

LETTERS TO THE EDITOR

Secretory carcinoma of the breast in postmenopausal women

Dear Editor,

Secretory carcinoma is a rare malignant neoplasm of the breast that typically affects children and young adults, although it can occur at any age. Most cases of secretory carcinoma are estrogen receptor (ER) and progesterone receptor (PR) negative. Secretory carcinoma does not show human epidermal growth factor receptor 2 (HER2) over-expression and HER2 gene amplification (triple-negative breast cancer). Despite this triple-negative immunophenotype, the clinical course of secretory carcinoma is typically indolent. The presence of axillary lymph node metastasis has been reported in up to 30% of the cases [1,2]. Since it is a rare malignant neoplasm of the breast, there is no consensus with regard to the best treatment strategy for patients with this disease. Regarding systemic treatment, it would be plausible not to give intensive chemotherapy regimens like in classical high grade triple-negative breast cancer. Among my own 6358 breast cancer dataset, only one case with pure secretory breast cancer diagnosis was found. She was a post-menopausal woman at the age of 56 with palpable mass on the left breast. She had no family history of breast cancer. BRCA mutation status is pending. On her history, she described a mass already existing more than one year. Radiological results showed multifocal-multicenter left breast mass with no distant metastases. Core biopsy showed grade II secretory carcinoma with triple-negative breast cancer subtype and Ki-67 score 5%.

Then she underwent left simple mastectomy and sentinel lymph node biopsy. Pathologic stage was T2-multifocal-multicenter, with largest tumor 4 cm in size, and NOMO. Four cycles of adjuvant adriamycin and cyclophosphamide were initiated. Because of the rarity of secretory carcinoma of the breast, the published experience with this subtype of breast cancer has largely been limited to case reports and small case series. However, de-escalating systemic adjuvant treatment would be preferable in this rare breast cancer type.

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High tumor grade might be associated with pathologic complete response after neoadjuvant chemotherapy in ER-positive, HER2-negative breast cancer patients

Dear Editor,

The Oncotype DX® assay has been validated in predicting response to adjuvant chemotherapy in breast cancer. Its role in neoadjuvant chemotherapy (NCT) has not been established. Pease and colleagues reported that high Oncotype DX recurrence score (RS) was associated with pathologic complete response (pCR) after NCT in a total of 989 of ER-positive, HER2-negative breast cancer patients [1]. pCR was achieved by 42 (4.3%) patients. Interestingly, grade 3 tumors were also significantly associated with pCR compared to grade 1-3 tumors (7.7 vs 3.5%) in this study cohort. Additionally, the authors did not mention about Ki67 index of tumors. Since Oncotype DX RS testing is costly, pathological characteristics implicating higher proliferation index markers such as high tumor grade and

higher Ki67 index might be useful alternative predictive markers for NCT. This issue merits further investigation.

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Discordance between larger tumor size and less lymph node metastases in metaplastic breast carcinomas: Any biological rationale behind this fact?

Dear Editor,

Triple negative breast cancer (TNBC) comprises approximately 15 to 20% of all breast cancer cases. Many studies have detected less lymph node metastasis in TNBC than sporadic breast cancers. Takala and colleagues [1] investigated the clinicopathologic features, treatment and outcomes of 78 patients with metaplastic breast carcinomas (MpBCs). They reported that most tumors (85%) were TNBC. Interestingly, 82% were node-negative. Tumor size was associated with worse outcome in their group. However, no association was found between worse outcome and number of positive metastatic lymph nodes. The discordance between tumor size and lymph node status in MpBCs might be explained with their unique metastatic biology pattern. Furthermore, we studied capillary and lymphatic invasion in tumors of patients with TNBC. Capillary invasion was more commonly observed than lymphatic invasion in patients with TNBC [2]. These results explain the fact that more hematogeneous metastasis and less lymph node metastasis were observed in patients with MpBCs [3].

