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LETTERS TO THE EDITOR

Is it rational to extend the duration of preventive endocrine treatment in hormone receptor positive ductal carcinoma *in situ*?

Dear Editor,

Ductal carcinoma *in situ* (DCIS) is frequently detected by mammogram and accounts for >20% of all breast cancer diagnoses. The standard of care for DCIS is breast-conserving surgery (BCS) with radiation or mastectomy, and 10-year survival exceeds 97% [3]. According to NCCN panel, five years of tamoxifen or aromatase inhibitors use may be considered as a strategy to reduce risk of ipsilateral breast cancer recurrence in ER-positive DCIS treated with breast-conserving therapy [1-3].

Five years of tamoxifen or an aromatase inhibitor for all patients with HR-positive early breast cancer is considered standard; however, there are now data to support an extended approach using up to 10 years of treatment [4]. In common practice, clinicians sometimes extrapolate data about the10 years of endocrine use in early breast cancer for ER- positive DCIS breast cancer patients and mistakenly recommend 10 years of endocrine prevention in ER- positive DCIS. However, there is no data available to support extended endocrine treatment in DCIS.

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PD-L1 in oral squamous cell carcinoma

Dear Editor,

Programmed cell death-1 (PD-1) gene - located on chromosome 2 (gene locus: 2q37.3) - encodes a cell surface membrane protein of the immunoglobulin super-family. It acts as an immunoinhibitory receptor of the CD28 family, involved in tumor immune escape process. PD-1 is expressed in pro-B-cells involved in their differentiation, whereas its role in apoptotic death process in under consideration. Concerning its downstream pathway, PD-1 interacts with two potential ligands, PD-L1 and PD-L2 transmembrane proteins implicated in different levels of expression in specific functions regulation [1]. Programmed cell death ligand-1 (PD-L1), also known as CD274 (cytogenetic band:9p24.1), is expressed predominantly in most hematopoietic cells and also in epithelial cells, including pancreatic islet cells and vascular endothelial cells. Additionally, PD-L1 is expressed on the thymic cortex, on thymocytes and in the thymic medulla. Also, dendritic cells express PD-L1 reducing the initial phase of activation and expansion of self-reactive T cells. Concerning PD-L2, also known as CD273 (cytogenetic band:9p24.1), its expression is restricted to macrophages and dendritic cells. The PD-1/PD-L1 pathway delivers inhibitory signals that regulate both peripheral and central tolerance. Its main role is the inhibition of T lymphocyte proliferation, survival and other functions (cytotoxicity,cytokine release). Furthermore, it causes apoptosis of tumor-specific T cells and also differentiation of $CD4^+$ T, inducing resistance of tumor cells to cytotoxic T lymphocyte (CTL) lineage attack. Aberrant overexpression of PD-L1 enhances the inflammatory process and also allows cancers to evade the host immune system by suppressing T cell activation and inducing peripheral tolerance [2].

High PD-L1 expression seems to be correlated with an elevated metastatic ability of malignant cells leading also to poor prognosis in a variety of malignancies including colon cancer, breast carcinoma, esophageal cancer, non-small cell lung cancers and melanoma. In ovarian and renal cell carcinomas and also in glioblastomas, PD-L1

overactivation is also a poor prognostic factor. Concerning the molecular mechanisms of its deregulation, epigenetic changes such as PD-L1 promoter DNA methylation may predict survival in some cancers after surgery. In oral squamous cell carcinoma (OSCC), some recently published studies have shown that although its prognostic role is still controversial, PD-L1 expression, determined by immunohistochemical staining, could be an independent prognostic marker, especially for patients who are male or who are smokers. Interestingly, the study group showed that PD-L1 overexpression was detected predominantly in female patients, correlated also with distant metastasis [3]. Additionally to this PD-L1+ category, distinct gene expression patterns of OSCC demonstrating combined PD-L1 overexpression in malignant tissue and also in detected circulating tumor cells (CTCs) are characterized as eligible for anti-PD-L1 targeted immunotherapy. According to the corresponding molecular and clinical findings, patients characterized by diffuse strong cytoplasmic PD-L1 expression in CTCs overexpression were associated with increased tumor size and lymph node metastasis, leading to a limited life span. The study group concluded that PD-L1+ CTCs should be a specific category eligible for anti-PD-L1 targeted immunotherapy [4]. Novel anti-PD-L1 strategies are referred to a plethora of very promising agents - fully humanized or not monoclonal antibodies - such as atezolizumab, avelumab, durvalumab, tremelimumab, nivolumab, and also ipilimumab [5].

