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Special histologic subtypes of estrogen receptor positive breast cancer by quantitative RT-PCR

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Background: Invasive estrogen receptor positive (ER+) breast carcinoma is morphologically characterized by many histologic subtypes. Some special histologic subtypes have been reported to be prognostically significant (Rosen, 2009). We report here the histologic subtypes of estrogen receptor positive breast carcinoma and their associated patterns of observed gene expression as measured by the 21 quantitative gene Oncotype DX® assay.

Material and Methods: 100,000 tumor specimens successfully examined in the Genomic Health laboratory from July 2005 through May 2009 were included in these analyses. Academic surgical pathologists reviewed all specimens for invasive carcinoma and categorized them by histologic subtype using World Health Organization criteria (IARC 2003). Quantitative expression of 16 individual cancer related genes was measured on a scale from 0 to 15 (relative to reference genes), where a one unit increment is associated with a approximate 2-fold change in expression. Recurrence Score (RS) was calculated using the published equation (Paik et al, NEJM 2004). Descriptive statistics for the RS and the individual genes [estrogen receptor (ER), progesterone receptor (PR), HER2, invasion gene expression (IGE) and proliferation gene group (PGG): ki-67, cyclin b1, survivin, STK15, MYBL2] among the different subtypes were obtained.

Results: The vast majority of the cancers (94.3%) were ductal, lobular, or mixed. Using ducial carcinoma as the comparator, papillary carcinoma had the highest ER (10.9) and PR (9.2) with low IGE and lowest RS. Medullary-like tumors (4.8 per 1000 cases) had the lowest ER, negative PR, higher PGG and highest RS which may make them more responsive to chemotherapy. The RS, on average, was lower for the classic lobular, mixed ductal/lobular, solid/alveolar lobular, tubular, cribriform, mucinous, and papillary subtypes. The special histologic subtypes (tubular, cribriform, mucinous) were characterized by higher PR, lower IGE, lower PGG and higher ER (except for tubular carcinoma that may reflect bias in submission for RS testing).

Conclusion: Histologic subtypes are characterized by differential gene expression profiles. The special subtypes of invasive breast cancer tend to have higher ER, PR and lower proliferation and invasion gene expression; however, outlier cases are not infrequent within each of the special subtypes of invasive breast cancer in this large observational cohort of estrogen receptor positive tumors.

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Frequency of low ER-positive tumors by RT-PCR in patients with low recurrence scores in Europe and Middle East

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Background: The Recurrence Score (RS), derived from the quantitative RT-PCR analysis of 21 individual genes, has been shown to quantify the likelihood of distant recurrence and of chemotherapy benefit in hormone-treated patients with estrogen receptor (ER)-positive breast cancer. We examined the frequency of low Recurrence Scores (<18) in the lowest quartile of ER-positive expressing samples submitted for Oncotype DX® testing in Europe and Middle East (EME).

Material and Methods: Since January 2006, a quantitative ER value has been provided with all RS results. Tumor specimens submitted by EME physicians that were successfully examined in the Genomic Health laboratory from February 2008 through October 2009 were eligible. Quantitative expression of 16 individual cancer related genes was measured by the pre-specified 21 gene Recurrence Score assay on a scale from 2 to 15 (relative to reference genes), where a one unit increment is associated with an approximate 2-fold change in expression. ER status by RT-PCR (with ER positivity prespecified as ≥6.6) has been shown to be highly concordant with ER by Central IHC (93% in Badve et al, JCO, 2009; 96% in Habel, ASCO Breast 2007). For the ER pos tumors by RT-PCR, the RS by risk group was analyzed by quantitative ER by quartiles.

Results: 2,645 tumors were eligible for analysis, 29 cases were excluded from the analysis because they were ER-neg by RT-PCR, leaving 2,616 evaluable tumors. The distribution of quantitative ER by quartiles for the low (<18), intermediate (18–30), and high (≥31) RS groups is shown in the Table. Of the 652 samples in the lowest ER-pos quartile, ER values ranged from 6.6–9.1 and 31.9% of these low ER-pos expressing tumors had RS <18.

Er					RS group		
Quartile	Min	Max	Average	Number	Low	Intermediate	High
1	6.6	9.1	8.5	652	31.9%	54.3%	13.8%
2	9.2	9.9	9.6	653	56.4%	35.4%	8.3%
3	10	10.7	10.3	684	65.1%	26.6%	8.3%
4	10.8	12.5	11.4	627	69.4%	21.5%	9.1%

Conclusion: Many low ER-pos expressing tumors have low Recurrence Scores. However, patients with a RS <18 have been shown to have a good prognosis and minimal, if any, chemotherapy benefit. (Paik et al., JCO, 2006; Albein et al., SABCS 2007). The Recurrence Score incorporates other important biological pathways beyond ER that provide additional clinically meaningful information.

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Ductal carcinoma in situ of the breast: interobserver reproducibility of three classification schemes

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Background: Several systems have been proposed for the classification of ductal carcinoma in situ of the breast (DCIS). The objective of the study is to determine the degree of diagnostic agreement among pathologists between three DCIS classification systems.

Material and Methods: 43 cases with a diagnosis of DCIS were reviewed by two pathologists and selected for interobserver analysis. Thirteen pathologists, one of them a specialist in breast pathology, received the same set of digitized images of microscopy of the DCIS cases in JPG format, and answered a questionnaire containing the criteria to compose the three classification systems studied – Holland, modified Lagios and Van Nuys. For this purpose a computer program was created, which organizes the information collected from each pathologist, supplying the histological grading of the cases for the three classification systems. The results were analyzed using percentagewise agreement and the Kappa test.

Results: Diagnostic agreement for the three DCIS of the breast classification systems presented K values that varied from 0.27 to 0.37. Among the three classifications studied the best agreement was for Van Nuys, showing a Kappa index of 0.37. Analysis of subgroups of pathologists showed that there was greater diagnostic reproducibility for the group of specialists compared to the group of pathology residents for the Van Nuys and modified Lagios systems ($p = 0.005$ and 0.023, respectively). The accuracy similarly accompanied the results of the interobserver agreements, with Kappa indices varying from 0.13 to 0.84 for the Holland classification, 0.23 to 0.81 for the modified Lagios classification, and 0.23 to 0.74 for the Van Nuys classification.

Conclusion: Comparing the three classification systems, better agreement was obtained for the histological grade with the Van Nuys scheme. Pathologists specialized in breast pathology showed greater reproducibility for all the criteria evaluated. Diagnostic accuracy was superior for the classification of Van Nuys compared to modified Lagios and Holland.

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Reasons for over- and underestimation of lymphatic vessel invasion in breast cancer

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Background: Lymph vessel invasion (LVI) can be decisive for treatment and prognosis of breast cancer patients but often it is over- or underestimated in the routine practice.

Aim of our study was to establish the reasons leading to over- or underestimation of LVI in breast cancer, which occur in the routine practice and to create a reliable and applicable protocol for its appropriate evaluation.

Materials and Methods: Archival formalin-fixed, paraffin embedded tissue materials from 40 cases of invasive breast cancer were randomly selected and revealed from the archives of our department. The breast cancer specimen had been processed according to standard laboratory protocols. Tumors had been classified and staged according to the WHO criteria. Immunohistochemic staining with D2–40, according to protocol of the manufacturer DAKO® was used to selectively mark lymphatic vessels. Statistical analysis was performed using the chi-square test, calculated by Statgraphics Plus®.

Results: The possibility for peri-tumor lymphatic evaluation depended significantly on the amount of peri-tumor tissues analyzed χ^2=14.48; p = 0.0007 (n = 40). In general, the presence of LVI correlated with axillary lymph node (LN) status χ^2=8.37; p = 0. 0116 (n = 40). When analised in more than 3 mm of peri-tumor tissues, LVI matched significantly better with axillary LN status than when analyzed in peri-tumor tissues less than 3 mm wide χ^2=8.65 p = 0.0343; (n = 35). D2–40 played decisive role in the differentiation of LVI from post-fixation tumor tissue shrinkage.

Discussion: We believe that underestimation of lymphatic invasion in breast cancer can be reduced by evaluation of at least 3 mm of peri-tumor tissues. Overestimation can be practically avoided by the application of specific endothelial marker. The application of large section technique may be the most appropriate approach for LVI evaluation in breast cancer.

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Turnaround-time reduction of pathological examination

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Background: Reduction of waiting time is very important for patient service because short turnaround time (TAT) of pathological examination allows for rapid response including medical decision-making by clinicians that may increase patient satisfaction. Pathological examination of breast specimens tends to take longer TAT because breast tissue contains abundant fat and its diagnosis routinely requires results of IHC staining. To shorten the TAT of breast cancer cases, improvements of routine work and rescheduling of procedures have been performed in our hospital.

Material and Methods: 202 breast cancer specimens, performed surgical resection (preservation resection or mastectomy) from 2007 November to 2008 May, were typically examined according to the protocol as follows. Specimens were fixed with formalin injection immediately after tissue removal. On the second day, tissue specimens were cut for pathological samples, and samples for IHC (ER, PgR, HER2) were selected at the same time. The whole of the cancer areas including intraductal spread was cut for pathological examination. After cutting sections, fixation and delipidation were accelerated by supersonic wave and thermostat bath. On the third day, pathological reports with results of IHC and digital images (demarcated cancer area with separate colors accordingly invasive or non-invasive lesions) were submitted to clinicians through electronic-pathology-data-record system (Dr. Helper, FUJITSU, Japan). In our pathology section, there are two full-time pathologists and six technicians.

Results: Average number of slides was 36.2/case (excluded LN samples). In 202 cases, TAT's (after-operation days, excluding holidays) were consumed to complete each diagnosis as follows, 2 days for 78 (38.6%); 3 days for 89 (44.0%); 4 days for 25 (12.4%); 5 or more days for 10 (5.0%) cases. Less than 20% of all cases required 4 or more days mainly because of necessity of additional samples and staining.

Conclusions: In more than 80% of the surgical cases, final pathological reports including result of IHC and digital images were completed within three days after operation. To compare with previous period before practice of this protocol, average TAT of breast cancer cases was obviously shortened. These procedures do not need special equipment or extra manpower and thus this protocol for breast cancer specimens is available in other laboratories.

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Characteristics of invasive micropapillary carcinoma of the breast: Is it related to the triple negative breast cancer?

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Background: Invasive micropapillary carcinoma (IMPC) of the breast is a rare and associated with high incidence of lymph node metastasis and poor outcome. The aims of this study were to provide a comprehensive analysis of clinicopathologic and immunohistochemical characteristics of IMPC and to elucidate the differences between IMPC and invasive ductal carcinoma (IDC).

Methods: Sixty-one patients of IMPC were identified by retrospective review of database from Jan 2004 to December 2008. 221 patients were randomly selected among the IDC patients who received operation during the same period. Two groups were compared with uni- and multi-variate analysis.

Results: We observed significant differences in mean number of metastatic lymph nodes (6.1 vs. 1.9, p = 0.001), positivity of lymph node (70.6% vs. 45.2%, p < 0.001), and presence of lymphatic vessel invasion (75.4% vs. 34.8%, p < 0.001) between IMPC and IDC patients. Although it has been known that triple negative breast cancer (TNBC) have lymphotropic tendency in their early T stage, 11.8% (26/221) of IDC and 3.3% (2/61) of IMPC patients were TNBC in this study (p = 0.050). In multiveriate analysis, IMPC histology showed no correlation with disease-free survival (DFS) and the lymphatic vessel invasion was a significant predictor of DFS.

Conclusions: The results of this study confirm that IMPC is unique subtype of breast cancer that is commonly accompanied by axillary lymph node metastasis and shows poor outcome, although it rarely presents the pattern of TNBC. Lymphatic vessel invasion rather than histology of IMPC seems to be more closely related to DFS.

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Basal-phenotypes in breast carcinoma - morphological, immunohistochemical and clinical analysis

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Background: The basal-like breast cancer sub-type represents probably a new treatment challenge for oncologists. The aim of the study was to analyse morphological, immunohistochemical and clinical features in breast invasive carcinomas which diagnosed as basal-like type of invasive ductal carcinoma (BLIDC) from needle core biopsies (NCB).

Methods: We reviewed 21 (11.7%) breast carcinomas (20 primary ones (T1-T4) and one after 7 years recurrence carcinoma (r T1) for hematoxylin-eosin slides, immunohistochemistry for ER, PR, HER-2, CK 5/6, CK17, CK 18, p53, *BRCA1* testing, clinical information. Morphological aspects as architectural features (sheets, nests, tubular formation, ribbon-like formation), intensity of lymphocytic infiltration, necrosis, fibrous and/or hyalinised stroma, nuclear pleomorphism, mitoses has been studied. Semiquantitive evaluation of basal cytokeratine positive cancer cells has been performed. Overexpression of p53 cases has been examined.

Results: BRCA1 cases of BLIDC (3/21) were triple negative and just a case overexpressed p53. All sporadic BLIDC (18/21) were ER, PR negative but 3 cases were 3+ scored and 4 cases 2+ scored for HER-2. Overexpresion of p53 was noted in 11/18 carcinomas. At least one basal cytokeratin CK 5/6 or CK17 was positive in all cases. 5–30% cancer cells expressed CK 5/6 in 53% BLIDC and there were more than 30% positive cells in 29% BLIDC. CK 17 was expressed in 10–30% neoplastic cells in 36% BLIDC and more than 30% positive cancer cells were noted in 56% cases. CK 18 was positive in all BRCA1 cases and 75% sporadic cases carcinoma cells.

Conclusions: CK 17 is recommended as first basal marker in NCB for immunohistochemical confirmation of basal-like type when amount of cancer cells is small.

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The prognostic factors of breast cancer related with axillary lymph node metastasis in T1 breast cancer

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Background: Axillary lymph node metastasis can occur even in breast cancer sized less than 2 cm. There are several prognostic factors related to the lymph node metastasis in breast cancer. We aimed to investigate the clinicopathologic factors that affect the node metastasis in T1 breast cancer. **Methods:** We reviewed the medical records and pathologic reports of all breast cancer patients who had undergone surgical procedure from 2001 to 2006. Among these patients, we retrieved 230 T1 breast cancer patients divided them into two groups according to the presence or absence

Conclusion: The aim of the pilot study is one of education, with the key objective to promote improvement in the quality of diagnostic HER2 ICC interpretation.

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Audit of breast biomarkers markers, HER2.ER & PR in the UK: an update by the UK National External Quality Assessment Scheme for Immunocytochemistry and In Situ Hybridisation (UK NEQAS ICC & ISH)

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Objective: Between 2007 and 2008, UK HER2 positivity rate was on average 15% (range 9–35%). Since 2008, a Web-based breast biomarker database has been established, allowing users to input HER2 IHC/ISH and ER and PR results.
Method: Individual laboratories are requested to input their HER2 IHC/ISH, ER and PR ICC results directly into a secure web database.
Results: The current UK HER2 positivity rate remains at 15%. Individual ER and PR data show the average positive rates to be 82.3% and 68.7%, respectively. The UK audit showed the following breast biomarker status (1) ER+/PR-/HER2+ (60.5%) (2) ER-/PR-/HER2- (12.3%) (3) ER+/PR-/HER2- (11.0%) (4) ER+/PR+/HER2+ (6.2%) (5) ER-/PR-/HER2+ (5.1%) (6) ER+/PR-/HER2+ (3.1%) (7) ER-/PR+/HER2- (1.3%) and (8) ER-/PR+/HER2+ (0.4%).
Conclusion: The audit database has provided individual UK laboratory and overall UK breast biomarker status. In some cases the audit has led to laboratories re-testing their cases. The data also provides insight into whether such cases of ER-/PR+/HER2- (1.3%) and ER-/PR+/HER2+ (0.4%) are genuine or due to other pre-analytical or analytical phases as indicated by previously published studies.

