product of collagen I degradation, have been observed in patients with BMs. The aim of this preliminary study was to evaluate the usefulness of TRACP5b, ICTP and bone alkaline phosphatase (BAP) in patients with BMs from BC.

Patients and Methods: A group of 11 women (median age 68 years, range 56−72 years) with BC and radiologically confirmed isolated BMs (cases), and a group of 14 age- and stage-matched women at the time of surgery without BMs (controls) were retrospectively reviewed. All patients serial measurement of TRACP5b, ICTP, and BAP. The cut-off values considered were 3.6 U/L, 4.2 U/mL, and 68 U/mL for TRACP5b, ICTP, and BAP, respectively. The odds ratios (OR) calculation with the 95% confidence interval (95% CI), the Fisher exact probability test, and the t-Student test were used to compare variables.

Results: The mean levels of TRACP5b, ICTP, and BAP (cases *vs.* controls) were 6.2±2.8 *vs.* 3.2±1.2 (t= 3.62, p = 0.0014) U/L, 8.3±6.4 *vs.* 4.2±1.6 (t = 2.32, p = 0.029) U/mL, and 151.3±98.6 *vs.* 72.5±26.4 (t = 2.87, p = 0.0085) U/mL, respectively. The corresponding OR were 7.20 (95% CI 1.06–48.64, p = 0.043), 6.41 (95% CI 1.09–37.73, p = 0.041), and 1.60 (95% CI 0.32–7.84, p = 0.42), respectively, while the OR for TRACP5b and ICTP together was 9.77 (95% CI 1.55–61.64, p = 0.014).

Conclusion: Our preliminary study shows that in patients with BC the elevation of both TRACP5b and ICTP correspond to a 9.8-fold higher risk of having BMs.

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Metastatic Breast Cancer − a Retrospective Analysis of Abdominal/pelvic Metastasis of Breast Origin

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Background: Breast cancer is the most common neoplasm in women, accounting for approximately 32% of women's tumors, with a life time risk of 1 in 10. Metastatic breast cancer is a heterogeneous disease with distinctive histological and biological features, clinical behaviours and therapy response.

The aim of study was to analyze the combined Estrogens (ER) and Progesterone (PgR) phenotypes and the Proliferation Index (Ki-67) in primary and in corresponding abdominal/pelvic metastases to compare biological features of the tumors.

Material and Methods: 21 patients with primary invasive breast cancer and corresponding abdominal or pelvic recurrences (1999–2009) entered to the study. Metastasis were localized: 16 in ovary, 1 in cervix, 1 in endometrium and 3 in omentum. Hormonal receptors were tested on 18/21 primary breast cancer and on 20/21 metastatic samples. Ki-67 was assesed on 13/21 primary breast cancer and on 19/21 metastasis. HercepTest was performed on 18/21 metastatic samples. ER, PgR and KI-67 status was classified according European guidelines. HER−2 was evaluated according to FDA-approved scoring system.

Results. Twelve out of 18 (66.6.1%) primary evaluable cases were ER+/PgR+ and 6 (33.4%) ER−/PgR-; whereas only 3/20 of metastatic sites resulted ER+/PgR+ (15%), 5 (25%) ER−/PgR+, 3 (10%) ER+/PgR- and 9 (45%) ER−/PgR-. 4/13 (30.7%) primary breast cancer and 7/19 (36.8%) metastatic cases had an high Ki67; moreover, 14 metastases were HER−2/neu negative whereas in 4 cases HER−2 was overexpressed.

Six patients (mean FU: 64 months; 12–120 months) had follow up data: after the first event, 5 were treated with Chemotherapy and Tamoxifene, whereas 1 was treated with Radiotherapy and Tam. Receptor expression was higher in primary than in secondary lesions and receptor-negative primary tumours showed receptor-negative recurrences.

Conclusions. Our data revelled that loss of ER and PgR expression in abdomen and pelvic recurrent breast cancer have high incidence. Moreover, breast cancer metastases, that arise from ER and PR positive primaries, fail to respond to endocrine therapy because of the development of ER negative lesions, indeed 30% of metastatic sites evidenced a triple negative (ER, PgR, HER−2/neu) status.

