JBUON 2019; 24(4): 1735-1738
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

LETTERS TO THE EDITOR

Definition of luminal B HER-2-negative breast cancer subtype should be revisited

Dear Editor,

Luminal B HER-2-negative subtype (LBHN) is one of breast cancer subtypes according to different clinicopathological features and treatment response. This subtype shows a poor prognosis and is less sensitive to endocrine therapy [1]. However, strict definition of LBHN is still bothersome. The St. Gallen International Expert Consensus 2013 defined luminal A as ER-positive, HER2-negative, Ki-67 low, and PR high and LBHN as ER-positive, HER2-negative, and either Ki-67 high or PR low [2]. It means that the St. Gallen International Expert Consensus did not use "grade (G)" to differentiate luminal A from luminal B. Deniz and colleagues in their recent article [3] evaluated the prognostic relevance of patho-anatomical factors among different tumor-biological subsets (Luminal A-like, LBHN, HER2 type and triple-negative) of breast cancer. This analysis confirmed that tumor size, nodal stage and tumor subtypes were independent prognostic factors in high-risk early breast cancer. In this study, due to missing values of Ki67, luminal A-like type was defined hormone receptor-positive, HER2 negative,G1/G2, and LBHN was defined as hormone receptor-positive, HER2 negative, G3 [3]. In conlusion, it is impossible to say that these two different definitions of LBHN as described above overlap each other in terms of prognosis and molecular characteristics. This issue needs to be clarified in larger studies.

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CA-125 might be good predictive tumor biomarker for earlier detection of serosal metastases including the ovarian metastasis in high-risk invasive lobular breast cancer

Dear Editor,

CA-125 is a well-characterized tumor biomarker. It is a large transmembrane mucin located on the surfaces of epithelial cells of the fallopian tube, endometrium, other epithelia, and to mesothelial cells lining the pleura, pericardium, and peritoneum. Serum CA-125 is increased in a number of clinical settings including ovarian cancer [1]. Invasive lobular breast cancer (ILBC) has a predilection for metastasizing to atypical intra-abdominal sites (peritoneum, gastrointestinal tract and ovaries). Inoue et al. reported that an extremely high rate (68.8%) of peritoneal metastases was observed in long-term follow-up for metastatic breast cancer patients with ILBC [2]. In our own breast cancer dataset, we had 545 ILBC cases with 148 high risk features among 6045 breast cancer cases. We encountered 27 ILBC cases with peritoneal and/or ovarian metastases. All of them had serum CA-125 lvel over 50 U/ml. There is no data yet available in the current literature showing the importance of predictive value of serum CA-125 level during follow-up in high risk ILBC cases. This issue merits further investigation.

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HER2 status in residual disease after neoadjuvant treatment might determine sensitivity to trastuzumab emtansine

Dear Editor,

Human epidermal growth factor receptor 2 (HER2)-positive early breast cancer patients who received neoadjuvant chemotherapy plus anti-HER2- targeted therapy with residual invasive disease at surgery have higher risk of disease recurrence or death compared to patients with a pathological complete response [1,2]. A recent challenging study by von Minckwitz et al. [3] reported that among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant trastuzumab emtansine (T-DM1) than with trastuzumab alone. However, detailed information about the residual disease was not defined. Although the authors declared this limitation, persistence of HER2-positive disease in residual disease might signify real trastuzumab resistance in which T-DM1 works better compared to the patients who had loss of HER2-positive status in residual disease. This issue merits further investigation.

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Topoisomerase IIa deregulation in nasopharyngeal carcinoma

Dear Editor,

Topoisomerases represent a class of nucleic enzymes, which affect the topological structure of DNA. The main members of the family are Topoisomerase I (gene location 20q11), Topoisomerase II alpha (gene location 17q21) and Topoisomerase IIb (gene location 3p24). Topo IIa and b isomers' combined action promote temporarily cutting and rejoining the DNA double helix. Winding and unwinding of the DNA double strand is a critically important molecular mechanism for replication, transcription and repair of chromosome structure. Topo IIa, with a molecular mass of 170 kDa, is expressed in proliferating cells in late S phase with a peak in G2/M phases, where it is believed to be the primary mediator of chromosome condensation. Correlating Ki-67 to Topo IIa duration of expression, Topo IIa protein level seems to provide a better estimation of the number of actively proliferating cells and for this reason it could be used as a reliable marker of proliferation. Furthermore, topoisomerases' inhibition promotes cell death and for this reason they are targets for specific chemotherapy. Some clinical studies have shown that adjuvant chemotherapy based on a combination of anthracyclines (doxorubicin) with etoposide and fluorouracil/cyclophosphamide or carboplatin/paclitaxel is very effective in patients with breast, colon, endometrial or also ovarian cancer that demonstrate aberrant protein expression due to gene amplification predominantly [1].

