostic groups: good prognosis patients – the patients with negative lymph nodes and with all favorable additional prognostic factors; intermediate prognosis patients – the patients with negative lymph nodes without favorable additional prognostic factors; poor prognosis patients – the patients with positive lymph nodes.

Systemic adjuvant treatment

Adjuvant systemic therapy is defined as the administration of chemotherapy or endocrine therapy after primary surgery for breast cancer in order to control clinically occult micro-metastasis. This treatment is able to eradicate occult metastasis before drug resistance appears.

Breast cancer is one of the most chemosensitive tumors. Additionally, the breast cancer cells, which express estrogen receptors (ER) or progesterone receptors (PR) are sensitive to hormonal therapy.

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) provided a metaanalysis of 100 and more prospective randomized clinical trials regarding the efficacy of adjuvant treat-

Tab. 2. EBCTCG (Lancet, 96; EBCTCG, Lancet, 98).

	Relative risk reduction	
	relapse	death
castration	25%	24%
tamoxifen	45%	22%
chemotherapy	35%	27%

Tab. 3. Relative risk reduction (modified according to EBCTCG, Lancet, 98).

		survival			relative reduction	
		death	relative reduction			
Good prognosis	Observation	90%	10%	10%.....100%	20%	
	Chemotherapy	92%	8%	8%.....80%		
Intermediate prognosis	Observation	71%	29%	29%.....100%	25%	
	Chemotherapy	78%	22%	22%.....75%		
Poor prognosis	Observation	41%	59%	59%.....100%	21%	
	Chemotherapy	53%	47%	47%.....79%		

For example 90% of the patients with LN negative with positive prognostic factors are expected to survive 10 years. After addition of systemic adjuvant chemotherapy, 92 % can survive 10 years. This means that in the first case 10% of the patients will die after 10 years and in the second group only 8 % will die. If we compare these two numbers, there is 20% difference between these two groups. If we apply the same to a group of patients with middle or high risk, we would lower the recurrence rate by about 20%.

ment for breast cancer. Results of this overview had a major influence on the treatment of women with early-stage breast cancer.

The EBCTCG analysis showed significant improvement in the overall survival and reduction of relapses for patients treated with systemic adjuvant treatment and suggested an important principle; that the proportional reduction in the risk of relapse as a result of a treatment is generally constant regardless of the patients absolute risk of relapse (Tab. 3). Absolute benefit is improving as the risk of relapse increases (Fig. 2).

The efficacy of hormonal therapy is comparable to chemotherapy for patients with positive hormonal receptors (ER/PR+) and is of lower toxicity (Tab. 2). Therefore for this group of patients, hormonal therapy is considered the first option of adjuvant systemic therapy. Overall the additional value of endocrine therapy to chemotherapy is less than additive, therefore the use of combination of hormonal therapy and chemotherapy is recommended for patients who have a higher risk of relapse.

A significant survival advantage following systemic therapy is seen in patients with intermediate to poor prognosis. On the other hand, for women with a good prognosis the benefit of adjuvant systemic therapy is very low. In this group of patients it is strongly recommended to consider the effect of adjuvant systemic treatment in comparison to adverse drug reactions. The toxicity of the drug should not outweigh the possible effect of therapy.

The benefit of adjuvant systemic treatment could be achieved by appropriate consideration of the individual risk of recurrence and possible efficacy and toxicity of systemic adjuvant treatment.

Conclusion

Local-regional treatment is able to reduce local relapses of the breast cancer, but only adjuvant systemic treatment (hormonal, chemotherapy) can prolong the overall survival time. For low risk patients the magnitude of the benefit should be considered in light of the risk associated with adjuvant systemic treatment.

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