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Immunocytochemical staining of breast biomarkers HER2, ER and PR; potential pitfalls of false positive/negative staining: findings of the UK NEQAS ICC & ISH

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Objective: Breast HER2, ER and PR are routinely used in diagnostic immunohistochemistry. Many laboratories use commercially available standardised HER2 IHC kits, however, few laboratories use a 'standardised kit' for ER & PR, with a 'home-brew' method being the method of choice. This study highlights the results obtained from UK NEQAS HER2 ICC, ER & PR assessments.
Method: Unstained HER2 cell lines and ER/PR tissue sections are distributed on a quarterly basis for participants to stain and, return for assessment by a panel of expert assessors.
Results: HER2 ICC pass rates continue to improve, with participants using a standardised HER2 ICC kit showing a pass rate of 81% compared to 43% for those using a 'home-brew' method. With ER the for poor performance is mainly due to false negative staining of mid expressing ER tumours. In contrast, poor performance PR assessments tend to be due to false positive staining of PR negative tumours. This was principally observed with the rabbit monoclonal SP2 antibody, whose usage by NEQAS participants has decreased from 11% (2006) to 1% (2011).
Conclusion: There is still more scope for improvement in breast biomarker immunocytochemistry, with laboratories encouraged to validate their methodologies and include proper control material to gauge the sensitivity and specificity of the ICC methods.

033

Single detection kit, double antibody cocktail (D2-40 p63) protocol for identification of lymphatic vascula invasion in breast tissues containing extensive intra ductal/-lobular tumour growth

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Objective: When accessed on D2-40 stained slide lymphatic vascular invasion may present interpretatic difficulty, especially in breast tissues containing extensiv intaductal/-lobular tumour growth because of the positivi observed in both lymphatic endothelial cells (LECs) a myoepithelial cells (MECs). The available multiple sta detection kits are time and resource consuming. The aim this study was to develop an antibody cocktail (D2-40/p6 single detection kit protocol for identification of lympha vascular invasion in breast tissues.
Method: Formalin-fixed, paraffin embedded tissues fr 130 breast cancer patients were examined. Immunostaini was analysed in corresponding fields of consecutive tiss slides, stained according to standard protocols with D2- p63 and D2-40/p63 cocktail, single detection kit.
Results: When stained with D2-40/p63 cocktail, lymph vessels demonstrated "continuous" intermediate to str cytoplasm staining (LEC reactivity for D2-40) reac distinguishable from the "bead-like" staining observed MEC of distorted duct lobular units (weak to miss cytoplasm D2-40 staining, strong p63 nuclear stainii The suggested antibody cocktail proved to be m effective than D2-40 alone in the identification of lymph

vascular invasion in cases containing extensive intraductal/-lobular tumour growth.
Conclusion: The suggested staining protocol enabled an effective interpretation of the nature of tumour cell harbouring D2-40 positive structures in all studied cases.

034
Breast carcinoma with neuroendocrine differentiation: clinicopathological features in five cases
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Objective: Primary breast carcinomas with neuroendocrine differentiation are rare tumors. This tumor has controversial results in terms of its prognosis and treatment approaches.
Method: Five neuroendocrine breast carcinoma cases immunohistochemically positive for synaptophysin and/or chromogranin in more than 50% of tumor cells were evaluated in terms of their clinicopathological and immunohistochemical features. None of the cases had tumor focus in non-mammary sites.
Results: All patients were women and aged from 40 to 81 years. In all cases, tumors were unilateral with a diameter ranging from 1.5 to 3.5 cm. Two of five cases showed multifocality. All tumors were evaluated as nuclear and histological grades 2. Tumors were classified as solid cohesive in 2, solid papillary in 1, cellular mucinous in 1 and invasive ductal carcinoma with psammomatous features in 1. All tumors included solid or cribriform type in situ ductal carcinomas with or no necrosis. All tumors showed strongly and widely distributed estrogen and progesterone receptors positivity. None of the tumors displayed Her 2/neu overexpression. Lymphovascular invasion and axillary lymph node metastasis were not determined in any cases.
Conclusion: It should be kept in mind that neuroendocrine differentiation can appear in several histological patterns such as mucinous differentiation, papillary/micropapillary formation, solid-nested growth. Therefore, any breast tumor with this morphology should search carefully for neuroendocrine markers.

035
Expression of Tenascin-C in correlation with Sox2, Nanog, BMI1 and Oct4 expression in breast cancer
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Objective: Tenascin-C (TNC) is a glycoprotein in the extracellular matrix which reappears in the condition of wound healing and some neoplasms such as breast cancer. Therefore, we investigated the connection between TNC and transcription factors and proteins which are involved in the self-renewal in cancer stem cells.
Method: Paraffin sections from 120 breast cancer patients were used for automated immunohistochemistry (IHC) with two different antibodies targeting TNC. Postive paraffin sections for one or both TNC- antibodies were screened for Ki67, Nanog, Oct4 and Sox2 and BMI1. IHC positive breast cancer cell lines were stained on cell slides with Ki67, Nanog, Oct4, Sox2 and BMI1. The expressions of TNC, Nanog, Oct4, Sox2 and BMI1 of these breast cancer cell lines were also analyzed in rt-PCR.
Results: A total of 50 paraffin sections were positive for one or both TNC antibodies as well as for Nanog, Oct4, Sox2 or BMI1. The rt-PCR experiments with TNC positive breast cancer cell lines presented also a high expression rate of Nanog, Oct4, Sox2 and BMI1.
Conclusion: These results reveal a correlation between Tenascin C and Nanog, Oct4, Sox2 and BMI1 which are involved in self-renewal of cancer stem cells.

036
Angiogenesis-associated parameters in metastatic breast carcinoma: correlation with the MAPK and Akt pathways, proliferation and apoptosis
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Objective: Vascular endothelial growth factors A (VEGFA) and C (VEGFC) and their receptors VEGFR1, VEGFR2 and VEGFR3 are expressed in neoplastic cells. The aim of our study was to investigate for relations between factors of angiogenesis, the MAPK and Akt pathways and parameters of cell proliferation and survival in metastatic breast carcinoma (MBC).
Method: Tissue microarrays consisting of duplicate, 1.5-mm cores from 72 MBCs were immunostained for VEGFA, VEGFC, VEGFR1, VEGFR2 VEGFR3 phospho-p44/42MAPK, phospho-Akt1/2/3, phospho-S6 ribosomal protein, bcl-2 and Ki-67. The immunoreactivity was assessed by H score, except for Ki-67 where the percentage of positivity was recorded. Pearson correlations between parameters were calculated by SPSS 16.0.
Results: VEGFA was correlated with bcl-2 (p=0.001, R=0.402), VEGFC with Ki-67 (p=0.001, R0.386) and VEGFR1 (p=0.017, R0.280), VEGFR1 with VEGFR3 (p<0.001, R0.416) and phospho-S6 protein with VEGFR1 (p=0.002, R0.361), VEGFR3 (p=0.002, R0.360) phospho-Akt (p=0.01, R0.301), phospho-p44/42MAPK (p<0.001, R0.506) and Ki-67 (p=0.021, R0.274).

J Biomed Clin Res Volume 3 Number 2, 2010

Original Article

ACTIVATED LYMPHOCYTES ASSOCIATED TO THE LYMPHATIC VASCULAR WALL MAY CAUSE OVERESTIMATION OF LYMPHATIC ENDOTHELIAL CELL PROLIFERATION IN BREAST CANCER

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Summary

Proliferation of lymphatic endothelial cells (LEC) is often assessed using the Ki-67 nuclear proliferation marker. The presence of proliferating (activated) lymphocytes associated with the lymphatic vascular wall may obscure the results from evaluation. The main aim of the retrospective study was to compare LEC proliferation in breast cancer to that of non-cancerous mammary tissue in the context of possible Ki-67 positivity of activated lymphocytes. The study was carried out on 23 representative paraffin- embedded tissue samples from invasive breast cancer and 12 representative samples from non-cancerous mammary tissue. LEC proliferation was quantified and compared in the context Ki-67 positivity of lymphocyte infiltrates. In cancer, there was a significant difference at the 0.05 level of the distributions of the total number of Ki-67-stained cell nuclei, and those verified as proliferating lymphatic endothelial cells alone p=0.041. When compared, the median values for LEC proliferation in non-cancerous mammary tissue did not differ from those of LEC proliferation in breast cancer W =154.0; p=0.547; n=20. LEC proliferation was not associated with the lymph-node status (t= - 1.43; p=0.171; n=19). The protocol suggested for LEC proliferation in breast cancer may be more accurate and may eliminate some factors that obscure the overall results from evaluation.

Key words: overestimation, lymphatic endothelial cell proliferation, breast cancer

ИМУНОХИСТОХИМИЧНО ПРОУЧВАНЕ НА СЪДОВЕТЕ ПРИ ФЕНОМЕНА „СЪДОВЕ В СЪДОВЕТЕ", НАБЛЮДАВАН ПРИ ХИСТОЛОГИЧНИ МАТЕРИАЛИ ОТ МАМАРЕН ПАРЕНХИМ

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IMMUNOHISOCHEMICAL EVALUATION OF THE PHENOMENON "VESSELS WITHIN VESSELS" IN HISTOLOGICAL SPECIMENS FROM BREAST PARENCHYMA

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РЕЗЮМЕ

Феноменът „съдове в съдовете" е описан за пръв път от Merchant S. и сътр. в хистологични материали от матка и гърда. Според данните от това проучване съдово-съдовите комплекси в миометриума се състоят от венозни съдове в лумена, на които се откриват артерии.

Поради това, че същността на този феномен понастоящем е несигурна, решихме да проучим имунохистохимично „съдовете в съдове", наблюдавани в мамарния паренхим, за да определим тяхната същност и морфология.

Изследването е проведено върху 130 архивни материала от мамарен паренхим със специфични ендотелни маркери – D2-40 и CD34.

„Съдовете в съдове" са наблюдавани в 16 (8.13%) от изследваните материали. Установи се, че съдовите комплекси са изградени от голямокалибрен "външен" лимфен съд и протрузия на мамарна строма, с централно разположена артериола, намираща се в лумена на по-големия „външен" съд. Установи се, че протрузиите в лимфатичния лумен са в състояние да редуцират лумена на относително голямокалибрени колекторни лимфатици до размера на преколекторни лимфатици. В случаите на туморна емболизация на голямокалибрените лимфни съдове феноменът „съд в съда" е трудно установим, тъй като стромал-

Съдово-съдовите комплекси вероятно функционират като динамични регулаторни клапи, регулиращи лимфния дренаж и/или помпен механизъм. Смятаме, че потенциалът на лимфния дренаж при гърдата трябва да се оценява и функционално, а не единствено морфологично. От морфологична гледна точка тези съдово-съдови комплекси се явяват сериозен замъгляващ фактор при извършването на морфометрични проучвания върху лимфната система на гърдата.

Ключови думи: ЛИМФАТИЧНИ ФУНКЦИОНАЛНИ КЛАПИ, ГЪРДА, D2-40, СЪДОВЕ В СЪДОВЕТЕ

SUMMARY

The phenomenon "vessels within vessels" was initially described by Merchant S. et al. in uterine and mammary parenchyma. According to the data presented in that study, the vassculo-vasscular structures, observed in the uterus are composed of veins surrounding arteries.

Since the nature of this phenomenon is still uncertain, we decided to study it using the immunohistochemical method in order to determine the nature and morphology of these vascular complexes within the breast.

The study was carried out among 130 archival [illegible] from breast parenchyma, using specific

ПРОИЗХОД НА ТУМОР-АСОЦИИРАНИТЕ ЛИМФАТИЦИ ПРИ РАКА НА ГЪРДАТ – МОРФОЛОГИЧНО ПРОУЧВАНЕ НА ТУМОРНАТА ЛИМФНОСЪДОВ ВАСКУЛАРИЗАЦИЯ

И. Иванов[1], С. Поповска[1], Т. Бетова[1], Г. Байчев[2]

ORIGIN OF THE TUMOR-ASSOCIATED LYMPHATICS IN BREAST CANCER – MORPHO LOGIC STUDY OF THE TUMOR'S LYMPHATIC VASCULARISATION

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РЕЗЮМЕ

Понастоящем категоризирането, произходът и клиничното значение на тумор-асоциираните лимфни (ТАЛ) съдове при рака на гърдата (РГ) е обект на сериозни дискусии.

Целта на настоящето проучване е да се изясни хисто-морфологично същността на ТАЛ.

Обект на ретроспективно проучване са 23 случая с инвазивен карцином на гърдата и 15 случая с нормален мамарен паренхим.

Имунохистохимичното изследване се извърши върху 4 μм тъканни срези съответно с първично антитяло D2-40, CD68 и Ki-67 по съответни протоколи на фирмата производител – DAKO. Отчете се лимфнисъдовата плътност (ЛСП), средният брой ендотелни клетки, заграждащи лумена на един съд, пролиферативната активност сред лимфоендотелните клетки и моноцитната инфилтрация. Резултатите се обработиха статистически.

В нормалния мамарен паренхим се установи наличие на слаба, цитоплазмена позитивност за D2-40 сред миоепителните клетки. Лимфните съдове, в нормалния паренхим, се разполагаха сред интерлобуларната строма. ИТЛ се разполагаха сред прорастнат от тумора и от части запазен мамарен паренхим. Установената ЛСП при тях беше значително по-ниска от тази на нормалния мамарен паренхим t=3.43; p=0.02. ПТЛ не показаха отклонение в ЛСП спрямо нормалния мамарен паренхим t=-0.08; p=0.93. ПТЛ обаче бяха сигнификантно дилатирани t=-12.03; p<0.0001 и често свързани наличието на CD68 позитивни клетки. При всич групи се установи лимфно-ендотелна пролифер тивна активност под 1%.

Основният път на туморна лимфо-васкулариз ция, при най-често срещаните морфологичн варианти на РГ, е посредством прорастване око съществуващи лимфни съдове. Наличието клетъчна трансдиференциация, както и лимфн ендотелната пролиферация, която не може категорично да отхвърлим, по-скоро имат допълва и модифициращ характер.

Ключови думи: ГЪРДА, ТУМОР-АСОЦИИРАН ЛИМФАТИЦИ; ЛИМФАНГИОГЕНЕЗА

SUMMARY

There is still some controversy in literature abo the origin and clinical significance of tumor-associat lymphatics (TAL).

Aim of the present histo-morphologic study was demonstrate some detail concerning the origin of TA

Twenty three cases of invasive breast cancer a 15 samples of benign breast tissue were studied in retrospective study.

Immunohistochemical staining was preformed 4μm thick tissue slices with D2-40; CD68 and Ki- according to protocols of the manufacturer - DAK Microlymphatic vessel density (MLVD, average numb of endothelial cells, lining a lymphatic vessel, prolife tion activity of lymphatic endothelium and monoc

ИЗСЛЕДВАНЕ НА ПРИЛОЖИМОСТТА НА CHALKLEY ШАБЛОН ЗА ОЦЕНКА НА ЛИМФНАТА ВАСКУЛАРИЗАЦИЯ ПРИ КАРЦИНОМИТЕ НА ГЪРДА

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EVALUATION OF THE APPLICABILITY OF CHALKLEY GRATICULE FOR EVALUATION OF THE LYMPHATIC VASCULARIZATION IN BREAST CANCER

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Резюме:

Точността при Chalkley метода (базиран на броенето на точки) зависи до голяма степен от броя на точките върху шаблона, пропорцията на площта заета от обектите спрямо цялата площ на хистологичния материал и разпределението на обектите.