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Association between duration of ovarian function suppression and overall survival in premenopausal women with early breast cancer

Dear Editor,

Ovarian function suppression (OFS) with tamoxifen or aromatase inhibitors (AIs) improves disease-free survival in premenopausal women with breast cancer, mostly in those at higher risk of recurrence. However, duration of OFS was not described clearly in the literature. International expert consensus favored a period of 5 years of OFS, especially in patients at higher risk of relapse, such as younger age and/or with HER2-positive disease [1]. Furthermore, the SOFT study also showed a benefit of 5 years of tamoxifen plus OFS over tamoxifen alone, especially in younger breast cancer patients [2]. Taken all together, the ideal duration of OFS should be 5 years, especially patients at higher risk of relapse. However, toxicity is considerable and patients should be actively engaged in decision-making.

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Value of supraclavicular excision for locally advanced breast cancer patients

Dear Editor,

In particular, in the upfront surgery setting, supraclavicular node (SCN) excision can be performed along with breast surgery during the same operation in locally ad-

vanced breast cancer; however, the benefit of aggressive regional therapy is controversial. Kim and colleagues evaluated the outcomes of upfront surgery followed by radiation therapy (RT) for ipsilateral SCN and/or internal mammary (IMN) node-positive breast cancer [1]. One hundred fifty-

eight patients were included; among these, 91 patients were SCN-positive, 54 were IMN-positive, and 13 were SCN- and IMN-positive. Regarding regional treatments for SCN and IMN, SCN excision was performed in 59 (37.3%) patients, IMN excision in 10 (6.3%) patients, SCN RT in 143 (90.5%) patients, and IMN RT in 68 (43.0%) patients. The authors concluded that more aggressive regional therapy such as SCN excision did not improve locoregional control or survival. Among the SCN excision positive group, 54.4% of all cases were having HER2-positive tumors and only 36.8% of these cases received adjuvant trastuzumab. In current practice, neoadjuvant chemotherapy is commonly recommended in these locally advanced breast cancers [2]. One would expect that non-complete responders with residual supraclavicular involvement after systemic neoadjuvant treatment would have better survival rates if SCN excision was performed. This issue merits further investigation.

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Co-morbidities might affect the outcome in octogenarian early breast cancer patients without surgery

Dear Editor,

Local treatment, that is radiotherapy and surgery, is the cornerstone of the treatment in early breast cancer in the elderly. However, evaluating life expectancy in the presence of serious co-morbidities is difficult. Geriatric assessment tools may provide additional useful information for decision making. Ojala and his colleagues investigated the outcome of treatment in patients over 80 years of age (octogenarian) with 446 early breast cancer at the time of the diagnosis with special interest in surgical treatment [1]. They reported that surgical treatment rate was high. Overall survival and breast cancer specific survival (BCSS) were better in surgically treated elderly patients compared to non-surgically treated patients. The authors noted that co-morbidities were not classified for multivariate analyses, one of the limitations of their study. However, when the events were examined in detail, death from other causes were statistically more frequent in non-surgically treated

octogenarian breast cancer patients (67% in patients without surgery vs. 41% in patients with surgery). This information might lead us to propose that co-morbidities might affect the outcome in octogenarian early breast cancer patients without surgery.

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Correlation between exercise and skeletal muscle index in early breast cancer patients: is it worth mentioning?

Dear Editor,

Exercise during and following treatment has been associated with reductions in breast cancer recurrence and disease-specific mortality rates of 30-60% [1]. Furthermore, regular exercise by itself increases skeletal muscle volume in the body, leading to increased skeletal mass index (SMI) [2]. Furthermore, Aleixo and colleagues [3] in their review article investigated muscle composition and outcomes in patients with breast cancer in a meta-analysis. They concluded that patients with sarcopenia had more severe chemotherapy toxicity as well as shorter overall survival (OS) and time to tumor progression. Interestingly, they found interestingly that SMI was prognostic for mortality risk in early breast cancer but not in metastatic, while low muscle

density was prognostic for OS in women with metastatic but not with early breast cancer. Therefore, positive correlation between exercise and SMI in breast cancer patients might explain why SMI is prognostic for mortality risk in early breast cancer [4].

