

LETTERS TO THE EDITOR

Secondary gastric cancer after breast cancer diagnosis might occur in younger lobular breast cancer patients

Dear Editor,

It is well-known that invasive lobular breast carcinoma has a greater propensity to metastasize to the gastrointestinal (GI) tract compared with other breast cancer subtypes [1]. Montagna and colleagues investigated the treatment and outcomes of breast cancer patients with GI tract involvement diagnosed at the European Institute of Oncology. They analyzed the clinicopathologic features of the GI metastases and compared them with those of the primary tumors according to their histologic type (ductal or lobular carcinoma). They reported that lobular breast carcinoma has a greater propensity to metastasize to the GI tract compared with other breast cancer subtypes and concluded that in the presence of GI symptoms, even if nonspecific, the GI tract should be thoroughly studied and systemic treatment, including hormonal therapy, should be considered [2]. However, in clinical practice, we see some cases with primary gastric cancer (GC) following breast cancer diagnosis or misdiagnosed as primary GC instead of metastatic breast cancer and treated accordingly. Mahar et al. [3] evaluated the population-risk of developing GC following breast cancer and they found that GC rates were similar to the general population for ductal breast cancer. Women aged 35-75 with lobular breast cancer had a significantly higher incidence of GC; women aged 40-44 had the highest risk. In conclusion, careful pathological revision of

the breast cancer cases presenting as diffuse growth pattern and the endoscopic and clinical features of linitis plastica in stomach to exclude primary GC is needed, especially in younger lobular breast cancer patients.

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Which type of flap is more resistant to radiotherapy in breast cancer?

Dear Editor,

Breast cancer is the most common type of malignancy in women. Although mastectomy is the treatment of choice in breast cancer, dependent of course on a number of factors, it is one of the interventions that causes women's body image to deteriorate. In cases where this method is applied, breast reconstruction is important. The main purpose of this process is to offer a good cosmetic result and improve the patient quality of life. Thanks to technological advances in implant materials and advances in microsurgical techniques, breast reconstruction has become a popular topic and has been increasingly applied. Approximately 40% of patients undergoing mastectomy are subjected to breast reconstruction and concurrent breast reconstruction rates increase by approximately 5% every year [1-3].

The most frequently used reconstruction method is with the patient's own tissue. Breast reconstruction with muscle and skin tissue taken from a specific part of the patient's body is called autologous breast reconstruction which has become more important over the years. Autologous breast reconstruction is referred to as early breast reconstruction if done within the first 2 weeks of mastectomy. In studies performed, independent of the type of reconstruction, total and major complication rates were found to be higher in early breast reconstructions than in later stage breast reconstructions. Patients with a history of radiotherapy (RT) to the breast and patients with multiple scars on the breast constitute the more appropriate patient group for autologous reconstruction. The choice of flap in the reconstruction is based on the breast volume and contour, the body type, the history of irradiation in the

breast and the presence of donor areas (adequate tissue presence, scarring, etc.). There are many flap donor sites for autologous reconstruction. These include pedicled latissimus dorsi musculoskeletal flap, pedicled and free transverse rectus abdominis myocutaneous flap (TRAM), free superior gluteal artery perforator flap (SGAP), deep inferior epigastric artery perforator flap (DIEAP), free transverse gracilis muscle-flap and free superficial inferior epigastric artery flap (SIEA). The most commonly used are pedicled and free TRAM flaps, SISAP and SIEA flaps [2-5].

The examination of RT technique, possible complications and long-term cosmetic results were more important in patients with breast cancer who had adjuvant RT after autologous breast reconstruction. The effects of autologous breast reconstruction on local recurrence, distant metastasis and survival were also investigated in this group of patients. There is insufficient information about these issues in the literature. Tran et al. in their study of concomitant autologous reconstruction in terms of local recurrence and distant metastasis did not find any difference [2]. In another study, the authors evaluated the oncological efficacy of adjuvant RT in the group without autologous breast reconstruction using emergency DIEP flap and they reported that there was no difference in local recurrence, distant metastasis and survival [3].