В настоящето изследване, проучваме възможностите за приложение на създадени от нас Chalkley шаблони за отчитане на лимфносъдовата васкуларизация при рак на гърдата. Резултатите отчетени с Chalkley шаблоните са сравнени с резултатите за относителна съдова площ отчетени посредством компютърен образен анализ.

От настоящето проучване се изрежда, че трудно може да се постигнат оптимални резултати при изследването на лимфносъдовата васкуларизация при карциномите на гърдата с Chalkley шаблон.

Ключови думи: Chalkley шаблон, лимфна васкуларизация, рак на гърдата

Özgün Araştırma/*Original Article*

doi: 10.5146/tjpath.2014.01244

Lymphatic Vascularization in Primary Breast Cancer: HER2 Overexpressing Tumors Contain More Lymphatics than Steroid Receptor Positive, Triple-Positive and Triple Negative Breast Carcinomas

Primer Meme Kanserinde Lenfatik Vaskülarizasyon: HER2 Overekspresyonu Gösteren Tümörler; Steroid Reseptör-Pozitif, Triple-Pozitif ve Triple-Negatif Tümörlere Kıyasla Daha Fazla Lenfatik Damar İçermektedir

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ABSTRACT

Objective: The aim of this study was to examine the relationship between the immunohistochemical subtypes of invasive breast cancer and lymphatic vascularization.

Material and Method: One hundred and seventy nine cases of randomly selected invasive breast cancer patients, surgically treated between 2004 and 2007, were retrospectively studied. These were classified into steroid receptor positive (steroid receptor positive/ HER2 negative), triple positive (steroid receptor and HER2 positive), triple negative (steroid receptor and HER2 negative) and HER2 overexpressing (steroid receptor negative /HER2 positive) carcinomas. Appropriate immunostaining and in-situ hybridization techniques were applied and results were statistically analyzed.

Results: The median intra-tumor lymphatic vascular density and the median intra-tumor relative lymphatic vascular area were found to differ significantly among the studied groups of breast cancer (KW =49.8611; p<0.0001 and KW =21.5122; p=0.0001 respectively). There was no significant difference in the incidence rate of axillary node involvement among the studied groups of breast cancer ($\chi 2$=1.66; Df=3; p=0.6460).

Conclusion: The present study indicates that HER2 overexpressing breast carcinomas have a consistent increase of intra-tumor lymphatic vessel counts as compared to all other subtypes. It is suggested that the newly formed vessels are probably not the only essential factor for lymphogenic spread of HER2 overexpressing breast carcinomas as they are not related to an increased incidence of lymph node metastases compared to the other studied subgroups.

Key Words: Breast neoplasms, Estrogen receptor, Progesterone receptor, HER2, Lymphangiogenesis

ÖZ

Amaç: Bu çalışmada, meme kanserlerinin immünhistokimyasal alt tipleri ile lenfatik vaskülarizasyon arasındaki ilişkinin saptanması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 2004-2007 yılları arasında opere edilmiş, rastlantısal olarak seçilen 179 invaziv meme kanserli hasta alındı. Hastalar, steroid reseptör pozitif (steroid reseptör pozitif/ HER2 negatif), triple pozitif (steroid reseptör pozitif ve HER2 pozitif), triple negatif (steroid reseptör ve HER2 negatif) ve HER2 aşırı ekspresyonlu (steroid reseptör negatif ve HER2 pozitif) olarak 4 alt tipte sınıflandı. Olgularda gerekli immünhistokimyasal ve in situ hibridizasyon incelemeler yapılarak, bulgular istatistiksel olarak değerlendirildi.

Bulgular: Ortanca intratümöral lenfatik damar yoğunluğu ve ortanca intratümör lenfatik damar alanı, alt tipler arasında anlamlı olarak değişkenlik gösterdi (KW =49.8611; p<0.0001 ve KW =21.5122; p=0.0001). Alt tipler arasında aksiller lenf nodu tutulumu açısından anlamlı farklılık saptanmadı ($\chi 2$=1.66; Df=3; p=0.6460).

Sonuç: Bulgularımız HER2 aşırı eksprese eden meme karsinomlarının diğer alt tiplere kıyasla yüksek sayıda intratümöral lenfatik damar içerdiğini göstermektedir. Tümör içinde yeni oluşan damarların lenfojen yayılım açısından yegane faktör olmadığını ileri sürmekteyiz. Çünkü bu özellikleri gösteren tümörlerde diğer alt tiplere kıyasla lenf nodu metastazı sıklığında bir artış saptanmamıştır.

Anahtar Sözcükler: Meme tümörleri, Östrojen reseptörü, Progesteron reseptörü, HER2, Lenfanjiyogenez

(Turk Patoloji Derg 2014, 30:124-132)

Received : 18.11.2013 **Accepted** : 27.01.2014

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SIS OF THE INCIDENCE AND CHARACTERISTICS OF THE CASES MONARY THROMBOEMBOLISM, DIAGNOSED BY AUTOPSY FOR A FIVE YEAR PERIOD

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CT

on: The actual causes and diseases related to formation of thromboemboli ɔnary thromboembolism are different and some of them may be ated as potential risk factors.

ıim of this retrospective study was to evaluate the incidence of pulmonary ıbolism diagnosed by autopsy. We also tried to find out the relation of age, the underlying cause of death from pulmonary thromboembolism.

A total of 1649 autopsies, performed during a five year period (2008-2012) artment of Pathology at University Hospital Pleven were systematically The autopsy documentation was retrospectively studied and the retrieved atistically analyzed.

ulmonary thromboembolism was found in 143 (8,62%) of the autopsies. : 95 (66,43%). They were found to die from pulmonary thromboembolism ntly younger age- median age was 67 (3-91 years) compared to females- : 74 (34-91 years) (K-W=11,4323; p=0,0007). Chronic pulmonary diseases ıderlying cause of death in 51 (35,66%) of the patients. Conditions related rgery were the underlying cause of death in 32 (22,38%) of the cases, y cardio-vascular diseases- in 21 (14,69%), diseases of the central nervous 19 (13,29%), malignant tumors- in 11(7,69%) and the remaining 9 (6,29%) ɔther underlying cause of death. **Conclusion:** Male individuals older than at suffer from severe chronic respiratory diseases might be at greater risk of thromboembolism with fatal outcome.

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BREAST DENSITY EVALUATION: A COMPARISON BETWEEN ASSESSMENT BY A RADIOLOGIST AND THE COMPUTER-ASSISTED THRESHOLD TECHNIQUE

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ABSTRACT

Traditionally, mammographic density (MD) of the breast has been assessed by a radiologist visually. This subjective evaluation requires significant experience to distinguish the relative proportions of the fibrous connective tissue and adipose tissue in the mammary gland correctly.

The aim of this study is to compare the capabilities of the different methods (visual and computer-assisted) for assessing mammographic density.

Our sample in this study consists of 66 patients with digital mammography. The mammographic density has been evaluated using the four-grade scale of the American College of Radiology (ACR); visually, visually using an analog scale and semi-automated using UTHSCSA Image Tool 3.0, Image J and Adobe Photoshop CS6 software.

The average mammographic density calculated using the different methods is as follows: 34.8% (from 10% to 70%); 32.1% (from 10% to 60%); 23% (from 0% to 70.9%); 22.7% (from 2.5% to 78.1%) and 22.5% (from 1.5% to 72.4%).

There is a strong correlation between the results obtained visually and those calculated using a computer-assisted measurement ($p < 0.0001$). A strong correlation was found also between the results acquired using the different semi-automated programs ($p < 0.0001$).

Precise measurement of mammographic density is of great importance for the mammographic screening and evaluation of breast cancer risk. The semi-automated methods, used for this purpose are objective, accessible and reproducible tools and have some advantages over the subjective visual assessment.

KEYWORDS: mammography, breast density measurement

РХИВ
БРОЙ 11 2011

ОКУЛТНА ХЕПАТИТ В ВИРУСНА ИНФЕКЦИЯ И ИНТРАВЕНОЗНА ХЕРОИНОВА ЗЛОУПОТРЕБА

Д. Любомирова, И. Маринова, С. Невати, Р. Иванова, И. Иванов

Abstract

Khirurgiia (Sofiia). 2009;(6):27-30.

[Is the Gail model for breast cancer risk assessment valid for the Bulgarian women?].

[Article in Bulgarian]

Baitchev G, Christova P, Ivanov I.

Abstract

INTRODUCTION: The quantitave assessment of the breast cancer risk is a fundamental for the process of preventation and early diagnosis.

AIMS: The aim of present study is to determinate the validity of the Gail model used in USA for the Bulgarian population, and to assess the relative influence of each risk factor over the common breast cancer risk.

MATERIALS AND METHODS: The object of our study were 315 women with histologically proved breast cancer. Retrospectively breast cancer rick was assessed for all patients by using Gail model. The following data were used: family history, previous benign biopsies, proved atypia, age of menarche, age of first birth and patient's age at the moment of detecting the breast cancer.

RESULTS: In 186 (59%) patients no high risk is present after Gail model assessment and in the others 129 (41%) patients high risk for development of breast cancer is detected (> 1.7% for 5 years). Statistical reliability for the influence of each factor was found except for the previous benign biopsies.

CONCLUSION: The results give us a reason to recommend Gail model as routine method for breas cancer risk assessment for the Bulgarian population for patients between 35 and 70 years old.

PMID: 20506776 [PubMed - indexed for MEDLINE]

Original Article

LIVER DAMAGE FROM HEROIN MISUSE, COMBINED WITH HCV INFECTION: CLINICAL AND MORPHOLOGICAL CHANGES

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Summary

The aim of the study was to assess more data on the severity of liver damage in heroin addicts (HA) with proved hepatitis C viral (HCV) infection. The study included 20 patients with chronic viral hepatitis C (CHC), of which ten had a documented history of intravenous heroin misuse. The two groups of patients were compared according to biochemical changes, characterising the liver damage (serum levels of ASAT, ALAT, GGT, APH and total bilirubin), serum level of HCV RNA, ultrasound images visualizing grades of steatosis, histological changes assessed by METAVIR and histochemical changes, evaluated using PAS, Gomori and Van Gieson reactions. Our study confirmed the presence of liver damages in both groups but the role of heroin as an independent damaging factor could not be elicited.

Key words: heroin abuse, chronic hepatitis C, liver

АРХИВ

БРОЙ 11 2012

ИНТРАВЕНОЗНА ХЕРОИНОВА ЗЛОУПОТРЕБА И ХРОНИЧЕН ВИРУСЕН ХЕПАТИТ С

Д-р Д. Любомирова[1], д-р Р. Иванова[2], д-р И. Иванов[2], доц. д-р И. Маринова[1]

http://www.medinfo.bg/spisanie/2012/11/statii/intravenozna-heroinova-zloupotreba-i-hronichen-virusen-hepatit-s-1403

J Biomed Clin Res Volume 5 Number 1, 2012

Original Article

DOUBLE ANTIBODY COCKTAIL (D2-40/P63) PROTOCOL FOR IDENTIFICATION OF LYMPHATIC VASCULAR INVASION IN BREAST TISSUES: ADVANTAGES OF THE PROTOCOL

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Summary

Recently it was found out that D2-40/p63 double immunostaining of defined lymph vessel invasion has additional prognostic value in some node-negative breast carcinomas. The aim of this study was to test the efficiency of our modification of D2-40/ p63 double antibody cocktail, used with single detection kit protocol to identify lymphatic vascular invasion (LVI) in breast tissues. Formalin-fixed, paraffin-embedded tissues from 130 breast cancer patients were examined. Immunostaining for α-SMA, collagen IV, p63 and D2-40 was performed in accordance with protocols provided by the manufacturer (DAKO). An additional immunostaining with D2-40/p63 was performed according to a protocol modified in our laboratory. Using D2-40 staining only, two cases of extensive lobular cancerization by ductal carcinoma in-situ (DCIS) and two cases of solid low-grade DCIS were misdiagnosed as lymphatic vascular invasion. In cases with in-situ carcinomas /extensive intraductal and/or lobular tumor growth, the D2-40 / p63 cocktail proved useful in identifying true LVI. The strength of inter-method agreement between evaluation of LVI on D2-40-stained slides and D2-40 / p63 stained slides in breast carcinomas was very good (κ=0.90). The suggested single detection kit, double antibody cocktail (D2-40/ p63) staining protocol enabled effective interpretation of the nature of tumour cell harbouring D2-40 positive structures in all the cases we studied.

Key words: D2-40/p63, breast cancer, ductal/ lobular carcinoma in-situ, lymphatic vascular invasion

J Biomed Clin Res Volume 6 Number 2, 2013

Original Article

STUDY OF THE CARRIER STATE FOR FIVE BRCA1/BRCA2 DELETERIOUS MUTATIONS IN BULGARIAN WOMEN WITH BREAST CANCER

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Summary

Genetic testing for BRCA1/2 mutation is a well recognized medical management tool. Identification of healthy carriers of such mutations allows effective risk reduction procedures to be performed. There is no data reported on the founder mutations in the Bulgarian population. To evaluate the contribution of genetic factors to breast cancer (BC), we investigated the carrier state of Bulgarian women with BC for five common (according to BIC database) deleterious BRCA1/2 mutations. The list of patients diagnosed with BC between January 2011 and April 2012 was obtained from the Cancer Registry of University Hospital, Pleven. Eighty-two women with BC were interviewed and a pedigree was constructed of each of them. The patients were classified into seven categories, according to personal, disease and family history. Based on the preliminary prepared selection criteria and the personal family history, we defined a target group of 33 Bulgarian women with BC. They were screened for five deleterious mutations: 5382insC in BRCA1 and 6174delT, 6079del4, 8138del5, 5946delCT in BRCA2, by DNA sequencing. The genetic analysis detected none of the tested mutations. Two polymorphic variants were found in BRCA2 gene: c.5744C>T (rs4987117, SNP database) in exon11E in one patient and c.7806-14T>C (rs9534262, SNP database) in exon17 in 22 patients. In conclusion, without basic information on the founder mutations in the population, the genetic screening for the specific mutations in a small group of tested patients is ineffective.

Key words: BRCA1, BRCA2, Breast cancer, Bulgarian population, polymorphism

Original Article

THREE-DIMENSIONAL RECONSTRUCTION OF ARTERIAL-LYMPHATIC VASCULAR COMPLEX (VESSEL WITHIN THE VESSEL) IN BREAST TISSUE

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Summary

The phenomenon "vessels within vessels" was initially described by Merchant S et al. as arteries found free-floating inside the lumen of veins. We have described another version of the "vessels within vessels"complex, composed of arteries found inside the lumen of lymphatic vessels. The purpose of the present study was to describe the structure of the lympho-arterial vascular complex in a breast tissue specimen from a male subject using three-dimensional tissue reconstruction. A histological specimen from a 64 year-old male subject diagnosed with gynecomastia was used. The tissue sample was sectioned in a multi-step manner. An overall of approximately 150μm thick tissue material was sampled. Immuno-staining with anti-CD34 antibody and anti-podoplanin antibody was performed. Three-dimensional reconstruction of the vessel within the vessel structure was performed with "Reconstruct" software When the reconstruction of the breast parenchyma was revealed as a 3D image, it became apparent that the arterial vessel was situated inside the lymphatic vessel and could be followed along the entire length of the vascular segment studied. We have proved that these vascular complexes are not artificial phenomenon and do exist. The function of the vascular complexes is still uncertain, and is probably related to lymph propulsions in the initial collector vessels.

