

Breast cancer – extracapsular extension in the sentinel lymph node

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Invasive breast cancer is the most common malignancy in women. At present, in the majority of cases it is recognized at an early stage. Its most common site of metastasis is the axilla region, and for women without clinically suspected lymph nodes a sentinel lymph node biopsy (SLNB) is the method of choice in diagnostics and treatment process. It allows, in many cases, axillary lymphadenectomy to be avoided and the risk of complications after a surgical treatment to be diminished. Extracapsular extension (ECE) of nodal metastasis, defined as extension of cancer cells through the nodal capsule, is an important prognostic factor. The aim of this paper is to review the literature on ECE in the sentinel lymph node (SLN).

Key words: breast cancer, sentinel lymph node, extracapsular extension

Introduction

For the last decade, axillary lymphadenectomy (ALND) has not been mandatory for patients with 1-2 sentinel nodes with macrometastases who were undergoing lumpectomy and adjuvant radiotherapy as part of their treatment, according to an ACOSOG Z0011 trial or an AMAROS trial. The outcomes of these trials showed no differences in recurrence and survival between patients who had undergone ALND and those who had not undergone ALND, but the presence or absence of extracapsular extension was not analyzed in these trials [1–3].

ECE can be connected with poor prognosis and its diameter should be determined, because in many cases this factor determines the necessity of performing an ALND or regional lymph node radiotherapy.

Biological subtype of breast cancer and positive SLN

Luminal tumours are the most common breast cancer and they represent about 70% of all cases of breast cancer [4–7]. In most patients with Luminal A cancer, surgery is used up-front.

In women with clinically negative lymph nodes, SLNB is the method of choice instead of an ALND. Some authors point to different factors influencing the presence of metastases in the sentinel lymph nodes, such as: age, the diameter of the tumour, grade, and the lobular type of the cancer. Luminal A breast cancers are usually of low histological grade with slow growth and a good prognosis, however quite frequently, the illness is more advanced at the moment of diagnosis [8–9]. For women with Luminal B HER2 negative cancer, an additionally high Ki-67 factor is connected with the possibility of a positive sentinel lymph node [10–11].

For triple negative or HER2 positive cancer patients, the strategy of treatment has changed lately and therapy usually starts with chemotherapy [12]. For patients with an overexpression of the HER2 receptor, the probability of metastasis to SLN and ECE is much higher [11]. Systemic treatment leads, in more than 40% of patients, to a complete pathological response (ypT0N0) and very often SLNB is advised. However, for women with clinically suspected or with metastasis diagnosed before treatment an ALND is mandatory. On the other hand, for triple

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negative or HER2 positive T1 patients, with tumours less than 1 cm in diameter, surgery is an up-front strategy [12–16].

ECE in a sentinel lymph node and correlation with non-sentinel lymph node (NSLN) metastases

In most of the papers presented, ECE in sentinel lymph nodes is connected with metastases to NSLNs. More metastatic SLNs are connected with a higher probability of positive NSLNs. The ratio between metastatic sentinel lymph nodes and removed sentinel lymph nodes is very important. The higher the ratio, the greater the probability of metastases to NSLNs [17–21]. In his paper, Palamba showed that for patients with ECE the probability of the occupation of additional lymph nodes by cancer cells is much higher – 84.6% for massive, 58.5% for minimal, and only 14.5% for sentinel lymph nodes without extracapsular extension [22]. Similar conclusions were presented by Gooch et al. The risk of metastases to NSLNs was connected with the diameter of ECE. For infiltration greater than 2 mm, or for lesser than 2 mm, or for no extracapsular infiltration, the probability of the occupation of more than four axillary lymph nodes was 33%, 8.5% and 2.5%, respectively [10]. In yet another paper, this feature was also presented, but it was not an independent factor for disease free survival (DFS) and overall survival (OS) [23]. Schwentner, analyzing the outcomes of 324 women showed that the probability of increasing pN status (pN1 to pN2-3) was much higher in patients with ECE after performing an axillary dissection [24].

The diameter of ECE in the sentinel lymph node

In the literature, we do not meet a correct definition of extracapsular extension in connection with its clinical meaning. In pathological reports, however, very often, we find only the sentence that ECE is present and in some that ECE is absent which can be understood as the true absence of ECE or as the situation that this feature was not assessed by the pathologist. In the analysis presented by Vane et al., in a group of 3502 patients, information on ECE was available for about 60% of them [10]. Nottegar et al. have performed an analysis of proper papers concerning the issue of ECE, and five articles were included by them in their meta-analysis. In four out of the five articles, the analysis was connected only with a short piece of information that ECE was present or absent without estimation of its diameter [25]. The lack of information on the diameter of the ECE can be accepted in a situation where an axillary dissection was performed and there is a huge number of metastatic lymph nodes, which is connected with poorer prognosis and the necessity of systemic treatment, not only for cancers with worse prognosis (triple negative or non-luminal) but also for patients with luminal ones. After SLNB and the presence of ECE, it is mandatory to estimate the diameter of the ECE, because not only is it connected with prognosis, but it also influences the planning of further therapy. The relevance

for prognosis of extracapsular extension was proven in patients with other cancers [26–28].

In the 5th edition of The American Joint Committee of Cancer (AJCC) Cancer Staging Manual, the presence of ECE was recognised and named as subcategory pN1biii, but was removed from following editions [29]. This factor has also not been assessed in clinical trials. In the ACOSOG Z0011 trial, patients with ECE were excluded from the analysis and in the AMAROS trial this factor has not been evaluated. The authors pointed to the fact that the diameter of the ECE can influence both DFS and OS. When this diameter exceeded 2 mm, the risk of locoregional failure was greater than 20% and influenced DFS [30–32]. Nevertheless, this fact was not confirmed by others. In their paper Choi et al. presented the fact that in cases of ECE less than 2 mm the risk of recurrence was the same as for patients without ECE [33].

Similar conclusions were shown by Barrio et al. However, the mean time of observation was only 21 months, there were no nodal failures in patients with ECE in sentinel lymph nodes and they were not treated with an axillary dissection, but rather biologically oriented systemic treatment and locoregional radiotherapy were used. The risk of nodal failure in this group was only 1.5% [34]. The research of Kanyilmaz et al. has shown that the extent of the ECE is a prognostic factor for survival in pT1-2N1 breast cancer patients with a diameter of extracapsular extension greater than 1 mm. This factor, according to the authors, was connected with shorter OS and DFS [35].

Conclusions

In an era of diminishing surgical treatment in the breast area and axilla region, it seems to be very important to precisely estimate the diameter of any extracapsular extension in the sentinel lymph nodes. In an era of biologically directed systemic treatment and conformal radiotherapy, it is probable that we can avoid the harmful consequences of surgical procedures in many patients [12].

Pathologists should include the diameter of the ECE in their reports to help, much more so than presently, clinicians take decisions about the best oncological treatment for women with breast cancer. As the data mentioned shows, a diameter of 1–2 mm for an extracapsular extension in SLN is crucial (pivotal). The prognostic importance of ECE must also be confirmed by future clinical trials.

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