Complex tissue changes caused by radiotherapy also affect autologous breast reconstruction. RT causes a number of short and long-term side effects on the breast skin, vascular structures and collagen synthesis. RT causes vascular damage, hypoxia, hypovascularity and hypocellularity in tissues. In patients with autologous reconstruction, the negative effects of RT on vascularity and collagen synthesis caused wound healing problems, tissue fibrosis, lower quality of skin and subcutaneous tissues, reduced the success of reconstructive procedures, and may lead to inappropriate aesthetic results [2-4]. In the literature, there are few studies examining the types of flaps in which the RT is applied after mastectomy and the resistance of the flaps to RT. Yun et al. reported that deep epigastric perforator flaps were superior to TRAM pedicled flaps between autologous flaps in patients undergoing postoperative RT after mastectomy. It has also been stated that this group of patients may be preferred in latissimus dorsi and muscle protective free TRAM flaps [1]. Chang et al. in their study comparing DIEP and TRAM flaps in both flaps found no difference in terms of acute and chronic complications. However, concurrent reconstructions revealed that more shrinkage was found in the flaps after radiotherapy [5]. Myung et al. reported that in patients undergoing autologous breast reconstruction, the volume of flap was reduced by 12.3% in the flap volume after adjuvant RT [5]. O'Connell et al. reported that there was no difference between patient satisfaction in early and

late breast reconstruction in DIEP flap reconstruction that required postmastectomy RT [4]. In their study, Tran et al. suggested that patients who receive radiotherapy should postpone breast reconstruction. However, it was stated that optimal timing is not known after RT [2].

As a result, breast reconstruction is a part of breast cancer treatment in recent years. Autologous breast reconstruction, which is widely used nowadays, is presented as a good option for women to have a more natural appearance after reconstruction. However, autologous breast reconstruction is a matter of discussion concerning time and method. Especially after mastectomy, the location, timing, technique, toxicity and cosmetic results of RT should be investigated in patients with myocardial flap or myocutaneous flap. There is a need for studies investigating which type of flap is more effective and reliable in patients with priority for RT.

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CA 19-9 in follow-up of patients with colorectal cancer: Should it stay or should it go?

Dear Editor,

The serum carbohydrate antigen (CA) 19-9 is used as a prognostic and monitoring tumor marker in patients with gastrointestinal malignancies. CA 19-9 is not an appropriate

tool for screening in view of its expression among healthy individuals and elevation in various nonmalignant conditions [1,2]. Herein, we describe a 72-year-old woman with normal preoperative levels of serum carcinoembryonic antigen (CEA) and CA 19-9 who presented in 2014 with slightly

increased CA 19-9 value of 45 U/mL (cutoff level 37 U/mL) three years after successful surgery for right-sided colon cancer (T3N1M1) and adjuvant FOLFOX chemotherapy. She had no complaints and did not notify weight loss or change in bowel habits, while the laboratory tests, including CEA, were within normal limits. The colonoscopy did not manifest cancer recurrence and any abnormal findings were not displayed by abdominal ultrasound, computed tomography scan and chest X-ray. The esophagogastroduodenoscopy and gastric biopsies revealed *Helicobacter pylori*-negative chronic inactive gastritis without gastric atrophy or metaplasia. In the next three years CA 19-9 was measured repeatedly and showed again elevated values (range 45-90 U/mL). No recurrence was observed and the patient remained asymptomatic along with normal CEA levels, blood count, biochemistry and imaging findings.