Key words: lymphatic-arterial vascular complex; male breast; 3D tissue reconstruction

РОЛЯ НА ПАТОЛОГОАНАТОМИЧНИТЕ АУТОПСИИ В СЪВРЕМЕННАТА ТУМОРНА ЕПИДЕМИОЛОГИЯ –АНАЛИЗ НА 1649 СЛУЧАЯ ЗА 5 ГОДИШЕН ПЕРИОД

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THE ROLE OF PATHOLOGOANATOMICAL AUTOPSIES IN CONTEMPORARY TUMOR EPIDEMIOLOGY – AN ANALYSIS BASED ON 1649 CASES FOR A FIVE YEAR PERIOD

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ABSTRACT

The classification of neoplasms and the evaluation of their prognostic and predictive factors is part of the daily routine of every pathologist. While there is increasing role of biopsies, the number of performed autopsies is steadily decreasing. We expect that the overall results from autopsies will be representative for the incidence of diseases in the whole population. The aim of the following investigation was to study the incidence of malignant tumors, based on 1649 pathologoanatomical autopsies and to analyze if the results are representative for the Bulgarian population for the same period of time. A total of 1649 autopsy reports, created over a period of five years (2008-2012) in University Hospital "D-r G. Stranski" – Pleven, were retrospectively studied. The total number of malignant neoplasms diagnosed by autopsy during the five year period was 193 (11,70%). Malignancies were found in 130 (67,36%) male patients and in 63 (32,64%) female patients. The three most common causes of death from malignant tumors were: lung cancer and cancer of the trachea- 31 (23,85%); followed by colorectal cancer- 24 (18,46%) and pancreatic cancer - 13 (10,00%). The most common malignancies in female patients were leukemias- 10 (15, 87%), followed by colorectal cancer - 8 cases (12,70%) and lung cancer and cancer of the trachea - 7 (11,11%). The remaining causes of death from oncologic diseases comprise of 47,69% of male and 60,32% female individuals. The evaluation of mortality rates by gender from malignant tumors based solely on autopsy reports from the archives of University Hospital "D-r G. Stranski" – Pleven demonstrated serious discrepancies when compared to the general population statistics. The contemporary diagnostic methods allow early diagnosis and reduce the importance of autopsies as a method of tumor epidemiology.

Key words: *malignant neoplasms, mortality rates, pathologoanatomical autopsies*

СЕНТИНЕЛНА ЛИМФНА БИОПСИЯ ПРИ ЕНДОМЕТРИАЛЕН КАРЦИНОМ – НАШ ОПИТ

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Резюме

Цел. *Целта на проучването бе да се изследва възможността за детекция на сентинелени лимфни възли (СЛВ) при ендометриален карцином, използвайки метода на Altgassen et al.*

Пациенти и методи. *На 12 пациенти с ендометриален карцином бе инжектирано 4 мл метиленово синьо на 8 места субсерозно. След 10 мин бе извършена оценка на лимфния статус.*

Резултати. *Отчете се 91.6 % успеваемост като само при една пациентка не се визуализираха СЛВ, а при друга се намери СЛВ само едностранно. Не се отчетоха странични ефекти.*

Заключение. *Този метод за детекция на СЛВ е многообещаващ, бърз и лесен за изпълнение, но се налага извършването на допълнителни изследвания за да стане част от стандарта за оперативно лечение на ендометриалния карцином.*

Ключови думи: *ендометриален карцином, сентинелен лимфен възел*

SENTINEL LYMPH NODE BIOPSY IN ENDOMETRIAL CANCER - OUR EXPERIENCE

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Abstract

Purpose. *The objective of the study was to determine the feasibility of a method described for the first time by Altgassen et al. of labeling sentinel lymph nodes in patients with endometrial cancer using blue dye.*

Patients and methods. *4 ml of blue dye was administreted in 12 patients with endometrial cancer subserosaly at eigth sites. After 10 min sentinel lymph nodes were harvested.*

Results. *Detection rate was 91.6 %., In only one patient there was no detection of sentinel lymph node and in one patient the sentinel lymph node was marked only in one hemipelvis.*

Conclusions. *This method for detection of sentinel lymph nodes in patients with endometrial cancer is promising, fast and easy to implement, but need to conduct additional studies to become part of the standard for the surgical treatment of endometrial cancer*

Key words: *endometrial cancer, sentinel lymph node*

C-KIT MUTATIONS IN GASTROINTESTINAL STROMAL TUMORS – MORPHOLOGICAL, BIOLOGICAL AND GENETICAL ASPECTS

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Abstract. Gastrointestinal Stromal Tumors(GISTs) are defined as mesenchymal tumors and 95% of them showed mutation in KIT gene. Our aim is to investigate the significance of C-KIT mutation for GISTs. bio- genetical mehanizm and detected by immunohistochemistry. Three cases were observed in the stomach. per one of the small bowel, rectum, colon and the rest were extragastrointestinal . Of these tumors five were classified as benign . three as malignant and one was diagnosed as borderline tumor.Immunohistochemical analysis showed C-KIT (CD117) positivity in all cases. Indentification and expression of C-KIT mutation with immunohistochemical method is the gold standard for diagnosing GISTs.

Key words: Gastrointestinal Stromal Tumors, C-KIT, Immunohistochemical analysis

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JOURNAL OF BIOMEDICAL & CLINICAL RESEARCH

СЛУЖЕБНА БЕЛЕЖКА 057/2016

Редакцинната колегия на научното медицинско списание на МУ-Плевен "Journal of Biomedical & Clinical Research" (JBCR) издава настоящата служебна бележка на д-р Иван Иванов в уверение на това, че статия JBCR#248, със заглавие: **Statistical analysis of the forensic autopsies, performed in the department of forensic medicine of UMHAT-Pleven for the period 2009-2013 (preliminary report)**
с автори Dancho P. Dekov, Ivan N. Ivanov, Sergey D. Kostadinov, Savelina L. Popovska, Petko I. Lisaev, Plamen D. Dorovski е предвидена за публикуване в списание JBCR в брой 1, том 9, 2016 год.

10.03.2016 г.
гр. Плевен

Проф. д-р М. Средкова:
/Зам. гл. редактор JBCR/

КЛИНИЧНО И МОРФОЛОГИЧНО ПРОУЧВАНЕ НА ПРОМЕНИТЕ ПРИ IRRITABLE BOWEL SYNDROME

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Резюме:

Irritable Bowel Syndrome (IBS), е заболяване, характеризиращо се със спазъм, коремна болка, подуване и метеоризъм, запек или диария.

Цел. Клинично и морфологично проучване на промените в дебелото черво при пациенти с irritable bowel syndrome и сравняването им с произволна група за контрола .

Материал и методи: Извършено е ретроспективно проучване на две групи пациенти от Отделенията по Гастроентерология и Клинична патология на УМБАЛ-Плевен. Първата група са 20 пациента с диагноза IBS,отговаряща на Римските критерии II, и са подразделени в субгрупи съобразно водещия симптом-с диария,със запек,с болки,подуване и метеоризъм. Втората група е контролната група включваща 10 аутопсирани пациента.Групите са изследвани рутинно хистологично и хистохимично. Извършвана е оценка на хроничния възпалителния инфилтрат, който е оценяван полуколичествено на степени от 0-4ст,а мастоцитите са оценявани количествено, като за увеличен брой клетки се счита над 20/HPF.

Резултати: При морфологичното изследване се отчита увеличен брой лимфоцити,плазматични клетки, мастоцити и единични еозинофилни левкоцити, предимно при пациенти с диариен синдром и абдоминална болка, а при субгрупата със водещ симптом запек е установено по-малък брой инфламаторни клетки и мастоцити.В контролната група само у един пациент е установена втора степен на възпалителния инфилтрат,а мастоцитите са в норма.

Извод :Клинично диагнозата е подчинена на Римските критерии,а морфологичния субстрат е хроничното неспецифично възпаление.

Ключови думи: Irritable bowel syndrome,Римски критерии,хистология,мастоцити

IRRITABLE BOWEL SYNDROME-ПАТОФИЗИОЛОГИЯ, ИМУНОХИСТОХИМИЧНА ДИАГНОЗА И МЕНИДЖМЪНТ

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Резюме:
Irritable bowel syndrome (IBS) е функционално-чревно заболяване в чиято основа лежи хроничното възпаление.Поставихме си за цел да проучим хистологичната алтерация на дебелочревната мукоза при пациенти с IBS чрез прилагането на ИХХ метод за верифициране на мастоцити, хроничен възпалителен инфилтрат,ентерохромафинни клетки, ентерични нервни окончания и техните патофизиологични корелации.

Материал и методи: Извършено е ретроспективно проучване на 30 бр.пациенти разделени в две групи както следва - 20 пациента с диагноза IBS и контролна група от 10 аутопсирани пациента. Групите са изследвани имунохистохимично, с антитела насочени срещу CD 117 антигена за верификация на мастоцити, CD 3 за лимфоцити, синаптофизин за ентерохромафинни клетки и неврон-специфична енолаза за окончание на ентеричните нерви по протокол на фирмата DAKO.

Резултати: От имунохистохимичното изследване се установи - увеличен брой CD3 позитивни лимфоцити и CD117 позитивни мастоцити.Констатираните промени са предимно при пациенти с диариен синдром и абдоминална болка, а при пациенти със запек е установено по-малък брой инфламаторни клетки и мастоцити. Позитивно оцветяване на ганглийни клетки за неврон-специфична енолаза, както и увеличеният брой ентерохромафинни клетки е установено в малък брой пациенти от двете групи.

Извод: Прилагането на ИХХ метод дава възможност за точна верификация на хроничния възпалителен инфилтрат и хвърля яснота върху патофизиологичните механизми на IBS.

Ключови думи: Irritable bowel syndrome,Имунохистохимия, патофизиология, мениджмънт

ЕНИГНЕНИ ЕПИТЕЛНИ ТУМОРИ НА КЛЕПАЧИТЕ

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ct:
nign eyelid lesions total up 15% of the face tumors and 5-10% of the skin

To find the occurrence, type and subtype of the benign eyelid tumors and the urgical intervention.
gn tumors were studied, all of which were analyzed with 8 indicators. Rou- cal technique was used.
s: The benign eyelid tumors were 24%. 25% of them belong to the squa- oma, 19,5% to seborrheic keratosis, 22,3% to naevus and haemangioma, rocystoma and fibropapilloma, 5,5% to xanthelasma and 2,7% to oma.
ariations among the benign eyelid tumors are due to the histological structure

words: eyelid, benign tumors, adnexal tumors

СТАТИСТИЧЕСКИ АНАЛИЗ НА ПАТОЛОГОАНАТОМИЧНИТЕ АУТОПСИИ ОТ УМБАЛ-ПЛЕВЕН ЗА ПЕРИОДА 2008-2012 ГОДИНИ (ПРЕДВАРИТЕЛНО СЪОБЩЕНИЕ)

И. Иванов, Д. Деков*, С. Поповска

Key words: *pathologoanatomic autopsy, autopsy rates, statistical analyses*

Statistical analyses of the results from pathologoanatomic autopsy performed in the Department of Pathology (University Hospital Pleven) during the period 2008-2012. (A preliminary report)

I. Ivanov, D. Dekov, S. Popovska

The present study is an analysis of the causes of death and the autopsy rates among patients treated at the University Hospital "D-r G. Stranski" - Pleven. Protocols of all performed autopsies (n=1649) during the period 2008- 2012 were studied. A detailed information on the most important death related characteristics of studied population are presented. These included: number of performed autopsies, the causes of death by rate, autopsies rates by gender, age, duration of hospitalization, data concerning the department at which the patient died. The concurrence rate between clinical and pathologic diagnoses is analyzed. We found that there was a tendency toward decrease of the number of autopsies per year over the studied 5 year period. In nearly 1/4 of the cases there was disagreement in clinical and pathologic diagnoses. In conclusion, we believe that the clinicopathological conferences are a necessity, that may improve and optimize the diagnostic and treatment protocols.

Катедра Обща и съдебна медицина, Медицински университет - Плевен

тът на съвпадение между клинична и патологоанатомична диагноза, както и други признаци.

A STUDY OF THE FREQUENCY AND LOCALIZATION OF THE GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS DIAGNOSED AND OPERATED AT THE UNIVERSITY HOSPITAL - PLEVEN IN 2014

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ABSTRACT

Objective: Over 90% of neuroendocrine tumors (NETs) in Bulgaria were reported to arise in the gastrointestinal tract. Our objective was to study the incidence and localization of the gastroenteropancreatic NETs, diagnosed for one year.

Methods: The present retrospective study explores the incidence and localization of the gastroenteropancreatic NETs, diagnosed and operated for one year period (during 2014) in UMHAT "Dr. Georgi Stranski", Pleven.

Results: Seven cases of gastroenteropancreatic NETs were diagnosed and treated for the studied period. Most common primary sites were: pancreas in 4 (57.14 %) cases and 2 in colon (28.57 %) cases. According to the morphological criteria, 2 (28.57 %) were well differentiated NETs, 3 (42.86 %) were moderately differentiated, and 2 (28.57 %) were poorly differentiated NETs. One of them was mixed adenoneuroendocrine carcinoma. All cases demonstrated immunoexpression of Chromogranin A and Synaptophysin in addition to the distinct neuroendocrine morphology. Distant site metastases were observed in 5 (71.43 %) cases.

Conclusion: According to our results, most of the gastroenteropancreatic NETs were well and moderately differentiated and located in pancreas. A considerable number of patients had distant metastasis at the time of diagnosis. The expression of Chromogranin A and Synaptophysin supported the morphological diagnosis of gastroenteropancreatic NET.