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Are bilateral and unilateral interval breast cancers different?

Dear Editor,

Around 20-25% of breast cancers are diagnosed after a negative screen (i.e., no referral) and before the next scheduled screen, the so-called interval cancers [1]. Breast cancer is infrequently diagnosed bilaterally with only 2.2% of breast cancers diagnosed in a systematically screened population being bilateral. In screen-detected cancer, bilateral breast cancer has a different pathological profile compared to unilateral breast cancer, including a larger proportion of invasive lobular cancers and less lymph node involvement [2]. However, data about bilateral interval cancers do not exist in the literature. van Bommel and colleagues investigated the incidence of bilateral interval breast cancers and compared their characteristics with those of unilateral interval breast cancers [3]. They reported that bilateral interval cancers comprised 3.2% of all interval cancers and invasive bilateral interval cancers were more frequently of the lobular subtype and had a more favourable histological grade than unilateral interval cancers. The authors did not compare the molecular subtypes of unilateral and bilateral interval cancers. It is commonly known that interval breast cancers had a higher frequency of triple-negative or HER2-positive cancers and a lower frequency of hormone receptor-positive cancers than screen-detected breast cancers [4]. Then it would be expected that bilateral interval cancers might more commonly show characteristics of luminal subtype compared to unilateral breast cancer. Secondly, in this study only synchronous contralateral cancers were evaluated. Synchronous breast cancers are more frequently of the same histologic type as the index cancer [5]. In the study by van Bommel et al. [3], 37.5% of all index cancers were of lobular type, but none of 24 contralateral cancers were of lobular type. This issue needs to be clarified as well.

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The role of radiotherapy following mastectomy and reconstruction

Dear Editor,

Breast reconstruction which doesn't exclude oncologic follow-up principles is a continuum of surgical interventions that aims to regain the impaired body image due to partial or complete loss of breast and surrounding tissues as a result of resections performed for local control of breast cancer. Breast construction is performed to protect body integration, to solve psychological problems, to obtain social gains and to return patients to normal life by restoring self-confidence [1]. Based on National Cancer Database reports, breast reconstruction rate increased from 13% in 1998 to 27% in 2007 in USA. A similar increase has been reported in Europe. The frequency of breast reconstruction is directly related to patient's age, facility where surgery is performed and the opinion of oncologic surgeon against breast reconstruction.

Today, breast reconstruction following mastectomy is performed as immediate reconstruction (simultaneously with mastectomy), delayed-immediate reconstruction (2 weeks after mastectomy) and delayed reconstruction if patients will receive radiotherapy (3 months after radiotherapy). In many studies, it has been shown that immediate reconstruction is a safe approach with local recurrence rate of 2.3-5.5% and that it doesn't cause increase in risk for local recurrence [2]. Despite the advantages of immediate reconstruction, there is no consensus optimal protocol regarding simultaneous reconstruction in combination with adjuvant therapies. Occasionally, it is considered that delayed reconstruction is more accurate and medically safer approach (advanced stage or radiotherapy following mastectomy) although patients prefer immediate reconstruction.

Breast reconstructions are classified as autologous or implant-based reconstruction according to the technique employed. Both autologous and implant-based reconstructions have poor tolerance to radiotherapy. Radiotherapy in a patient scheduled to reconstruction with prosthesis increases the risk for capsular fibrosis while radiotherapy leads to contraction, fibrosis and hyper-pigmentation in autologous tissue. In a study evaluating immediate tissue expander/implant reconstruction and post-mastectomy radiotherapy, Cordeiro et al. reported that the implant loss rate was 9.1% in implants that received radiotherapy and 0.5% in those not and that the rate of grade 4 contracture was 6.9% in implants that received radiotherapy and 0.5% in those that did not. However, autologous reconstruction is accepted as gold standard in patients with locally advanced cancer who are candidate for adjuvant radiotherapy at the postoperative period [3]. In a meta-analysis assessing the relationship between radiotherapy and autologous and implant-based reconstructions, it was found that radiotherapy after reconstruction increased risk for complication by 4.2-fold. In addition, no significant difference in complications was observed between immediate and delayed autologous reconstructions. When implant-based and autologous reconstructions were compared, it was seen that morbidity was higher in implant-based reconstructions by 79% [4]. In a meta-analysis assessing radiotherapy in implant-based reconstruction, the failure rate was 18.6%. This rate was reported as 30% in post-expander radiotherapy whereas 7.7% after implant-based reconstruction [5].