Although CA 19-9 is harnessed nowadays mostly to the follow-up of patients with pancreatic cancer, CA 19-9 was discovered as a tumor-associated antigen in colorectal cancer (CRC). Data regarding the usefulness of CA 19-9 in CRC are not conclusive. Stikma et al. claimed that CA 19-9 could be used as a complementary marker for recurrence in patients with CRC and normal CEA level, whereas Burz et al. did not find an association between CA 19-9 and the risk of tumor relapse in CRC patients [3,4]. Serum CA 19-9 could also be increased in cancers of the stomach, esophagus, biliary tree, liver, lung and ovary, as well in cholangitis, cholecystitis, pancreatitis, diabetes mellitus, chronic hepatitis, inflammatory bowel disease, liver steatosis and cirrhosis, benign kidney and lung diseases, autoimmune and thyroid disorders, endometriosis and ovarian cysts, but all of them were ruled out [2]. CA19-9 could be elevated due to smoking cessation in cancer patients and even among heavy tea drinkers, but the patient did not stop smoking during the follow-up and did not report for heavy tea consumption. Chronic gastritis is the most reasonable cause for the persistent elevation of CA 19-9 in the present case. Similarly, Yildiz et al. discovered that erosive gastritis could increase

serum CA 19-9 in patients without cancer [5]. Large prospective studies are needed to evaluate the role of CA 19-9 in the follow-up of patients with CRC. Physicians should be cautious when they encounter inexplicable elevation of serum CA 19-9 during follow-up of CRC patients on account of limited CA 19-9 specificity. Although the significance of CA 19-9 as a tumor marker in CRC is still questionable, its use to monitor recurrence in CRC patients could probably be warranted if CA 19-9 cutoff value >100 U/mL is set [1,2].

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Interleukins in nasal polyps and nasopharyngeal carcinoma

Dear Editor,

Nasal polyps represent a unique neoplastic-like entity in patients with chronic rhinosinusitis (CR). CR is a persisted (>12 weeks) inflammation of the nasal cavity and paranasal sinuses which is characterized by a variety of pathogenetic and environmental factors. Nasal polyps are derived from an inflammatory substrate by the influence of specific molecular aberrations. CR with nasal polyps is a heterogeneous clinicopathological entity implicated with asthma and chronic allergic rhinitis. Extensive genetic analyses have shown that among the molecules that are involved in its genetic base, interleukins (ILs) play a critical role in their development and progression [1]. ILs is a family of proteins that act as cytokines expressed mainly by leukocytes. Since now, approximately 50 ILs have been already identified and cloned. ILs are mainly produced by CD4 T lymphocytes, and also by macrophages, monocytes

and other cells, such as endothelial ones. They participate in the normal function of the immune system by enhancing the production and differentiation of the B, T cells and eosinophils. In fact, ILs modify signalling pathways that affect the inflammatory/immune response in a variety of epithelia. Concerning nasal polyps combined with CR, IL-4 (5q31.1), IL-5 (5q31.1), and IL-13 (5q31.11) are found to be overexpressed [2]. Additionally, another study group analyzing IL-25 (14q11.2) suggested that its overexpression is involved in the progression of CR with nasal polyps and these ILs are potential targets for novel targeted therapeutic agents, such as monoclonal antibodies [3].

In contrast to the previous referred benign, inflammatory neoplastic-like process, nasopharyngeal carcinoma (NPC) represents the main malignancy in the corresponding anatomic region characterized also by a severe and extended T-lymphocytic infiltration. Mechanisms of deregulated immune response in NPC include ILs aberrant

expressions. IL-18 (11q23.1) induced secretion is present combined also with IL-12 (3q25.33) [4]. The corresponding study group considered the IL-18 expression as more important compared to IL-12, although both of them synergistically enhance T cells and NK cells activation inducing the of IFN-gamma production. In conjunction to this, the role of ILs based genetic predisposition in NPC seems to be an interesting field for molecular investigation. Analyzing IL-10 (1q32.1), a study group concluded that IL-1082 A/G polymorphism should be a surrogate genetic marker for estimating the risk for NPC development, instead of other polymorphisms including IL-10-819 T/C and IL-10-592 A/C [5]. All the previous referred studies show that ILs are implicated in benign (nasal polyps) and also in malignant entities such as NPC, reflecting their critical role in the pathobiology of the altered nasopharyngeal cell micro-environment.