Keywords: *gastroenteropancreatic NETs, incidence, localization*

ЗАБОЛЯВАНИЯ НА МЛЕЧНАТА ЖЛЕЗА

Под редакцията на Г. Байчев

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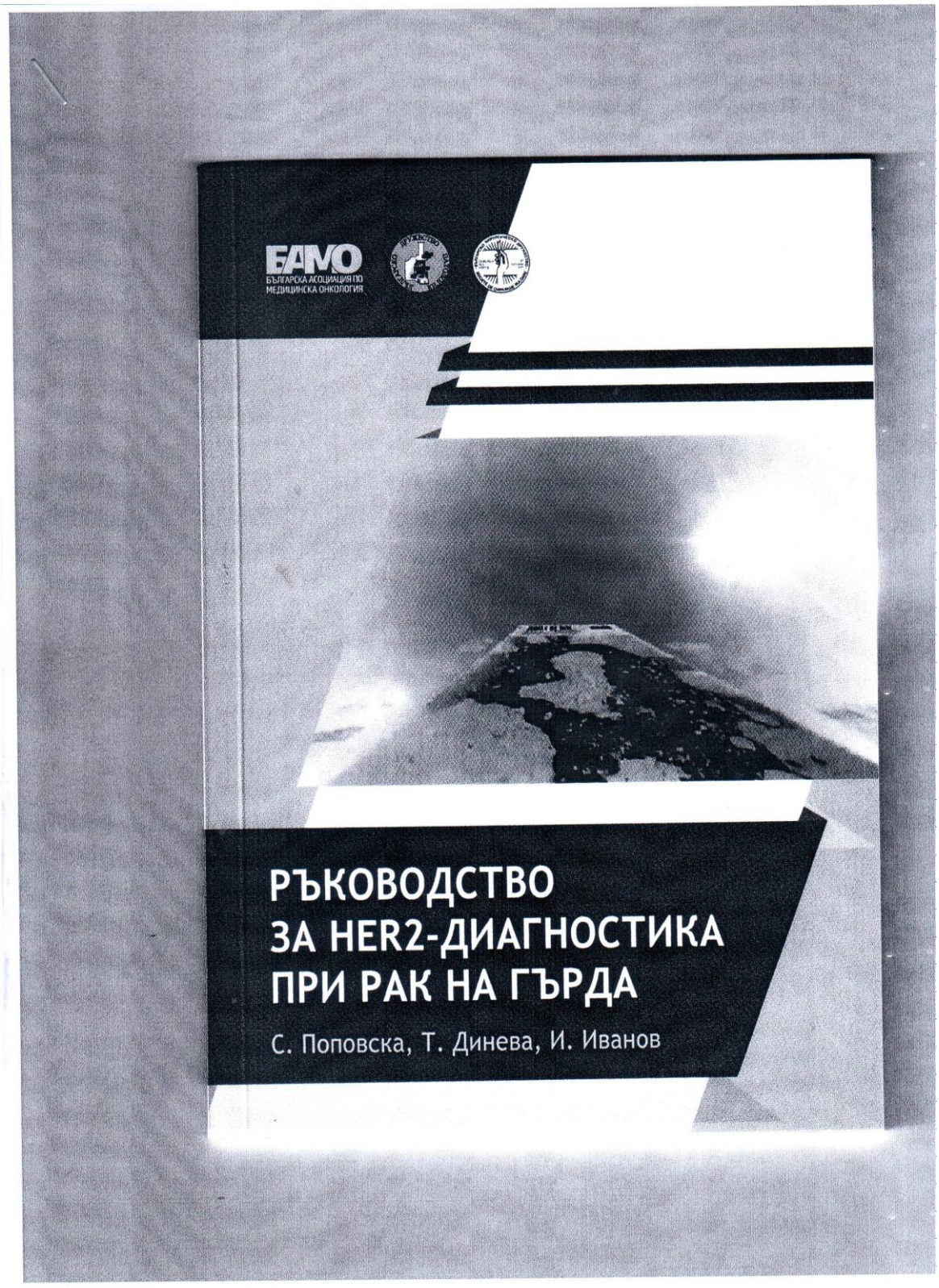
София, 2014 г.


БАМО
БЪЛГАРСКА АСОЦИАЦИЯ ПО МЕДИЦИНСКА ОНКОЛОГИЯ
РЪКОВОДСТВО
ЗА HER2-ДИАГНОСТИКА
ПРИ РАК НА ГЪРДА
С. Поповска, Т. Динева, И. Иванов

LINICAL CASES OF FAMILIAL BREAST CANCER IN ULGARIAN PATIENTS

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reast cancer (BC) is the most frequently diagnosed cancer and a leading use of cancer death in females in Bulgaria (34. 1 per 100 000 women in 011). In 2009, 3809 new cases of BC have been diagnosed. Familial clustering accounting for 20% of all BC cases. About 5-10% of all BC are due to heritance of highly penetrant gene mutations. The family history and gene utations increase the risk of BC, two-tree fold and 65-80%, respectively.

e present six pedigrees of family BC. In two of these cases there is a rong clustering of BC. Other cases reveal an association of breast cancer ith ovarian, pancreatic, prostate and gastric cancer. We pay attention to ealthy first degree relatives at high risk of developing BC during their lifetime. enetic test for mutation in highly penetrant genes and preventive procedures decrease the risk of BC should be offered to those relatives.

KEY WORDS: breast cancer, familial BC, associated cancers

SUSCEPTIBILITY GENE MUTATIONS IN BREAST CANCER P.39

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Breast cancer (BC) is the most frequently diagnosed cancer and leading cause of cancer death in females worldwide, accounting for 14% (458 400) of the total cancer deaths. Familial cases are 20% of all BC. Inherited germ line mutation in susceptibility genes is found in 5% of the cases.

AIMS AND METHODS

In order to summarize current evidence about genetic basis of BC we selectively review relevant articles published from January 2009 to December 2011 that were retrieved by searching in available Internet database.

RESULTS

Mutations in highly penetrant BRCA1 and BRCA2 genes are responsible for 40% of hereditary BC cases. The carriers of mutation have high risk (about 60-85%) of developing BC and increased risk of developing other associated cancers, such as ovary, Fallopian tube, prostate, male breast, pancreatic and peritoneum cancer. Other genes that include CHEK2, PTEN, TP53, ATM, STK11/LKB1, CDH1, NBS1, RAD50, BRIP1 and PALB2 have been described to be high or moderate penetrance BC susceptibility genes. However in still a part of familial hereditary breast cancers no relationship to any of these breast cancer susceptibility genes could be found.

CONCLUSION

About half of all hereditary cases of BC are due to a mutation in BRCA genes. Revealing the carrier status of such mutation could help women to take preventive procedures to decrease the risk of BC. Other susceptibility genes for BC have been identified recently. Clinicians should develop and implement evidence-based treatment and prevention on the basis of these new genetic findings.

KEY WORDS: breast cancer, susceptibility genes, hereditary BC

HISTOMORPHOLOGICAL SCREENING FOR BREAST CANCER PATIENTS SUITABLE FOR GENETIC TESTING FOR BRACA1

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Breast cancer (BC) might arise as sporadic or familial oncological disease. BRACA 1 mutation carriers suffering from BC require systematic follow up because of the increased risk of development of contralateral BC or carcinomas at various primary locations (ovary, stomach and pancreas).

AIMS/OBJECTIVES

Aim of the following investigation was to study the population of Bulgarian BC patients who are potential carriers of BRACA1 mutation using the methods of histopathology.

METHODS

Two hundred and sixty two cases of invasive BC were studied in a retrospective study. According to the morphological criteria as potential BRCA1 mutation carriers were considered, patients whose tumors were high histological grade, growing in a solid growth pattern, with foci of necrosis and lymphocytic infiltrates (mainly invasive ductal and medullary carcinomas). Additionally the immunohistochemical profile of BC of potential BRCA1 mutation carriers should be either triple negative phenotype (ER, PgR and HER2 - negative) or basal-like (ER, PgR and HER2 – negative, CK5/6, CK14 or EGFR positive). The frequency of potential BRACA1 mutation was calculated.

RESULTS

According to the stated morphological and immunohistochemical criteria, potential BRACA1 mutation might be expected in 17 (6.49 %) of cases in a random population of Bulgarian BC patients.

CONCLUSION

Approximately 6.5 % of BC patients in Bulgaria may benefit from genetic testing for BRACA1 mutation. Pathology reports might be used as initial screening questionnaire for genetic BRACA 1 testing.

KEY WORDS: BRACA 1 ...

and the high-grade tumors (χ^2 =11,97; p<0,001) were significantly related to loss of BRCA1 immunopositivity. Stromal reaction (χ^2 =0,05; p=0,821) and family history (χ^2 =0,00; p=1,00) were not associated with immunostaining for BRCA1. The presence of immunopositivity for p53 was significantly associated with loss of BRCA1 immunostaining (χ^2=10,70; p=0,001). High grade serous papillary ovarian carcinomas with more than 6% of tumor necrosis and p53 immunopositivity are most likely with BRCA1 mutation. These criteria might be used as a cost effective approach for selection of cases for BRCA1 mutation testing and treatment with platina based chemotherapy.

Key words: BRCA 1 mutations, ovarian cancer

INVESTIGATION OF TRIPLE-NEGATIVE BREAST CANCERS-MORPHOLOGICAL AND IMMUNOPHENOTYPIC CHARACTERISTICS

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Summary

Introduction: Breast cancer represents a variety of subgroups with unique biological and clinical characteristics. Basal-like variant of triple negative breast cancers (TNBCs) are aggressive cancers that affect young women. Expression of cytokeratins 5 and 17 identifies a group of breast carcinomas with poor clinical outcome.

Aim of the study: To examine the morphology and IHC characteristics of TNBCs and to identify the basal –like subtype of breast cancers.

Materials and methods: Retrospectively we have selected tumors based on the absence of IHC staining for ER, PgR and Her-2 (triple negative phenotype). Se[illegible] Caveolin-1 and p-cadherin were used as markers of basal and luminal differentiation.

Results: Among 77 TNBCs using the five-marker method for identification of basal –like cancers 80.55% were found positive.Positive for both EGFR and CK5 were 65.52% of tumors. Positive for EGFR and negative for Ck5 - 20.69%. According to the type of immunostaining TNBCs were subclassified into 2 categories-pure basal (40%) and baso-luminal (60%).

Conclusions: There is an evidence that the group of TNBCs is heterogeneous and does not comprise a 'single entity'. Triple negativity' should not be used as a surrogate marker for basal-like cancers.

Key words: triple negative breast cancer, basal-like breast cancer, immunohistochemistry

RING STUDY TO EVALUATE THE ACCURACY, RELEVANCE AND THE CORRELATION BETWEEN IMMUNOHISTOCHEMISTRY AND IN SITU HYBRIDIZATION IN DETERMINING THE HER 2 STATUS IN WOMEN WITH BREAST CANCER

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Summary

Introduction: The status of HER2 in breast cancer is predictive factor for the effect of targeted therapy. Presently there are two widely used methods for HER2 status testing immunohistochemistry (ICH) and in situ hybridization analysis. The correlation of the overall result (positive/negative) between IHC and in situ hybridization technique is of great importance for the clinical practice.

Aim: The aim of this study was to evaluate the correlation between the immunohistochemistry (ICH) and in-situ hybridiz[illegible]

was performed in accordance to standard laboratory protocols. HER2 status accessed by IHC and ISH was evaluated in accordance to recommendations of updated guide-lines.
Results: During the evaluation of the studied specimen we found out that over- and under fixation were associated with certain IHC and ISH staining artefacts. The use of fixatives different from 10% neutral buffered formalin also caused staining artefacts and interpretation problems. A total of 27% of discrepancies between IHC and ISH methods was found.
Discussion: The accuracy of all used methods was found to depend on the used tissue processing protocols. Pre-analytical, analytical and post-analytical stages, as well as the experience of technologist are of great importance for HER2 testing. Internal and external quality assurance evaluation can improve the diagnostic process and guarantee consistent tests results.
Key words: HER2, IHC, ISH, discrepancy

ASSOCIATION OF SNPS IN C1Q GENE CLUSTER WITH SOME OF IMMUNOLOGICAL PARAMETERS OF LUPUS NEPHRITIS

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Summary
Introduction: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease and one of its most severe manifestations is lupus nephritis (LN). Hereditary C1q deficiency is strongly related to SLE. But we found that single nucleotide polymorphism (SNP) of the C1q gene cluster – rs172378 is associated with susceptibility to LN in Bulgarian population. In present study we investigated whether the carriage of a particular genotype or allele of five different SNPs in C1q gene cluster affects the activity of lupus nephritis. Materials and Methods: Thirty eight patients with LN and 185 healthy controls, all from Bulgaria, were genotyped for five C1q SNPs, rs172378, rs587585, rs292001, rs294179 and rs631090 by quantitative real-time PCR methods. We also determined serum levels of C1q, C4, C3, anti-C1q autoantibodies, IgG-, IgM-containing circulating immune complexes (CICs) and hemolitic activity of C1q in relation to the SNPs genotypes.Results: We found that TT genotype of rs587585, rs631090 and rs294179 presents a risk factor in patients for having high levels of anti-C1q antibodies ($p=0.004$), high levels of IgG CICs ($p<0.0001$) and lower levels of C4 ($p=0.028$) respectively. The GG rs172378 genotype was bound with low hemolytic activity of C1q ($p=0.005$) and high levels of IgG CICs ($p=0.042$). We also found that haplotypes ATGCT, ACATT and GTGCT were associated in patients with higher IgM CICs ($p=0.023$), higher IgG CICs ($p=0.001$) and lower C1q ($p=0.019$) levels respectively. Conclusion: These results showed that the SNPs analysis for rs172378, rs587585, rs294179 and rs631090 could be used for evaluation of disease activity.
Key words: complement; C1q; lupus nephritis; SNP

MODULATION OF INSULIN SECRETION AND INSULIN SIGNALING BY SELENIUM

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Summary
The aim of this study was to present the current knowledge on the role of selenium (Se) in the synthesis and insulin signaling.
Selenium is an exogenous antioxidant, which

A RARE CASE OF MESOPHARYNGEAL TUMOR

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AIM

To present a rare case of an eighty-two-year old woman with dyspnea and dysphagia that became worse in the last few days.

METHODS

Physical examination, ECG, pulmonary function test (PFT), laboratory studies, X-ray, bronchoscopy (BS), gastroscopy (GS) and computed tomography (CT) were performed.

RESULTS

The patient was hospitalized in the pulmonology clinic Pleven with paroxysmal dyspnea, irritating cough, white sputum and nausea. Medical history revealed information about bronchial asthma in the past. The patient had no symptoms until now and did not take any medications for asthma. PFT results were normal.

CT scan revealed bronchiectasis and emphysema. BS showed no changes in the airways. GS showed only the presence of a hiatal hernia. Patient was discharged with recommendation for observation and examination after 1 month.

Four years later patient was hospitalized in ENT clinic with dyspnea and dysphagia. The examination revealed tumor in mesopharyngs. After the excision of the tumor the patient was discharged in good medical condition. Òhe histological results revealed that the tumor was lipoma.

диференцирани, без образуване на органоидни структури.

Ключови думи: тератоиден карциносарком, смесен мюлеров тумор, яйчник.

П 13
СЪЧЕТАНИЕ НА СМЕСЕН МЮЛЕРОВ ТУМОР НА МАТКАТА С ЛЕЙОМИОМ НА ЯЙЧНИКА

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Малигнените смесени Мюлерови тумори (ММТ) са 2 - 8% от всички злокачествени новообразувания на матката. Имат агресивен растеж и лоша прогноза. Обикновено диагнозата се поставя, когато процесът е твърде напреднал. Срещат се предимно при жени в постменопауза, като основният симптом е генитално кървене. Маточните ММТ могат да бъдат хомоложни или хетероложни по строеж. Като цяло, те са съставени от епителна и мезодермална компоненти. Обикновено епителната компонента доминира, както е и в представения от нас случай.

Описваме случай на 67г. жена, оперирана по повод на генитално кървене в менопаузата. Пробното абразио представя хистология на карциносарком. Постоперативно се намира бифазен смесен Мюлеров тумор на маточното тяло. Извършено е ИХХ-изследване с СК7, СК20, Виментин, S-100 протеин, ЕМА и гладко мускулен Актин.

В единия яйчник се намира лейомиом с диаметър 3 см.

Съчетанието на тези два редки тумора при пациентката я прави особено интересна от гинекологична и патологична гледна точка

П 14
ХИСТОЛОГИЧНА ДИАГНОЗА „АТИПИЧЕН ПОЛИПОВИДЕН АДЕНОМИОФИБРОМ НА МАТКАТА": КАК И ЗАЩО?