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Characteristics of Molecular Breast Cancer Subtypes Among Bulgarian Women

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Breast cancer is a heterogeneous disease from a clinical as well as biological point of view. Four molecular subtypes have been identified and have to be considered when decision for treatment is made.

The purpose was to compare the molecular subtypes by clinicopathological characteristics and prognostic value for female breast cancer in Bulgaria.

Data from the Bulgarian National Cancer Registry (BNCR) about female breast cancers, diagnosed in 2005–2009 were analyzed. All patients were followed-up until 01.01.2011. Four molecular subtypes were defined on the base of immunohistochemical status of estrogen (ER), progesterone (PR) receptors and HER2, recorded in BNCR database: Luminal A (ER+, PR+/−, HER2−); Luminal B (ER+, PR+/−, HER2+); HER2 (ER−, PR−, HER2+); TNBC (ER−, PR−, HER2−). Clinicopathological characteristics of the molecular subtypes − age, stage and grade were compared, using Chi-square test, Kaplan-Meier and Cox regression methods.

There were 18450 female breast cancers, registered in BNCR database and 9303 (51.4%) of them were classified into molecular subtypes. The proportions of Luminal A, Luminal B, HER2 and TNBC were 59.0%, 20.1%, 6.8% and 14.1%; five years survival was 78.7%, 75.1%, 61.7% and 67.2% respectively. The molecular subtypes differ by age, stage and grade ($p < 0.0001$). The risk of death was lower ($p < 0.0001$) for Luminal A (with 48%) and Luminal B (with 42%), compared with TNBC, after adjusting for age, stage and grade. HER2 and TNBC showed similar prognosis ($p = 0.427$).

The comparison of molecular subtypes showed clear differences in clinicopathological characteristics. The prognosis was better for Luminal A and Luminal B types. The lack of difference in prognosis between HER2 and TNBC types can be explained with relatively recent introduction, in 2008, of adjuvant treatment with trastuzumab for Bulgarian women.

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Bone Management by Bisphosphonate in Metastatic Breast Cancer Patients

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Background: Bone is one of a common involved site of metastasis in advanced breast cancer patients. Bisphosphonate (BP), especially zoledronate (ZOL) is regarded as not only an essential key tool to reduce skeletal associated events but also improve patients' survival.

We reviewed metastatic breast cancer (MBC) cases with the aim of evaluating improvement of patients' survivals and quality of life (QoL) by BP use.

Patients and Methods: From October 2002 to September 2011, 459 patients were diagnosed as MBC. Most of patients (345/459, 75.2%) were recurrent disease, and the rest (114, 24.8%) were primary advanced disease. Receptor statuses were as follows; estrogen-receptor positive (ER+) 63.2%, HER2+ 26.6%, triple-negative 13.3%. Patients who had bone metastasis (BM) at the time of diagnosis were 37.7% of MBC patients. BP administration was considered in patient having or newly developed BM to manage her bone lesion. Concomitant chemo-, endocrine or radiotherapy was performed in practical manners. After approval of ZOL in Japan (mid 2006), all of the patients who had been already given pamdronate or incadronate, were changed to receive ZOL.

Results: Total 296 patients, 64.5% of MBC patients, including patients who were BM-free at the initial diagnosis of MBC, were diagnosed as having BM. Estrogen receptor was positive in 77.4% of patients. About one-third of the patients complained bone pain at the time of BM diagnosis. Median survival time (MST) for all MBC patients was 1376 days, and there was no difference of MST between patients BM+ or BM-. Among BM+ patients, there was no significant difference of MST between having and not having bone pain at the time of BM diagnosis. BP was administered in 218 (73.6%) of BM+ patients and improved their MST from 1315 to 1461 days compared with BP non-users including BM- patients, although, there was no statistical significance ($P = 0.0721$).

Conclusions: As De La Haba *et al* previously displayed (2010 ASCO abstr. 630) appropriate ZOL use improves BM+ patients' survival. In the same manner, our retrospective observation showed a trend of survival benefit from BP. These facts confirm bone management by ZOL is

mandatory in MBC patients to improve their QoL, and will result in maintaining performance status and continuing chemotherapy.