Nasopharyngeal carcinoma (NPC) represents a specific, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. NPC is derived from the nasopharyngeal epithelia exposing a high invasive and metastatic potential negatively affecting patients' prognosis. Concerning its pathogenetic factors implicated in its rise and progression, Epstein-Barr virus (EBV) latent but persistent infection is considered the main one. EBV's oncogenic activity is mediated by the aberrant expression of specific critical proteins including LMPs and EBNA1 modified by endogenous EBV micro-RNAs (miRs) [2]. Concerning Topo IIa aberrant expression in NPC, a study group analyzed corresponding malignant tissues by immunohistochemistry and showed that protein overexpression of the marker was significantly correlated with tumor aggressiveness (advanced stage) modifying also potentially the response to novel target chemotherapeutic regimens [3]. Another molecular study based on a multi-gene functional and pathway enrichment analysis showed that a significant number of genes is implicated in NPC development and progression (179 up-regulated/238 down-regulated). Topo IIa deregulation is involved in specific gene signatures of the corresponding patients [4]. Finally, referring to the correlation between Topo IIa activation and EBV persistent infection, a study group concluded that a specific viral kinase (EBV BGLF4) stimulates the decatenation activity of topoisomerase II promoting chromosome condensation [5]. Also the observation that cellular chromatin becomes highly condensed upon EBV reactivation in host NPC cells was critical for explaining the EBV-mediated reorganization of nuclear architecture.

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Why do triple-negative metaplastic breast cancers tend to metastasize less frequently to lymph nodes?

Dear Editor,

Metaplastic breast cancers (MpBCs) usually present with a larger tumor size at primary diagnosis and most of MpBCs present with other poor prognostic indicators, showing lack of steroid hormone receptors expression as well as HER2, so called as triple-negative breast cancers [1]. Budzik et al. [2] found a positive correlation between hormone receptor and HER2 expression with lymph node metastasis. In other words, triple-negative MpBCs tend to metastasize less frequently to lymph nodes. The authors noted that MpBC (most probably triple-negative ones) is observed to metastasize to the bones and lungs with hematogeneous rather than lymphatic spread [2]. In our previous article we studied capillary and lymphatic invasion in tumors of patients with triple-negative disease and found that capillary invasion is more commonly observed than lymphatic invasion in patients with triple-negative tumors [3]. These results support the fact that more hematogeneous metastasis and less lymph node metastasis were observed in patients with triple-negative MpBCs [4].

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Thymidylate synthase expression at metastatic site might be more correlated with response to anti-thymidylate synthase agent in triple negative breast cancers

Dear Editor,

Capecitabine is a well-known anti-thymidylate synthase (TS) drug, commonly used in the management of metastatic breast cancer (BC), specifically in triple-negative breast cancers (TNBCs). Siddiqu and colleagues in their article [1] reported a novel fundamental role of TS in maintaining the de-differentiated phenotype of BC cells and its differential expression in the BC subtypes, with several potential therapeutic implications. They concluded that TS maintains the de-differentiated state of TNBCs. In patient tissues, TS levels were found significantly higher in poorly differentiated and in TNBCs, and strongly correlated with worse prognosis. My readout from this current study is that all 127 tumor samples were studied from primary site for TS expression. It would be more rationale to analyze TS levels taken from metastatic site that might be more correlated with response to anti-TS agents like capecitabine in TNBCs.

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The impact of receptor conversion on treatment efficacy and survival in breast cancer patients with brain metastases: Still debatable issue?

Dear Editor,

Brain metastases (BM) account for the majority of malignant brain tumors. Breast cancer is the second most common cause of BM. BM occur in 14-20% of breast cancer patients. We previously had described clinicopathologic characteristics and prognostic factors in 420 breast cancer patients with BM. The median overall survival from the date of BM was 6.8 months. Patients who had estrogen receptor (ER)-positive disease tended to have longer overall survival (10 months) compared with patients who had ER-negative disease (5.2 months; p=0.003). Patients aged ≤50 years tended to have longer overall survival compared with patients aged >50 years (p=0.047) [1]. However, we did not give detailed information about surgical excision rates for BM among 470 patients. We also did not describe discordance rates of hormone receptor and HER2 status between primary and metastatic tumor in the brain. A change of ER, progesterone receptor (PR), and HER2 status in distant metastases has frequently been reported. A recent metaanalysis including 39 studies assessing receptor conversion from primary breast tumors to paired distant breast cancer metastases showed that negative to positive conversion percentages were 21.5%, 15.9%, and 9.5% for ER, PR, and HER2, respectively [2]. The impact of receptor conversion on treatment efficacy and survival in breast cancer patients with BM have not been known yet. These patients might have a chance to use targeted endocrine and anti-HER-2 therapies which in turn might increase survival rate in BM [3]. Larger prospective studies are needed to confirm this proposal.

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