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Duration of trastuzumab maintenance in HER2-positive metastatic breast cancer patients with radiological complete remission: Robust predictive markers are needed!

Dear Editor,

Few data are available on the optimal duration of anti-HER2 therapy in metastatic breast cancer (MBC) with radiological complete remission (rCR). ESMO and ASCO guidelines support maintenance of anti-HER2 therapy, and it is now generally accepted that anti-HER2 therapy should be maintained until disease progression, except in the presence of unacceptable toxicity or at the patient's request [1,2]. Furthermore Steenbruggen and colleagues [3] investigated clinical characteristics associated with rCR and overall survival (OS) in a historic cohort of patients with HER2-positive MBC and studied the effect of stopping trastuzumab in case of rCR. They reported that 30 patients with rCR discontinued trastuzumab, of whom 20 (67%) are alive in ongoing remission after 78 months of median follow-up since rCR. The authors concluded that trastuzumab may be discontinued in selected patients with ongoing rCR. MBC patients with favorable tumor characteristics should be determined before stopping trastuzumab maintenance treatment. A subgroup of patients with HER2-positive MBC, especially those with hormone receptor negative and truly HER2-enriched subtype and those with a structurally intact HER2 receptor who are expected to be more sensitive to trastuzumab might not be good candidates for discontinuation of trastuzumab [4]. The objective efficacy of prolonged maintenance of trastuzumab compared with observation in HER2-positive patients achieving complete response to first-line treatment should be tested in randomized trials. In conclusion, the decision of whether

trastuzumab should be discontinued or not in such patients remains strongly controversial and robust predictive markers are needed.

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Why is letrozole concentration not associated with arthralgia in patients with breast cancer?

Dear Editor,

Letrozole as an aromatase inhibitor (AI) is used for the adjuvant or metastatic treatment of breast cancer in postmenopausal women. Adherence to letrozole becomes a problematic issue due to the development of AI-induced arthralgia. Letrozole is metabolized in the liver by CYP2A6 to become active ingredient. It is still unknown if plasma letrozole levels or CYP2A6 genetic variation is associated

with the development of arthralgia. Borrie and his colleagues [1] prospectively examined the association of arthralgia with circulating levels of letrozole and CYP2A6 genotype in postmenopausal women initiated on letrozole therapy. They found that CYP2A6 genotype was a significant predictor of letrozole plasma levels, but was not associated with the development of arthralgia. No rationale explanation why letrozole concentration is not associated with arthralgia in patients with breast cancer exists. One plausible factor

would be lower threshold plasma level of letrozole that may trigger arthralgia which is not associated with CYP2A6 genotype. Second possible explanation would be genetic determinants that induce arthralgia independent from plasma level of letrozole. Garcia-Giralt et al [2] showed that SNPs in CYP17A1, VDR, and CYP27B1 genes predict the risk of aromatase inhibitor-associated arthralgia. Taken all together, this issue needs further investigation.

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Inflammation and sarcopenia: The development of combined prognostic scores as a novel approach to predict survival of esophageal cancer patients

Dear Editor,

We read with great interest the meta-analysis entitled: 'Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis' [1]. This updated meta-analysis casts light on the controversial role of sarcopenia in predicting survival of esophageal cancer patients. More specifically, the authors demonstrated that preoperative sarcopenia is an independent adverse prognostic factor for esophageal cancer patients undergoing esophagectomy, in terms of overall and disease-free survival.

Nevertheless, inflammation is also considered a significant prognostic factor for impaired survival of esophageal cancer patients. A recent meta-analysis showed that inflammation-based prognostic markers, such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio, and lymphocyte to monocyte ratio (LMR), were correlated with poor overall survival/cancer-specific survival and event-free survival of patients with esophageal squamous cell carcinoma [2].