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Patterns of Care and Outcome of Locally Advanced Breast Cancer

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Background: Locally advanced breast cancer (LABC) comprise 5−10% of breast cancer cases. We present a review of practice patterns and outcomes in patients with LABC treated at our institution.

Patients and Methods: We reviewed 120 consecutive patient file records treated at our institution for LABC between 1998 and 2007.Patient and disease characteristics, treatment-related data and patterns of relapse were collected.

Results: Patients' median age was 49 years (range: 28−84 years). Median tumor size at diagnosis was 7cm (range (1−11 cm). Histology showed invasive duct carcinoma in 68% and invasive lobular carcinoma in 9.3% of patients. Estrogen receptors were positive in 67% and progesterone receptors were positive in 58% of the patients. In 31% HER2/new was over-expressed and 13% of the patients were triple negative. Nineteen patients (6.3%) underwent sentinel lymph node biopsy at diagnosis. Eighty-five percent of the patients received preoperative chemotherapy (CT) and 15% received hormonotherapy (11% aromatase inhibitors and 4% tamoxifen).Primary CT was antracycline-based in 37% and anthracycline followed by taxanes in 48% of the patients. Fourteen percent of the patients received Trastuzumab before surgery.

Type of surgery: 39% of the patients underwent lumpectomy, 56% had unilateral mastectomy and 3% preferred bilateral mastectomy. Tumor size was reduced to a median of 1cm (range: 0−10 cm).

Post-treatment pathological findings: 15% of patients showed no residual tumor (pathological complete response) and 42% had negative axillary lymph nodes. All patients received adjuvant radiotherapy and patients with hormone receptors positive received adjuvant hormonal therapy. At a median follow-up of 4 years (range:1−13), 67% of the patients had no evidence of disease, 10% developed local recurrence, 31% developed distant metastasis, 2% developed secondary breast cancer and 7% developed secondary non-breast malignancy. Median survival time was 11 years (range:8−10 years) with 5-year survival rates of 76%.

Conclusions: Management of LABC at our institution is consistent with the current clinical guidelines. In our patients, local recurrence rate was low (10%) and 31% of patients developed distant metastasis. In order to improve the LABC patients' outcome, it is mandatory to increase population awareness to early tumor detection and to optimize systemic treatment strategies according to histological subtypes.

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Oral Vinorelbine (VNR) and Capecitabine (CAP) − an Acceptable and Effective Combination Chemotherapy for Early Metastatic Breast Cancer (MBC)

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Background: Most guidelines recommended a sequential single agent approach for MBC because of toxicity with combinations. At our centre practice is divided between doctors, providing an opportunity to compare approaches. First line taxane-capecitabine is used, but severe toxicity limits its use to fit patients. The combination of oral vinorelbine (VNR) and capecitabine (CAP) has demonstrated additive efficacy with good tolerability, providing a combination option for patients not prescribed the taxane combination due to poor performance status (PS) or patient preference. We compared toxicity and efficacy of this combination with the same agents used sequentially.

Methods: An observation study of patients with MBC treated with 1st/2nd line oral VNR and CAP combined as a doublet or given sequentially. Combination dose: VNR 60−80 mg/m^2 day 1,8 q21 plus CAP 1000 mg/m^2 bd days 1−14, q21 for a maximum of 9 cycles; sequential dose: CAP 1250 mg/m^2 bd d1−14, q21, VNR 60−80 mg/m^2 day 1,8 q21, both given until disease progression. Patients were reviewed every 3 weeks and outcome and toxicity recorded.

