

## Comparison of clinicopathological characteristics and outcome of younger and older breast cancer patients

Dear Editor,

Younger women with breast cancer have poorer prognosis than older ones. These cancers are often hormone receptor-negative, high grade, and diagnosed at advanced stages. Although compared to younger patients, older patients are more likely to have low-grade, hormone receptor-positive breast cancers, a high percentage of older patients do not receive standard treatment based on current best practice guidelines [1-4]. The purpose of this report was to explore the differences between women with breast cancer who were in both extreme age groups, younger and older ages.

All patients > 75 years old and < 30 years old followed up at Hacettepe University Institute of Oncology were assessed. Statistical analysis was performed using the SPSS statistical package. The following independent variables were analyzed: age at presentation, surgical intervention, operation type, tumor type, tumor size, lymphovascular invasion (LVI), lymph node involvement, ER, PR and HER-2 receptor status, TNM stage, adjuvant radio-, chemo- and hormonal therapy, and disease recurrence. The follow-up duration was calculated as the length of time between the date of diagnosis and the date of death or last contact. Disease-free survival (DFS) was defined as the time from surgical resection to the first of any of the following events: relapse, second primary breast cancer, any second (non-breast) malignancy or death from any cause.

Out of a total study population of 1680 breast cancer women, 83 were < 30 years of age, with median age of 28.4 years (range 19-30) and 32 were > 75 years of age, with median age 77.1 years (range 74-88). The distribution of various clinicopathological factors did not differ significantly between the two age groups (operation type, tumor type, LVI, tumor stage, ER, PR and HER-2 receptor status, tumor and nodal stage (T1-4, N0-1)). Fifty-eight (80.5%) of younger breast cancer patients received adjuvant chemotherapy based on anthracycline + taxane or anthracycline-containing regimen and 95.8% (n=23) of older patients received only adjuvant hormonal therapy. Median follow-up time was 4.8 years. In the younger age group, 30 (36%) patients developed some kind of disease progression (locoregional recurrence 27.7%, metastatic disease 3.6%) and 7 patients died. In the older age group 7 patients (21%) experienced

some kind of disease progression (locoregional recurrence 9.4%, metastatic disease 12.5%) and 2 patients died. Significant difference was found in DFS between patients aged <30 years and those aged > 75 years (p=0.04).

In this study we demonstrated that the clinicopathological factors did not differ between younger and older age groups. Some recent studies report that older women have more advanced tumor stages at initial presentation, compared to younger patients [1-4]. We also documented that DFS in patients who were diagnosed before the age of 30 years was worse when compared with that of older women. Our data suggest that although other clinicopathological factors except age at diagnosis were the same, age does have some impact on long-term outcome of breast cancer patients [5].

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## Cutaneous metastasis from hepatocellular carcinoma

Dear Editor,

Cutaneous infiltration by malignant cells is a rare manifestation of hepatocellular carcinoma (HCC) and confers a dismal prognosis. A biopsy is essential to confirm the diagnosis [1].

A 68-year-old man presented to our Department with gradually worsening dyspnea, abdominal discomfort and loss of appetite. Clinical examination revealed no respiratory sounds in the right pulmonary base with stony dull percussion, conspicuous hepatomegaly and a firm, painless, nonulcerative, reddish skin lesion in his right shoulder measuring 2.5×2 cm in diameter. Chest X-ray revealed

right pleural effusion and thoracentesis was performed. Cytologic analysis of the effusion revealed metastatic adenocarcinoma. MRI of the upper abdomen was consistent with multifocal HCC, and the greatest lesion appeared in the segments VII and VIII measuring 9.5×8.5 cm. The MRI also revealed lytic bone lesions throughout the spine. His liver biochemistry classified him in Child-Pugh A category and  $\alpha$ FP was 62  $\mu$ g/L. Interestingly, his medical history was negative for hepatitis B and C infection. A core biopsy of the skin lesion was performed which was consistent with grade III metastatic carcinoma. Since the immunohistochemical features were hepatocyte paraffin 1 (HepPar1) strongly positive, TTF1 negative, CK5-6

negative and P63 focally mild positive, the skin lesion proved to be metastatic from HCC. The patient died 2 weeks after the diagnosis of HCC due to respiratory failure.

Extrahepatic metastases of HCC are unusual, with cutaneous metastases being extremely rare. Most reports are based on autopsy findings and in few case reports [2]. They may develop spontaneously or by seeding of tumor cells after percutaneous needle aspiration or ethanol injection therapy within the needle tract. They may also be encountered in the post-transplantation setting [3]. Cutaneous metastases confer a poor prognosis with a median survival of less than 5 months [2].