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Combination of radiotherapy and vemurafenib in malignant melanoma

Dear Editor,

Malignant melanoma (MM) is a potentially fatal type of cancer that is characterized by many genetic alterations and increasing incidence. Diagnosis of the disease in early stage makes curative treatment possible. However, due to the fact that curative treatment is not possible in advanced disease stages and recurrence is frequent, new treatment modalities are needed and various chemotherapeutic agents are tried. However, due to gene mutations and drug resistance, no significant response to treatment is obtained. In the last 4-5 years treatment options and the chances of success are very limited. With the application of the improvements in the genetics field to the clinic, very important successes have been observed in the treatment of MM and an increasing number of targeted drugs has been developed [1-4]. Studies report that most of the MM show somatic mutations that cause hyperactivation of protein kinase signal pathways. The most common somatic mutation is point mutation in the BRAF gene [1,2]. BRAF is a serine-threonine kinase involved in the RAS-RAF-MAPK signal cascade. Activation of this pathway was found to effect the growth and survival of MM cells. BRAF mutation is seen in 40-60% of MMs and 90% of this mutation constitutes V600E mutation. In MM, the BRAF mutation has been detected quite frequently and the role of BRAF inhibitors has been investigated [2-4].

Vemurafenib, a BRAF inhibitor, showed dramatic antitumor activity in phase III trials and was approved for MM therapy by the FDA 5 years ago. Vemurafenib has been shown to increase both progression-free survival and overall survival in patients with V600E mutations [2]. The response rate in phase I and II studies with vemurafenib in MM was 50% [1]. In BRIM-3 phase III study of 675 patients,

one group was given 960 mg vemurafenib twice a day and the other group was given dacarbazine. Disease-free survival (6.9 vs. 1.6 months), response rates (57% vs. 8.6%) and overall survival (13.6 vs. 9.7 months) favoring considerably vemurafenib [1].

The most common side effects of vemurafenib are dermatologic complications such as hyperkeratosis, redness and photosensitivity. In addition, arthralgia, itching, alopecia, nausea and diarrhea may be seen [3-5].

Vemurafenib is used as an effective agent in the treatment of MM, but the development of resistance to the drug limits its use and reduces its effectiveness. The most common cause of resistance to vemurafenib is thought to be reactivation in the MAPK signaling pathway [2-4]. New treatment targets to overcome resistance to vemurafenib during treatment have been investigated. Studies on this subject are ongoing. Both chemotherapy/immunotherapy and RT combination regimens have not been satisfactory. Recent studies suggest that patients with MM treated with BRAF inhibitors experience radiosensitization with increased frequency of side effects. It was emphasized that this may mean that it increases efficacy during the treatment of melanoma, though however, there is no clear information at this time [3-4]. Walter et al., one of the researchers investigating this subject, tested whether the BRAF inhibitors dabrafenib and vemurafenib together with ionizing radiation more effectively inhibited melanoma cells and they reported no synergistic effect was observed [3]. Strobel et al. administered a BRAF inhibitor (vemurafenib or dabrafenib) and radiation therapy (10 Gy and 35 Gy) to patients with unresectable stage III or IV disease and they reported that local response was good in the combination therapy but with increased risk of skin toxicity. However, they emphasized that this toxicity is generally tolerated by most

patients. As a result, it is stated that RT does not prevent such toxicity in sequential or simultaneous application [4].

There are very limited studies on the simultaneous combination of vemurafenib and radiotherapy in metastatic melanoma. In a review of Trino et al. in patients with melanoma brain metastases in combination with radiosurgery/stereotactic radiotherapy and BRAF/MEK inhibitors, the treatment of the combination has been shown to be effective and well tolerated. However, it was emphasized that there is a need for additional data from prospective studies to further investigate the effectiveness of the combination [5]. The currently ongoing study (ClinicalTrials.gov) NCT01721603 investigates the effectiveness of this combination. In this study, the role of stereotactic radiosurgery (SRS) in local therapy will be re-evaluated.

Studies on simultaneous or sequential use of vemurafenib and SRS/radiosurgery in metastatic melanoma continue. The current results indicate that the combined use of vemurafenib in the treatment of metastatic melanoma has shown a longer progression-free and overall survival. Skin toxicity is also tolerable. However, it is not known whether it has additive effect on radiation necrosis due to SRS in its combined use. Studies on this issue are needed.

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