Results: Between Oct07 and Jan11 33 patients whose PS or preference precluded a taxane doublet received the doublet. Outcomes were compared with 30 patients who received the agents sequentially. Doublet/singlet mean age 59/57.5 yrs and median PS 2/1. Most treatment was 1st line metastatic (64%/83%). Two patients unfit for FEC received the doublet adjuvantly. Median cycles: doublet 4.5/CAP 6/VNR 5; dose delays doublet 23%/CAP 10%/VNR 20%. Severe (G3/4) toxicity was generally less frequent with the combination than either single agent. G3/4 toxicity, doublet/CAP/VNR: haematological 11%/4%/29% (no neutropenic sepsis); gastrointestinal 0%/8%/4%; dermatological 0%/13%/0%; other non-haematological 0%/0%/13%. One patient stopped treatment due to erythema multi-forme (EM) and one due to palmar-plantar erythrodysesthesia (PPE). PFS (n = 16): doublet 6 m (range 0−31 m); CAP-VNR (n = 11) 7 m (range 3−29 m), VNR-CAP (n = 2) 17 m. Response rate for doublet: 50%. No response data available for single agent.

Conclusions: All-oral combination of VNR and CAP demonstrates effectiveness and good tolerability with minimal severe toxicity. G3/4 haematological toxicity and G3 PPE were less frequent with the doublet than with single agent VNR and CAP. The low incidence of PPE has been noted in previous phase II studies. Most patients find the combination acceptable, even those with poor PS. Our findings warrant further investigation in a randomised study to challenge the standard premise of sequential single agent therapy in MBC.

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Does 'PDO' Deserve T4b Status in Early Breast Cancer?

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Background: Clinically apparent skin involvement (T4b) in breast cancer is a morphological criterion for staging patients in the highest non metastatic stage (stage III B) irrespective of tumor size. This heterogeneous group shows inconsistency as a prognostic variable and hence results in a non-homogenous grouping of patients with different outcomes.

Material and Methods: A retrospective analysis of prospectively maintained computerized breast cancer database in Department of Surgical Oncology, AIIMS, New Delhi was carried out from 1995–2008. Inclusion criteria for the current study were tumor size less than 5cm (T1/T2) and pathological nodal involvement less than 4 nodes (pN1). Patients who received Neoadjuvant Chemotherapy were excluded from analysis. The study group was patients with T1/T2 tumors with clinical skin involvement (Ulcer,PDO), pN1 stage taken for upfront surgery. The control group was T1T2 patients without clinical skin involvement.

Result: Total 71 patients with PDO were compared with 695 early breast cancer patients in the control group. The distribution of age, tumor size, nodal burden and Hormone receptor positivity, and adjuvant therapy was comparable in both groups. There was no statistically significant difference in recurrence rates, disease free survival, and overall survival in patients with or without PDO in the two groups.

Conclusion: Presence of PDO does not impact survival in patients with small tumors and limited nodal disease. Patients with ulcer have significantly poor outcomes. Using PDO to classify breast cancer patients with small tumors as stage III B results in a heterogeneous grouping of patients with different survival outcomes.

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Bone Marrow Micrometastases in Breast Cancer. Changes in Hematologic Parameters

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Background: Bone marrow plays the key role in distant metastases formation and at the same time has no clinical symptoms. The purpose of the study was to define a complex of changes in hematologic parameters, associated with bone marrow micrometastases (BMMM) in breast cancer (BC) patients.

Material and Methods: Fifty patients with breast cancer treated in the Ulyanovsk regional oncology center were recruited into the trial. 37 patients (74%) had distance metastases, other 13 (74%) − locally-advanced disease. Bone marrow was obtained by biopsy from both anterior iliac crests under local anesthesia and was studied by cytological, histological and immunocytochemical (ICC) methods. The analyses was made using monoclonal antibodies against cytokeratins PAN, clone MNF 116, DAKO. Positive test was defined as detection of 1 metastatic cell per million myelokaryocytes. In ICC-positive cases we also determined tumor cell receptor status and proliferative activity with Ki-67.

Results: Nineteen (38%) of the 50 BC patients presented with BMM. The bone marrow involvement was detected more frequently (12/19) by ICC. Combinations of diagnostic techniques failed to improve detection of BMMM. Of the 12 cases with bone BMMM detected by ICC all had receptor-negative tumor cells and low Ki-67 expression. Bone metastases were discovered in half of patients free from bone marrow involvement. 26.7% of patients with non-skeletal metastases were bone marrow-positive.