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Атипичният полиповиден аденомиофибром (атипичен полиповиден аденомиом, АПА) е рядък маточен тумор, който обикновено се среща при жени в репродуктивна възраст с абнормно генитално кървене и често пъти – с анамнеза за инфертилитет. За първи път е описан като отделна нозологична единица от Mazur през 1981 година. Хистологично лезията представлява бифазна пролиферация на ендометриални жлези с различна степен на архитектурен комплекситет и цитологичен атипизъм в миофиброматозна строма. Акцентирайки върху потенциалния риск от развитие на миометрална инвазия, Longacre et al. предлагат за случаите с изразен комплекситет на жлезите (висок архитектурен индекс) наименованието АПА с нисък малигнен потенциал. Основен диференциално-диагностичен проблем при АПА е изключването на миовазивен високодиференциран ендометриоиден аденокарцином в кюретажни материали. Това разграничаване позволява избор на метод на лечение, съхраняващ репродуктивните възможности при пациентки с желание за бременност.

Базирайки се на своя опит с 15 диагностицирани и имунохистохимично изследвани случаи с маточни аденомиофиброми, авторите дискутират клинико-морфологичните особености и имунохистохимичния профил на тази необичайна маточна неоплазма.

П 15

РЯДКА ЛОКАЛИЗАЦИЯ НА МЕТАСТАЗА В ПЕНИСА

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Пенисът е изключително рядко обект на биопсично изследване по повод на метастатични лезии.

Преставяме случай на 39 г. мъж с хематогенна метастаза в пениса 12 месеца след нефроуретеректомия и цистопростатектомия по повод тумор на пикочния мехур. При макроскопското изследване се намира туморна формация, ангажираща двустранно кавернозните тела при интактна уретра. Хистологично, туморната тъкан е с характеристика на high-grade неоплазма със солиден растеж, съставена от клетки с обилна базофилна цитоплазма, везикуларни ядра, висока миготична активност; с обширни фокуси на кръвоизливи, некрози; с наличие на туморни емболи в лимфни капиляри и фокуси на периневрална инвазия. Туморът инфилтрира кавернозните тела двустранно, пробива tunica albuginea и околни меки тъкани, включително и кожата до нивото на ретикуларната дерма. Намерени са метастази и в ингвиналните лимфни възли в дясно.

При проведеното имунохистохимично изследване се установи позитивна реакция за цитокератин /CK AE1-AE3 и негативна реакция за HMWC, Chromogranin A, Synaptophysin. Пролиферативната активност, определена чрез Ki 67, е около 90 %. Случаят е преценен като метастаза от недиференциран карцином .

В медицинската литература са широко дискутирани причините за рядкото развитие на метастази, дори при дисеминирани неоплазми, независимо от богатата васкуларизация на пениса. Авторите обсъждат различни хипотези за тяхното възникване, като най-фаворизирано е развитието им по венозен път чрез ретроградeн транспорт от малкия таз, следван от ретроградeн лимфогенен път при ингвинални метастази и на последно място - артериален път.

П 16

СРАВНИТЕЛНО МОРФОМЕТРИЧНО ПРОУЧВАНЕ НА ТУМОР АСОЦИИРАНИТЕ ТЪКАННИ МАСТОЦИТИ ПРИ РЕЦИДИВИРАЩИ УРОТЕЛНИ КАРЦИНОМИ НА ПИКОЧЕН МЕХУР

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Описаните от Ерлих през 1878 год. мастоцити са имунни клетки, които реагират на стимули, освобождавайки биологично активни медиатори. От широкия спектър медиатори, които отделят някои имат стимулиращ, а други инхибиращ ефект върху злокачествените заболявания. Поставихме си за цел да изследваме разпределението на мастоцитите при уротелни карциноми. Да съпоставим техният брой в първичните тумори на нерецидивиращи и рецидивиращи карциноми. Изследвани са ретроспективно биопсични материали извършени в УМБАЛ „Св. Марина“ Варна. За 5 годишен период (2007-2011 година) изследвахме 50 уротелни карцинома, от които 25 рецидивиращи, които

Анализ на пациенти, починали с ХОББ - брой хоспитализации, смъртност и ролята на диспансерното наблюдение

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Цел: Да се анализират пациентите, починали с окончателна диагноза ХОББ, като се сравни броят на хоспитализациите, смъртността и значението на диспансерното наблюдение от специалист.

Материали и методи: Ретроспективно са проучени 79 пациенти, починали с окончателна диагноза ХОББ в Клиниката по Пневмология и фтизиатрия - Плевен, за периода 2008-2012. Данните са събрани от архива на Отделението по клинична патология. Анализира се честотата на умирания и броя хоспитализации сред диспансерно проследяваните (ДП) пациенти и новооткритите (НО) случаи.

Резултати: Пациентите, починали по време на първата си хоспитализация са 53 (67%), като само 5 (6.3%) са ДП и 48 (60.8%) са НО. Починалите пациенти с повече от една хоспитализация са 26 (33%), като от тях 9 (11.4%) са ДП, а 17 (21.5%) са НО. Пациентите са разпределени в групите статистически значимо $\chi^2 = 5.96$, $p < 0.05$. С болничен престой помалко от 24 часа са 18 (22.8%) от хоспитализираните за 1 път и само 2 (2.5%) от пациентите с повече от 1 хоспитализация.

Заключение: Повечето от починалите пациенти с новооткрит ХОББ са в напреднала форма на заболяването по време на първата им хоспитализация. Скоро след постъпването им се отчита летален изход. Диспансерното проследяване на пациентите с ХОББ от специалист подобрява тяхната преживяемост.

Analysis of patients died with COPD - number of hospitalizations, mortality and the role of dispensary follow-up

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Aim: To analyze the patients who died with COPD as final diagnosis, by comparing the number of hospitalizations, mortality rate and the impact of the follow-up by a specialist.

Material and methods: Seventy-nine patients who died with final diagnose COPD in Clinic of Pneumonology at University hospital - Pleven for the period 2008-2012 were retrospective studied. Data was retrieved from the archives of the Department of Pathology at the University hospital - Pleven. Mortality rate and the number of hospitalizations among patients followed up (FU) and newly diagnosed (ND) were analyzed.

Results: Patients, who died during their first hospitalization were 53 (67%), as just 5 (6.3%) of them were FU and 48 (60.8%) were ND. Patients, who died after more than one hospitalization were 26 (33%), as 9 (11.4%) of them were FU and 17 (21.5%) were ND. The distribution of the patients in the different groups was statistically significant $\chi^2 = 5.96$, $p < 0.05$. Hospitalization stay less than 24 hours was observed in 18 (22.8%) patients, hospitalized for first time, while in the group with >1 hospitalization they were only 2 (2.5%).

Conclusion: Most of the ND patients, who died, were found to be in an advanced stage of the disease at the time of their first hospitalization. They died soon after they were admitted to hospital. The follow-up of COPD patients by a specialist seems to improve survival.

body weight, length and measured body fat, increased blood glucose, total cholesterol and triglycerides in the Fructose group compared to the controls.

Key words: high-fructose diet, obesity, body weight, blood glucose, blood triglycerides

RESEARCH ON EGFR STATUS IN PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA

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Sammary

Introduction: EGFR (epidermal growth factor receptor) is a member of superfamily of tyrosine kinase receptors, which play a role of oncogenes in many cancers. Mutations in EGFR continuously maintained activated EGFR signaling pathway, leading to uncontrolled growth of the tumor cells, and inhibition of apoptosis. Mutations in EGFR have been observed predominantly in adenocarcinoma (AC) type of non-small cell lung cancer (NSCLC). EGFR mutant gene is a potent target for molecular therapy with tyrosine kinase inhibitors (TKIs). Aim: To determine EGFR mutational status of selected tumors of patients with NSCLC, using qRT PCR techniques.Materials and methods: One hundred forty nine patients (41 women and 108 men) with NSCLC were studied for EGFR status in the period of July 2013 - May 2014. Results: The morphology of all 149 cases included 77 (51.7%) ACs, 35 (23.5%) squamous cell carcinoma (SCC), 2 NSCLC- NOS, (1.3%) 1 adenosquamous and 34 (22.8 %) were other types. Patients carrying activating mutations in the TK domain of EGFR were twelve (8.1%) found in 8 ACs , 2 SCCs and 2 in NSCLC- NOS type. The most frequent mutation is a deletion in exon 19 (58.3%), followed by a mutation L858R in exon 21 (25%). In one case two mutations S768I in exon 20 and G719X in exon 18 in male patient were found.

Conclusions: Evaluation of EGFR status is important because TKIs are effective in patients whose tumors harbor activating mutations in the tyrosine kinase domain of the EGFR gene.

Key words: NSCLC, EGFR activating mutations, qRT PCR

HISTOLOGICAL CRITERIA PREDICTING THE POSSIBILITY OF MUTATIONS IN BRCA1 GENE IN OVARIAN CANCER

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Summary

One of the important genes related to ovarian carcinoma is the BRCA1 gene. Carriers of BRCA1 gene are at increased risk of development carcinomas at other primary sites. Since BRCA1 mutation in ovarian carcinomas is found in less than 1/5- th of all the cases, genetic testing of all carcinomas is not a cost-effective approach.

The aim of the following investigation was to study the application of several histological and immunohistochemical criteria for selection of BRCA1 mutated tumors for genetic testing.

Twenty-nine serous papillary carcinomas were retrospectively studied. Characteristics including tumor grade, presence of tumor necrosis, stromal reaction of the tumor, family history and immunohistochemistry expression of p53 protein were evaluated and statistically analyzed. BRCA1 status was evaluated using immunohistochemistry.

Nineteen (65,52%) of the studied cases demonstrated loss of immunopositivity for BRCA1. The presence of tumor necrosis occupying more than 6% of histological specimen (χ^2 =5,15; p=0,023)

and the high-grade tumors (χ^2 =11,97; p<0,001) were significantly related to loss of BRCA1 immunopositivity. Stromal reaction (χ^2 =0,05; p=0,821) and family history (χ^2 =0,00; p=1,00) were not associated with immunostaining for BRCA1. The presence of immunopositivity for p53 was significantly associated with loss of BRCA1 immunostaining (χ^2=10,70; p=0,001). High grade serous papillary ovarian carcinomas with more than 6% of tumor necrosis and p53 immunopositivity are most likely with BRCA1 mutation. These criteria might be used as a cost effective approach for selection of cases for BRCA1 mutation testing and treatment with platina based chemotherapy.

Key words: BRCA 1 mutations, ovarian cancer

INVESTIGATION OF TRIPLE-NEGATIVE BREAST CANCERS-MORPHOLOGICAL AND IMMUNOPHENOTYPIC CHARACTERISTICS

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Summary

Introduction: Breast cancer represents a variety of subgroups with unique biological and clinical characteristics. Basal-like variant of triple negative breast cancers (TNBCs) are aggressive cancers that affect young women. Expression of cytokeratins 5 and 17 identifies a group of breast carcinomas with poor clinical outcome.

Aim of the study: To examine the morphology and IHC characteristics of TNBCs and to identify the basal –like subtype of breast cancers.

Materials and methods: Retrospectively we have selected [illegible]

Caveolin-1 and p-cadherin were used as [illegible] of basal and luminal differentiation.

Results: Among 77 TNBCs using the five-[illegible] method for identification of basal –like [illegible] 80.55% were found positive.Positive f[illegible] EGFR and CK5 were 65.52% of tumors. P[illegible] for EGFR and negative for Ck5 - 2[illegible] According to the type of immunostaining T[illegible] were subclassified into 2 categories-pure[illegible] (40%) and baso-luminal (60%).

Conclusions: There is an evidence that the [illegible] of TNBCs is heterogeneous and doe[illegible] comprise a 'single entity'. Triple nega[illegible] should not be used as a surrogate mark[illegible] basal-like cancers.

Key words: triple negative breast canc[illegible] basal-like breast cancer, immunohistochemistry

RING STUDY TO EVALUATE THE ACCURACY, RELEVANCE AND TH[illegible] CORRELATION BETWEEN IMMUNOHISTOCHEMISTRY AND[illegible] IN SITU HYBRIDIZATION IN DETERMINING THE HER 2 STATU[illegible] IN WOMEN WITH BREAST CANCE[illegible]

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Summary

Introduction: The status of HER2 in breast canc[illegible] is predictive factor for the effect of target[illegible] therapy. Presently there are two widely us[illegible] methods for HER2 status testin[illegible] immunohistochemistry (ICH) and in si[illegible] hybridization analysis. The correlation of th[illegible] overall result (positive/negative) between IH[illegible] and in situ hybridization technique is of grea[illegible] importance for the clinical practice

SU 17. UPPER URINARY TRACT CONGESTION DURING PREGNANCY – SYNDROME OF THE OVARIAN VEIN? CAUSES, DIAGNOSIS AND MANAGEMENT

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Aim: To find the causes for congestion in the upper urinary tract during pregnancy. **Material and methods:** Between 2007 and 2011, we diagnosed 66 cases with upper urinary tract congestion during pregnancy. In 61 patients (92%) it was right-sided, in 2 (3%) – left-sided and 3 patients (5%) had the stagnation bilaterally. The clinical symptoms were pain in the relevant waist area, fever and high temperature. The diagnose was confirmed by ultrasound study; in addition to drainage failures in the upper urinary tract, we investigated the ovarian vein split status and the position of uterus. The treatment was drainage of the relevant kidney by implanting ureteral stent, which was removed in the puerperium. **Conclusion:** We think that apart from enlarged uterus, the main cause for the upper urinary tract stagnation during pregnancy, predominantly in the right side, is the ovarian vein syndrome. In these cases the syndrome is temporary. It occurs mainly during the last trimester of pregnancy and disappears after the puerperium.

Key words: *stagnation, pregnancy, ovarian vein*

SU 18. SURGICAL MANAGEMENT OF HIGH-RISK LESIONS OF THE MAMMARY GLAND

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The management of premalignant breast lesions has become a significant clinical problem for the past 20 years, particulary due to their increased detectability.
The aim of this study is to analyze the frequency, morphology and management of such cases.
The subjects in this prospective study are 105 female patients, who were operated at the Thoracic Surgery Clinic of the Military Medical Academy in Sofia, Bulgaria between 2010 and 2014.
Of all diagnosed cases, 69 had ductal intraepithelial neoplasia (DIN) of which 38 were with atypical ductal hyperplasia and 31 - with intraductal carcinoma; 27 had lobular intraepithelial neoplasia (LIN), 16 patients of these had atypical lobular hyperplasia and 11 were with lobular carcinoma in situ. Finally 9 cases were diagnosed with papillary lesions of which 7 were with atypical papilloma and 2 were with papillary carcinoma in situ.
The purpose of the clinical examination, excluding cases of papillary lesions presenting with nipple discharge, is limited. Of all cases with DIN, 39.1% were pre-operatively mamographically diagnosed with microcalcifications. The cases with LIN were most often detected following a biopsy.
The main dilemma facing surgeons is the balance between the risks of a high-volume resection, leading in some cases to unnecessary cosmetic defects and a minimal excisional biopsy associated with an increased risk of recurrence or a consequent neoplasia.
Additional knowledge of predictive and prognostic factors as well as the development of genetic techniques will give an answer to these questions.

Key words: *premalignant breast lesions*

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УЛТИПЛЕНИ ИПСИЛАТЕРАЛНИ СИНХРОННИ АРЦИНОМИ НА ГЪРДАТА – БИОПСИЧЕН ПОДХОД В У, СОФИЯ

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Мултиплените ипсилатерални карциноми на гърдата се финират като инфилтративни карциноми в същата гърда, ито са макроскопски различими като отделни и подлежат на мерване с наличните към момента клинични и патологични хники. Мултифокалност и мултицентричност са често ползвани, но различни термини с определено съдържание, ето не винаги може да намери точния еквивален при юпсичното изследване, особено в условия на гефрирна агностика.