In conclusion, there is currently insufficient data regarding the optimal radiotherapy technique, potential complications and long-term cosmetic outcomes in cases which require adjuvant radiotherapy after breast reconstruction. The majority of methods used in breast reconstruction dates back 25 years ago and the most frequently used methods have a history of 10-15 years. Thus, there is no established algorithm today where implant technologies show progressive advances. The aim of breast construction should provide appropriate treatment with appropriate timing. This could be achieved by introducing such a treatment into the oncologic treatment plan.

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Are intramammary lymph node metastases significant in the staging of breast cancer?

Dear Editor,

Intramammary lymph node (intraMLN) metastases have received little attention as potential prognostic indicators for patients with breast carcinoma, especially in breast cancer patients presenting with positive intraMLN and negative axillary lymph nodes. Contemporary breast cancer staging information does not consider positive intraMLN unlike positive axillary lymh nodes [1]. However, some studies suggest that patients with stage I breast carcinoma and positive intraMLN metastases have been reported to have a poorer prognosis compared to patients with similar stage and negative intraMLN metastases [2,3]. Therefore, breast cancer with intraMLN metastases is considered to be stage II disease, even in the absence of axillary lymph node involvement. The role of adjuvant radiotherapy in such cases is still debatable and needs further investigation. In conclusion, intraMLN metastases are important for accurate staging and appropriate treatment of patients with breast cancer. Increasing use of sentinel lymph node biopsy leads to increased identification of intraMLN metastases which are clinically important for the final treatment of breast cancer.

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Importance of telomere length and telomerase activity in radiosensitivity

Dear Editor,

Telomeres are functional elements localized at the end of eukaryotic chromosomes, which control chromosomes during the replication process. The shortening of telomeric DNA after each cell division causes both aging and pathological conditions such as cancer [1,2]. The telomere's length has been studied in several human cancers and found to be shorter in some tumors (head-neck, bladder and colon cancer, renal cell carcinoma, glioblastoma), while longer in some others (chordoma) when compared to normal tissues [2,3]. In recent years, it was found that disease-free survival is poorer in patients with increased telomere length in various cancers. Several studies demonstrated its clinical and prognostic value but the results are contradictory [2-4].

For telomeres, shortening in each replication is restored by their lengthening via the telomerase enzyme. In humans, telomerase activity is only observed in embryonic cells and stem cells but not in normal cells and it is activated in tumor cells. It was found that there was increased telomerase activity in approximately 85% of breast, prostate, lung, liver, pancreas and colon cancers. Telomerase activation is one of the important mechanisms involved in immortalization and uncontrolled proliferation of tumor cells. These features make telomerase a potential target in the diagnosis and cancer therapy [1-3].

The roles of telomeres in radiosensitivity and chemosensitivity have been identified in recent years. In a rat study, it was found that rats with short telomeres displayed hypersensitivity against ionizing radiation and that these animals died due to acute radiation toxicity affecting the gastrointestinal system, lymphoid organs and kidneys. This study is important as it demonstrated a relationship between telomere length and radiosensitivity [5]. In addition, telomere dysfunction can trigger radiosensitivity as it is involved in repair process of DNA double-strand breaks [1,2,4].

Telomeres are promising regarding targeted therapies and telomere-specific potential treatments are being developed. Agents inhibiting telomerase include reverse transcriptase inhibitors, nucleoside analogs, isothiazolone

derivatives, and rhodacyanine and catechin components of green tea. Oral BIBR1532 inhibits the proliferation in human tumor xenografts on rats, and seems as the most promising agent among anti-telomerase agents so far [1,4,5].

Although studies on telomerase activity are widely performed worldwide, studies on telomere length is scarce and the number of comparative studies is exceptionally limited. Telomere length and telomerase activity are promising in the prediction of clinical course and development of targeted therapies in addition to their role in human cancer. Agents targeting telomere and telomerase in combination with radiotherapy will allow development of treatment plans with less adverse effects with lower doses of ionizing radiation as well as for the treatment of radio-resistant tumors. There is an obvious need for further studies in this field where our understanding is limited.

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