These results indicate that a combination between sarcopenia and inflammation could be a strong risk factor of unfavorable outcomes in esophageal cancer patients, since muscle wasting and inflammation are the hallmarks of cancer cachexia. The development of prognostic scores that incorporate inflammation markers and sarcopenia, has gained ground as an effective approach to predict survival of cancer patients. For instance, a cachexia index comprised of skeletal muscle index, albumin and NLR was associated with worse progression-free survival and overall survival of metastatic non-small-cell lung cancer patients [3].

Moreover, Lin et al examined the prognostic value of a new prognostic score based on LMR and preoperative sarcopenia (SLMR) for patients with resectable gastric cancer. This composite score predicted more efficiently overall survival of gastric cancer patients, compared to sarcopenia or LMR alone. Additionally, SLMR was incorporated into a prognostic model that included tumor size and TNM stage, leading to higher predictive accuracy [4].

Furthermore, results from a large prospective cohort of patients with early-stage colorectal cancer revealed a close relationship between sarcopenia and inflammation. Although NLR and sarcopenia were independently associated with poor survival of colorectal cancer patients, coexistence of high

NLR and sarcopenia was associated with a 2-fold increased risk of mortality, enhancing survival prognostication [5].

Conclusively, future research should emphasize on the development and evaluation of composite prognostic scores in esophageal cancer patients, since they seem to be better indicators of survival, rather than the use of single risk factors. The combination of sarcopenia and inflammation provides a more accurate basis for guiding postoperative follow-up and multimodal treatment, seeing that the simultaneous assessment of these two parameters might be a method for identifying high risk subgroups of patients that could benefit from prehabilitation programs.

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Comment on Raze's views on cancer and the introduction of chemotherapy

Dear Editor,

We read and enjoyed the fascinating article published in the 24th volume of this journal, entitled "Rhazes' (864-925) views on cancer and the introduction of chemotherapy" by Gregory Tsoucalas et al. We were filled with interest to find valuable information about a Persian physician and philosopher, Abu Bakr Muhammad ibn Zakariya al-Razi, which can show the keen manner of the authors in the history of medicine.

The bright spot of this paper lies with its introduction of Razi among the first ones who adhered to chemotherapy and one who described some pediatric disorders and the differentiation between smallpox and measles.

Nevertheless, there are some arguable points in this article. It writes that Razi was an Arab physician in the Arabo-Islamic medicine school and that he authorized the Al-Havi book. Moreover, it discusses that Razi was a pupil of Hunayn Ibn Ishaq (809-873), who dominated several medical doctrines such as Hindi medicine. Additionally, it argues that Razi learned medicine from Abu al-Hasan Ali ibn Sahl Rabban al-Tabari (a Persian physician), who lived in the 9th century AD [1].

According to our researches about the nationality of Razi, he was a Persian physician who lived during the Persian-Islamic era. In fact, the Islamic culture entered and grew in the context of Persian culture, building on ancient Persian achievements, which contained Unani/Greek medicine too [2].

Although Ishaq-ibn-Honayn was contemporary with Razi and resided and translated several non-Arabic texts to Arabic for physicians in Baghdad, there is no evidence to demonstrate the authority of Honayn in Indian medicine, whether compilation or translation. Nor can we find a document that shows Razi as a pupil of Ishaq-ibn-Honayn [3].

There is also some doubt as to whether Razi was a pupil of Tabari. According to Persian-Islamic historical texts,

Abu al-Hasan Ali ibn Sahl Rabban al-Tabari was a Persian physician born in 916 (death in 986 AD) [4], whereas Razi is considered to have lived through 864-925 AD. Therefore, Tabari was prior to Razi and it is inconceivable for Razi to be a pupil of Tabari.

Also, it is hypothesized that Al-Havi fi Al-Tib was not a book authorized by Razi; it seems to be a collection of Razi's or his pupil's pieces of handwriting, entitled in Persian as Konash Al-Havi [5].

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