Целта на настоящето проучване е анализ на отделните одели на множественост върху последователно изследвани юпсични материали, преминали през Клиниката по обща и инична патология и тяхното отражение върху дивидуалния диагностично-терапевтичен подход.

Биопсичната диагностика стои в основата на оценка туморите по отношение на градиране, стадиране и канно-базирани предиктивни фактори, включително цепторен статус, оценка на HER 2 статуса. Авторите се единяват около мнението, че мултиплеността в частните й рояви е важен момент, които следва да се интегрира в стоящия биопсичен подход, които пък е в основата на следващите терапевтични тактики.

Д-8

КАРЦИНОМЪТ НА ГЪРДАТА - ЕДНА ОТ НАЙ-ЧЕСТИТЕ ПРИЧИНИ ЗА СМЪРТ ОТ ЗЛОКАЧЕСТВЕНИ НЕОПЛАЗМИ, КОЯТО СРЕЩАМЕ ОТНОСИТЕЛНО РЯДКО ПО ВРЕМЕ НА АУТОПСИИ. АНАЛИЗ НА 1649 АУТОПСИОННИ ПРОТОКОЛА ОТ АУТОПСИИ, ИЗВЪРШЕНИ ПРЕЗ ПЕРИОДА 2008-2012 г. В УМБАЛ „Д-Р Г. СТРАНСКИ"

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Въведение: Съгласно данните на Националния раков регистър за 2010 година, на челните места по причини за смърт от злокачествени неоплазми при мъжете са тези, локализирани в трахея и бели дробове, колон и проста, а при жените– гърда, колон и трахея и бели дробове.

Материали и методи: Обект на ретроспективно проучване са 1649 аутопсионни протокола от аутопсии, извършени в УМБАЛ „Д-р Г. Странски" през периода 2008-2012 г.

Резултати: За проучвания период са установени 193 случая на пациенти със злокачествени неоплазми. При 158 случая (81,8%), злокачественото заболяване е прието за основно заболяване. При девет случая (4,7%), злокачественото заболяване се явява като конкуриращо заболяване на друга основна причина за смърт. В 26 (13,5%) от случаите, злокачественото заболяване е съпътстващо заболяване, нямащо непосредствено отношение към причината за смърт.

При анализа на честота на злокачествените неоплазми по локализации, на челните три позиции при мъжете попадат: трахея и бели дробове - 31 (23,85%), колон, сигма и ректум - 24 (18,46%) и панкреас - 13(10,00%). При жените са съответно: левкози - 10 (15, 87%), колон, сигма, ректум - 8 (12,70%) и трахея и бели дробове - 7 (11,11%).

Дискусия: Според настоящите резултати, при приблизително 1/6 от случаите, злокачествената неоплазма не е в пряка причинно-следствена връзка с настъпилия летален

съгласно данните от аутопсионни случаи е извън първите три най-чести неоплазми. Това вероятно се дължи на факта, че пациентите с рак на гърдата са най-често диагностично уточнени, клинично проследявани и не загиват в болнични заведения, или ако загинат, то близките отказват аутопсия.

Д-9

АКТУАЛНИ ПРЕПОРЪКИ НА ASCO/CAP 2013 И UK 2015 ЗА ТЕСТВАНЕ НА HER2 ПРИ КАРЦИНОМ НА ГЪРДА

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Точната диагностика е ключов фактор за приложение на персонализирани терапии за лечение на карцинома на гърдата. Тя е важна част от процеса на развитие на терапията, като резултатът от лечението зависи от надеждността на диагностичните тестове.

Интегрирането на персонализираната медицина в различни терапевтични области и добрата диагностична практика налагат прилагане на мултидисциплинарен подход, с изграждане на активна позиция и комуникация от страна на патолози, онколози, хирурзи, платци на здравни грижи, регулаторни органи и пациенти.

Разглеждат се обновените клинични препоръки за тестване на HER2 при карцином на гърда на Американска асоциация по клинична онкология и Колеж на американските патолози - ASCO/CAP от 2013 г., и препоръките в UK за HER 2 тестването, касаещи методология, алгоритъм и интерпретация на тестване на HER2 и необходимостта от ретестване.

Обсъждат се фактори от пред-аналитична, аналитична и пост-аналитичната фаза, оказващи влияние върху изследванията на HER2 с имуно-хистохимични и ин-ситу хибридизационни методики.

Дискутират се основни проблеми в HER 2 диагностиката в страната, като се предлагат насоки за подобряване на точността и възпроизводимостта на резултатите, за постигане на по-висока терапевтична ефективност и оптимизиране на съотношението полза-риск за всички пациенти с карцином на гърда.

Ключови думи: карцином на гърда, HER 2, ASCO/CAP препоръки

П-7

ТУМОРИ НА ЕЗОФАГОГАСТРАЛНАТА ВРЪЗКА

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Езофагогастричната връзка е зона, която свързва две анатомични структури с различен хистологичен строеж. Съществуват терминологични различия в становищата на WHO, UICC и JGCA като затруднението идва от това, че тези тумори не се ограничават в т.нар. Z-линия, а пропагират към хранопровода и/или стомаха. Първоначалната концепция за аденокарциномите към която се придържаме и ние е предложена от Stein, Feith, Siwert, които включват пространството разположено на 5 см проксимално и дистално от Z-линията и ги разделят на 3 типа.

Настоящето проучване е извършено върху ендоскопски и резекционен материал за период от 5 години. Хистологично се установяват аденокарциноми, плоскоклетъчни карциноми, единични аденосквамозни карциноми и други неепителни тумори.

Представяме анализ на получените данни с разпределение по хистологичните видове, степен на диференциация, пол и възраст. Демонстрираме различни начини на метастазиране при аденосквамозните карциноми със стандартни хистохимични и имунохистохимични методи.

П-8

СЛУЧАЙ НА ЕКСТРАПЛЕВРАЛЕН СОЛИТАРЕН ФИБРОЗЕН ТУМОР НА СТОМАХА

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Солитарният Фиброзен Тумор е рядък мезенхимен тумор, описан за първи път в плеврата от Klemperer и Rabin през 1931г.С екстраплеврална локализация неоплазмата се среща в 0,6% от всички мекотъканни тумори, а с произход от стомах са изключително редки случаи.

Представяме пациент на 41г.със Солитарен Фиброзен Тумор локализиран в антралната част на стомаха .Клинично е проявен с болки в епигастриума, кървяща язва на стомаха, мелена и ендоскопска картина на ГИСТ, карцином или лимфом. Хистологичният отговор на ендоскопската биопсия е с насоченост към мезенхимна неоплазия за чиято хистогенеза е препърчано ИХХ изследване на оперативен материал. След извършването на парциална резекция на стомаха – Bilrot II, е намерен тумор със субмукозна локализация в антрума.Макроскопски новообразуването е солитарно с р-ри 30/25 мм, добре отграничено, плътно, гладка срезна повърхност, с жълтеникав цвят. При рутинното хистологично изследване се установи тумор съставен от източени фибробластоподобни клетки, снопчета колаген, разклонени малки кръвоносни съдове, умерена периваскуларна склероза със солиден и сториформен строеж. ИХХ изследване показа силна експресия за Vimentin, CD34, CD99, SMA, bcl-2, пролиферативен маркер KI67 -3,82% и негативна реакция за CKAE1/AE3, C-kit, S100, CD68, Desmin, EMA, p53.На база морфология и ИХХ профил се постави диагнозата бенигнен Солитарен Фиброзен Тумор.

Случаят е илюстрация за необичайна локализация на този тумор и диференциално дагностичните аспекти на източеноклетъчните неоплазми в този регион.

П-9

РЯДЪК СЛУЧАЙ НА ТИМИЧЕН КАРЦИНОМ ПРИ ТРИГОДИШНО ДЕТЕ

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Тимичният карцином е част от епителните тумори на тимуса, към които се числят още тимомите и тимичните невроендокринни епителни тумори. В 90% от случаите те се разполагат в предния медиастинум и са най-честите тумори в същата област(1,2). По епидемиологични данни тази група тумори не е променила честота си през последните 30 години, наблюдават се рядко и предимно у възрастни, с пикова честота

метастатичните мозъчни тумори от първичен белодробен карцином /Начев С. и сътр.2004,2005/. След 2003 г. броят на случаите с първичен тумор в белия дроб и метастази в мозъка се повишава значително както за мъжете, така и за жените като през периода 2009-2010 достига 16 - за мъжете и 11 - за жените. Така възникна идеята чрез изследване експресията на TTF1, p63, cytokeratin 7, synaptophysin, Ki67 и CD31 да се прецени сравнително: 1. пролиферативната активност на мозъчните метастази и съответните им първични недребноклетъчни белодробни карциноми; 2. броя на интратуморните съдове /авансиране на болестта, преживяемост/; 3. наличие на дивергентна диференциация в мозъчните метастази; 4. други биологични показатели свързани с туморната прогресия и метастазиране. Резултатите могат не само да увеличат нашите познания за биологията на изследваните тумори, но и да стимулират намиране на по-добра лечебна констелация.

П-12

МОЗЪЧНИ МЕТАСТАЗИ ОТ БЕЛОДРОБЕН КАРЦИНОМ - МОРФОЛОГИЧНО ПРОУЧВАНЕ ЗА 3 ГОДИШЕН ПЕРИОД

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Белодробният карцином често дава мозъчни метастази, които са обект на оперативна намеса и биопсична диагноза .

ЦЕЛ: Ретроспективен анализ на биопсични хистологични находки за периода 2012 – 2014 г.

МАТЕРИАЛ И МЕТОДИ: Диагностицирани са общо 39 мозъчни метастази. Биопсичният материал е с оцветяване по HE, van Gieson, PAS +Alcian blue.Направени са следните имунохистохимични маркери: CK 7, CK 20, TTF 1, p63, CEA.

РЕЗУЛТАТИ: По пол пациентите са 33 мъже и 6 жени. Възрастовият диапазон е между 41 и 88 г. Хистологично се касае за метастази от 19 аденокарцинома, 9 недиференцирани дребноклетъчни, 3 сквамозни карцинома. Останалите 8 са с комбинирана хистологична находка. В 3 от случаите пациентите са реоперирани за повторни метастази.

ДИСКУСИЯ: ДД проблеми са главно в три насоки.

При метастази от солидни или нискодиференцирани карциноми е важна ДД между аденокарцином и некератинизиращ сквамозен карцином.
При сигурна аденокарциномна метастаза е важно доказването на белодробната генеза,
което става с имунохистохимичен панел.
При метастаза от дребноклетъчен карцином може да се наложи ДД с мозъчен първичен невроендокринен тумор и с малигнена хематологична неоплазма, което също става имунохистохимично.

ЗАКЛЮЧЕНИЕ: Хистологичната и имунохистохимична диагноза на мозъчните метастази е важна не само за стадирането на тумора. В много случаи, мозъчните метастази от белодробен карцином са първична изява на болестта и предшествуват диагнозата на първичната локализация.

П-13
ГАСТРИНОМ В ПАРАПАНКРЕАТИЧЕН ЛИМФЕН ВЪЗЕЛ. КЛИНИЧЕН СЛУЧАЙ

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Гастриномите са невроендокринни тумори, които в над 80% от случаите са локализирани в т.нар. „гастриномен триъгълник". Най-често се откриват в стената на дуоденума, следвана от панкреаса, но са описани и редки случаи на първични тумори на ектопични места като перипанкреатични лимфни възли, стомах, йейунум, оментум, жлъчен мехур, яйчник, черен дроб.

Представяме случай на 66 годишна жена с оплаквания от киселини и болка по хода на хранопровода, гадене, повръщане, диария, появили се за първи път преди около половин година. Извършена е фиброгастроскопия, при която се откриват белези, характерни за синдром на Цьолингер-Елисон (язви по лигавицата на хранопровода и постбулбарно в дуоденума, както и хиперемирана лигавица на стомаха). Изписано е лечение с инхибитор на протонната помпа и прокинетик, препоръчано изследване на гастрин. След

Д-16

ИМУНОХИСТОХИМИЧНО И ИН СИТУ ХИБРИДИЗАЦИОННО ПРОУЧВАНЕ НА HER 2 СТАТУСА ПРИ СТОМАШЕН КАРЦИНОМ - РЕЗУЛТАТИ ОТ ЕДИН ЦЕНТЪР ЗА ПЕРИОД ОТ ЕДНА ГОДИНА

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Позитивен HER2 статус се наблюдава в между 6% и 30% от случаите на карцином на стомаха, като наличието му е свързано с по- неблагоприятна прогноза. HER2 статусът е и позитивен предиктивен фактор за прицелна терапия на това заболяване.

Цел на проучването е да се определи точният HER 2 статус и процента на позитивност при 80 пациенти с авансирал карцином на стомаха, на материали от ендоскопска биопия или след направена резекция на стомаха.

Методи на изследване: След верифициране на карцинома на H&E е проведено имунохистохимично (ИХХ) изследване с анти-HER2/neu (4B5) антитяло, Ventana. Имуноцветяване, определено като 2+ и 3+ е последвано от двуцветна сребърна ин ситу хибридизация (SISH) с UltraView Red ISH DIG Detection и ultraView SISH DNP Detection, Ventana кит.

Резултати: Разлика в HER2 експресията се наблюдава в зависимост от хистологичния вариант и локализацията на тумора. Като цяло HER2 гена е амплифициран при 8 (10%) от изследваните случаи. Амплификация на HER2 гена се установи при 3 от 14-те карцинома интестинален тип, при 2 от карциномите от смесен тип (2/8), при един случай на тубуларен карцином на стомаха (1/1) и при 2 от 15-те карцинома на стомаха при които типът е посочен като „неопределен".

При съпоставянето на HER 2 статуса, оценен на база ИХХ с този, установен със SISH се установи, че амплификация се наблюдава при 2 от 27 случаи с резултат от ИХХ, интерпретиран като „2+" и при 6 от 7 случаи с ИХХ, интерпретирана като „3+".

Изводи: Съгласно настоящите резултати амплификация на HER2 гена при карциномите на стомаха се

наблюдава относително рядко, но в границите на посочваните в литературата и то предимно при интестиналния субтип тип на стомаха. Амплификация на HER2 често корелира с ИХХ резултат, интерпретиран като „3+“ и по рядко „2+“.

Ключови думи: карцином на стомаха, HER2,ИХХ,SISH

ПОСТЕРИ

П-1
НЕВРОЕНДОКРИНЕН КАРЦИНОМ НА МЛЕЧНА ЖЛЕЗА - КЛИНИЧЕН СЛУЧАЙ

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Невроендокринните карциноми на млечна жлеза са изключително редки тумори – малко са и описаните случаи в литературата. Първият описан случай е от 1963 година, но критерии за диагнозата невроендокринен карцином на млечна жлеза се появяват едва през 2003 година, когато СЗО определя, че диагнозата се поставя при поне 50 % екпресия на невроендокринни маркери от туморните клетки. Основно правило в диагностичния процес е да бъдат изключени всички първични невроендокринни карциноми с друга локализация (бял дроб, гастроинтестинален тракт).