In Natsuizaka et al. study based on clinical records of 482 patients with HCC, metastasis to the skin was detected in only 4 patients (6.2%). The authors suggested that advanced intrahepatic tumor constitutes a risk factor for extrahepatic metastasis [1].

Peters stressed the association between cirrhosis in HCC and skin metastasis. Interestingly, skin metastases were found in 2.7% of cirrhotic patients with HCC while no such metastases were found in non-cirrhotic HCC patients [4].

A biopsy is always needed to establish the diagnosis. Histological examination may be difficult, given that the metastatic cells may be less differentiated than those of the primary tumor. Immunohistochemical assays are therefore needed to aid the diagnosis. HepPar1 is a G1k monoclonal antibody that recognizes a mitochondrial antigen expressed in normal and neoplastic hepatocytes. It is expressed in most adult HCC patients (82-100%), including fibrolamellar and clear-cell but not sclerosing variants, and in all hepatoblastomas. It has a reported specificity of 90% for HCC [5]. There-

fore, HepPar1 is a marker of hepatocellular differentiation which may be used for the diagnosis of cutaneous metastasis of HCC.

Medical oncologists should be alert and thoroughly examine HCC patients for skin nodules, even though cutaneous metastases are unusual.

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## Joint problems in breast cancer patients receiving adjuvant aromatase inhibitor

Dear Editor,

Breast cancer affects one in eight women during their lives. It is the second most lethal cancer in women just behind lung cancer. For many years, tamoxifen (TAM) was the cornerstone of endocrine therapy with a substantial body of evidence showing benefits in overall survival [1]. However, more recently, trials of aromatase inhibitors (AIs) have shown benefits over TAM in both metastatic [2,3] and subsequently in adjuvant treatment settings. The main advantages have been improvements in disease free survival and a more favorable toxicity profile, with lower rates of thromboembolic episodes and endometrial malignancy. The two main adverse effects of AIs were identified as a reduction in bone mineral density (BMD) and joint symptoms or arthralgia. In this study, we evaluated the breast cancer patients from our oncology clinic who were put on adjuvant AIs and developed joint problems as a side effect.

Two thousand female breast cancer patients treated at our Department between 2002 to 2011 were analysed. Of them, 1400 were treated with adjuvant AIs using different regimes (5 years TAM, then 5 years AI; 3 years TAM, then 2 years AI; or 5 years AI only). Their age ranged from 40 to 75 years (median 59). Out of this population, 200 (14%) developed arthralgia and 40 (3%) developed carpal tunnel syndrome. The mean onset of the arthralgia was 3 months. Pain was commonly found at the hands/wrist (62%), knee (60%), back (40%) and hip (37%).

The third generation AIs, anastrozole, letrozole and exemestane have become the standard of care in the management of both ear-

ly and advanced hormone-responsive breast cancer in postmenopausal women. Their main setback is the side effects they cause which include reduction in BMD and joint problems. It is postulated that these effects are caused due to the estrogen deprivation they cause in postmenopausal women. Oestrogens could be implicated in the pathogenesis of aromatase inhibitor-induced arthralgia (AIA) in a number of ways. For example, there is evidence that oestrogens may have an anti-nociceptive and pain modulating effects. This is particularly evident during pregnancy, when women have elevated thresholds for painful stimuli in the presence of increased levels of oestrogens.

Also, estrogen receptor (ER)- $\beta$  has been found in normal human synovia and therefore may have a role in the function of the synovial membrane. ER- $\alpha$  and  $\beta$  are found in normal cartilage, but are present at increased levels in osteoarthritic joints [4]. Type II collagen (CTX-II), the main structural protein of articular cartilage, may be influenced by oestrogens. Animal studies have investigated the effect of ovariectomy on cartilage turnover and degradation. Compared with controls, CTX-II correlated strongly with the severity of surface cartilage erosion ( $r = 0.74$ ,  $p < 0.01$ ). Thus, oestrogen deficiency is a process that may accelerate cartilage turnover and erosion. In fact, in a review, 11 out of 16 animal studies showed that ovariectomy resulted in cartilage damage. In a further rat study, type II collagen turnover was countered by the use of oestrogens, though other studies have shown variable results for exogenous oestrogen therapy [5].

It is clear that AIA remains an important clinical issue requiring further investigation. So far, the assumption is that oestrogen deprivation is the underlying pathological process, though the mecha-