Представяме ви случай на 42 годишна жена, оперирана по повод липом в дясна аксиларна област. По време на операцията освен липома са отстранени и 3 лимфни възела, които са били с увеличени размери и променена морфология. Хистологичното изследване на лимфните възли показва метастази от невроендокринен карцином с неясно първично огнище. След провеждане на допълнителни изследвания и

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ТЕМАТИЧНО НАПРАВЛЕНИЕ
"СОЦИАЛНА МЕДИЦИНА И ЗДРАВНИ ГРИЖИ"

Заседателна зала етаж 2

Първо пленарно заседание: 12.00 -18.00 ч. на 04.06.2015 г.
First section meeting

Председател: **Любомир Пировски, н.с.I.с**
Секретар: **Пенка Врачева**

1. Румяна Янева, Тихомира Златанова, Цветелина Петрова-Готова, Николай Попов
ФИНАНСИРАНЕ НА БОЛНИЧНАТА ПОМОЩ – МЕЖДУНАРОДЕН ОПИТ

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3. Пенка Врачева, А. Андонова
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6. Пенка Иванова
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7. Мария Радева
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8. Йоана Симеонова, Анжелика Велкова, Пенка Костадинова
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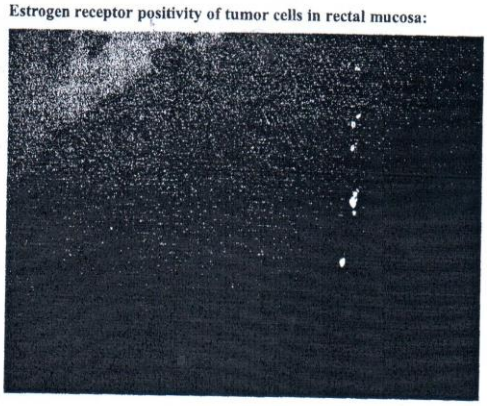
lesions in the mucosa of the rectum under a clinical suspicion of amyloidal deposits.
Method: The biopsies were routinely formalin fixed, paraffin embedded and stained with hematoxyllin eosin. Additional immunohistochemical analysis was performed using the following antibodies: Cytokeratin 7, Cytokeratin 20, E-cadherin, Gross cystic disease fluid protein 15, Estrogen receptor.
Results: Neoplastic cells were observed in the mucosa infiltrating in a discohesive manner sparing the epithelial lining. Typically some of the cells showed a signet ring appearance. The initial assumption was that it was a case of metastatic diffuse gastric carcinoma. The clinician found out that the patient had similar findings 5 years ago in the stomach and there was a suspicion of primary metastatic breast cancer but a primary lesion was never found. However the patient received antiestrogen therapy and the deposits receded. The tumor cells were positive for CK7, ER and GCDFP-15. Additional imaging techniques failed to present a primary lesion.
Conclusion: Minute metastatic deposits with discohesive growth in the gastrointestinal tract should exclude a primary breast lobular carcinoma since primary breast cancer can easily be overlooked.

Estrogen receptor positivity of tumor cells in rectal mucosa:



PS-17-017
Paget disease of the nipple: Co-expression of E- and P-cadherin
M. Lacerda*, A. S. Ribeiro, J. Paredes, F. Schmitt
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Objective: Paget disease of the nipple (PD): a model to study the co-expression of E- and P-cadherin as a putative mechanism of migration of the malignant cells to the epidermis.
Method: 45 cases of PD and DCIS and 26 biopsies of PD. P- and E-cadherins immunostaining using the streptavidin-biotin-peroxidase method. The P- and E-cadherin results were based on a semi quantitative evaluation. Paget cells (PC) and DCIS cells with membranous staining in at least 10 % of the neoplastic cells were scored as positive.
Results: Our series show in all the cases, in the epidermis, singly or closely packed clusters of PC. P and E cadherins were co-expressed in PC in all the cases except 2. PC closely packed: P-cadherin membrane expression is weaker among the neoplastic cells than with the surrounding cells; E-cadherin expression was homogenous. E-cadherin is expressed both in DCIS and in the PC. P-cadherin was expressed in DCIS and PC in all the cases except 2
Conclusion: Motility is the most common accept pathogenic mechanism in PC. Our findings reinforce the recently described role of P-cadherin in the impairment of E-cadherin function (J Pathol 229: 705–18, 2013)

PS-17-018
Blood vessels inside lymphatic vessels in the human breast: An unrecognized morphological and functionally significant structure or an artificial phenomenon?
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Objective: Arteries situated in the lumen of veins are known to exist and can be found in uterine tissue and rarely in breast tissues. Recently, we reported the presence of arteries inside lymphatic vessels. The aim of the present work is to present the morphological appearance and main features of a vascular complex composed of blood and lymphatic vessels that can be found in breast.
Method: Ten benign biopsy tissue specimens from breast (five from male and five from female patients) were analyzed. Immunostaining with D2-40 and anti-CD34 was performed. A partial three-dimensional reconstruction of an arterial-lympho-vascular complex was made.
Results: The presence of arteries situated inside lymphatic vessels was seen in all studied cases (sometimes after revising several tissue samples per patient). The arterio-lympo-vascular complex described is not an artificial phenomenon since it can be followed on series of tissue sections.
Conclusion: Arteries situated inside lymphatic vessels are an existing morphological structure, which can be found in breast tissues from male and female individuals. Their functional role is still unknown, but we assume that it may support lymph propulsion inside the initial collecting lymphatic vessels with an incomplete smooth-muscle layer.

PS-17-019
Additional immunohistochemical features in triple negative breast cancer
V. Barresi*, A. Ieni, R. Cardia, G. R. Ricciardi, V. Adamo, G. Tuccari
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Objective: To evaluate the immunohistochemical expression of androgen receptors (AR), E-cadherin (E-CAD) and Ki-67 in 45 formalin-fixed paraffin-embedded samples of triple negative breast cancer (TNBC).
Method: AR positivity was defined as >10 % positive neoplastic cells with nuclear staining, while E-CAD was semi-quantitatively analyzed as the percentage of cells showing membrane positivity. Ki-67 was scored by counting the positively stained nuclei per 1,000 malignant cells. Correlations between immunohistochemistry and clinico-pathological characteristics of TNBC or overall survival of the patients were investigated.
Results: Histological types were ductal (35; 77.7 %), lobular (7; 15.5 %), medullary (3; 6.6 %). 29 cases (64.4 %) showed a G3 tumor. AR were positive in 12/45 tumours (26.6 %). E-CAD was negative in 24/45 (53.3 %) cases. The Ki-67 index was ≥ 25 % in 17/45 (37.7 %).
Conclusion: The absence of AR expression and high Ki-67 index display a significant correlation with the ductal histotype and high histological grade (G3) ($p<0.001$) in TNBC. Moreover, the patients with negative AR and E-CAD and high Ki-67 expression showed significantly ($p<0.001$) worse overall survival than those with positive AR and E-CAD and low Ki-67 expression.

PS-17-020
Nodular pseudoangiomatous stromal hyperplasia of the breast: A case report
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Objective: Pseudoangiomatous stromal hyperplasia (PASH) is a benign proliferating lesion of the mammary stroma that may rarely present as a localized mass. A case of a large palpable nodular PASH is reported.
Method: A 22-year-old woman presented with a painless mass in her left breast. She underwent ultrasonography and core-needle biopsy and subsequent surgical excision of the mass.

P6.4

Familial and histopathological characteristics of breast cancer in Bulgarian women

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Breast cancer (BC) is the most common cancer in Bulgarian women with an average lifetime risk of 7%. There are some specific features of the familial and histopathological characteristics of BC among the different populations. The aim of this study was to establish the main familial and histopathological characteristics of BC in Bulgarian patients and to compare the data with the data concerning other populations. We studied 82 women, diagnosed with BC, recorded in the Cancer Registry of University hospital, Pleven, during the period from January 2011 to April 2012.The patients were categorized into seven categories, according to familial, clinical and histological features of BC: (1) with familial BC; (2) with no family history but with early-onset BC (< 50 years); (3) with no family history but with bilateral BC; (4) with no family history but with both BC and ovarian cancer; (5) with no family history but with triple-negative BC (TNBC); (6) without family history of BC but with family history of other associated cancers (ovarian, pancreatic, gastric and prostatic cancers); (7) without any of the criteria mentioned above. In our study, the familial BC cases accounted for 15% of all BC cases, early-onset BC - 23%, bilateral BC about 4% and TNBC -7.3%. The established data were similar to the reported data for other European populations. The collected information concerning the familial and histopathological characteristics of BC in Bulgarian women is useful for the clinicians to improve patient care and care of the closely related family members.

Key words: familial breast cancer, histopathological characteristics, Bulgarian women

PS-15-043

Polyarteritis nodosa presenting as orcheoepididymitis

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Objective: We report a rare case of polyarteritis nodosa with first symptoms orchiepididymitis and purpuric exanthema.
Method: Male patient 68 year old presented with fever, purpuric exanthema of lower limbs and orchiepididymitis. Computed tomography showed soft tissue approximate to the left ureter, pyomyositis of hip joint, total architectural destruction of right testicle, suspicious for tuberculosis. But mantoux Quantiferon was negative. We received right orchectomy. The testicle was yellowish, partially hemorrhagic.
Results: Microscopically, atrophy of testicular tubules and ischemic necrosis were detected. Careful examination showed chronic inflammation, thrombosis and fibrinoid necrosis of the tunica intima and tunica media of spermatic cord's and testis' (small and medium size) arteries. Thus, the diagnosis of polyarteritis nodosa was established.
Conclusion: Polyarteritis nodosa is a rare, systemic, necrotizing vasculitis affecting muscular arteries. It usually presents with weight loss, fever and abdominal pain. It is quite rare to present with orchiepididymitis and pyomyositis of hip joint. In recent years, we could find only one other case with orchiepididymitis, but without other general symptoms.

PS-15-044

Six year review including autopsy analysis of in-hospital deaths after Neck of Femur fracture

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Objective: This retrospective study reviews the rate and causes of in-hospital death after Neck of Femur (NOF) fracture in Southampton General Hospital (SGH) over a 6 year period and assesses discrepancy in pre- and post-mortem agreement. These findings are compared with a previous audit which revealed discrepancy between pre-mortem clinical impression and autopsy findings after in-hospital deaths in SGH.
Method: The study population includes all patients who died in SGH after NOF fracture from 2007 to 2013. Case notes were reviewed to determine the pre-mortem clinical diagnosis and then compared with autopsy findings to analyse major and minor discrepancies.
Results: 43 cases were referred for autopsy during the study period; of which 39 cases (90.1 %) were available for analysis. The most common causes of death found at autopsy were IHD (25.6 %), cardiac failure (25.6 %), infection (23.1 %) and MI (7.7 %). No thromboembolic events were identified. Results revealed complete agreement between pre-mortem clinical diagnosis and autopsy findings in 64.1 % of cases. Major discrepancy was found in 25.6 % of cases and minor discrepancy in 10.3 % of cases.
Conclusion: The audit reveals a decrease in major discrepancy compared with the previous audit. However, discrepancy remains between pre- and post mortem findings and highlights the importance of autopsy findings.

PS-15-046

A simple and cost-effective method to identify axillary lymph nodes in specimens from breast cancer patients after neoadjuvant chemotherapy

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Objective: One of the consequences of neoadjuvant chemotherapy in breast cancer is that it leads to a suboptimal amount of harvested lymph nodes. Many methods for optimization of lymph node identification are available but most of them require extensive tissue processing and additional equipment. The aim of the study was to present a simplified and cost-effective method for identification of small and hard to find axillary lymph nodes.
Method: A study was carried out on axillary dissection specimens from 17 female patients, treated with neoadjuvant chemotherapy. After classical sampling, the remainder of the soft and adipose tissue was consecutively processed in ethanol and xylene. The fat-free soft tissues were further sampled.
Results: There was a significant difference in the number of lymph nodes identified per case when the classical method of sampling, which allowed an average of 10.06 (SD+/−4.05) lymph nodes to be collected, was compared to a modified approach that combined the classical method with fat extraction and additional sampling of the cleared soft tissue, resulting in an average of 15.47 (SD+/−3.73) lymph nodes harvested per case (t=9.40; p<0.0001). In three cases (17.65 %), additional positive nodes were found.
Conclusion: The described method for lymph node identification was easy to apply and cost-effective.

PS-15-047

Chondroblastoma: review of fifty-five cases

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Objective: Chondroblastoma is a rare chondroid neoplasm accounting for 1–2 % of all benign bone tumors. It is more common in males and preferentially occurs in skeletally immature patients. However, both age and site distribution of cases may vary.
Method: We reviewed clinicopathological features of 55 cases evaluated with 84 biopsies between 1973 and 2013 years in a single center.
Results: Fifty-four percent of the cases (n=30) were male and median age at admission was 18 (range 5–60 years-old). The most common sites were femur (32.7 %) tibia (18.2 %) and humerus (14.5 %), followed by pelvic bones (10.9 %), feet (5.5 %), and fibula (3.6 %). Rare localizations as hands, patella, ulna, vertebrae and scapula (1.8 %, each) were also noted. Histologically, a secondary aneurysmal bone cyst was observed in 14.5 % of the cases, as well as giant cell tumor mimicking (5.4 %) and chondromyxoid fibroma-like areas (3.6 %). The latest recurrence was 6 years after diagnosis, malignant transformation has occurred in only one case (1.8 %). Rare localizations were more frequently seen in skeletally mature cases (p=0.028, chi-square).
Conclusion: The clinicopathological features of our series were consistent with literature. Presence of secondary aneurysmal bone cysts areas and giant cell rich morphology appears to be the major causes of diagnostic difficulties especially in core-needle biopsies.

PS-15-048

Histological findings in decomposition; Implications for conclusions drawn at autopsy

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Objective: To compare the histological findings of different organs in early decomposition, in order to inform their use as markers of time of death.
Method: Three domestic piglets (Sus scrofa) were euthanized in ethically-appropriate conditions and stored in a temperature-controlled environment at 7 °C. Serial samples of heart, lung, liver, kidney, spleen and pancreas were taken according to a standardized protocol over 3 weeks. Tissue samples were fixed in formalin, processed, embedded, cut and stained with haematoxylin and eosin according to standard local laboratory protocols. Tissue sections were reviewed by two pathologists.
Results: Decomposition was seen to progress faster in some organs than others. There was variation between the experimental subjects despite identical handling, sampling and processing. Apart from broad

kemia and shortly after induction therapy, died.
Conclusion: The present case suggests the importance of the morphologic and karyotype follow-up of patients on TKI therapy even after achieving CCR.

J12.07

Nested Methylation Specific PCR for MGMT promoter methylation test in prediction of radiotherapy and alkylating agents based chemotherapy of Ewing sarcoma tumor

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Introduction: MGMT (O6-methyl-guanine-DNA methyltransferase) is a protein with a specific enzyme activity that is involved in DNA repair. MGMT enzyme repairs DNA alkylation damage, introduced by classical chemotherapy, and also the double strand braking points introduced during radiotherapy. Epigenetic inactivation by promoter methylation of the MGMT gene is very well established. This gene is epigenetically silenced in a variety of cancers, especially glioblastomas, colon cancer, non-small cell lung cancer, gastric carcinoma, head and neck squamous cell carcinoma and also in Ewing sarcoma tumors.
Materials and methods. Ewing sarcoma tumors (2 specimens) were collected from diagnosed patients. Methylation specific (MS) PCR and Methylation specific MLPA methods were used for estimation of the MGMT transcription state through its promoter methylation pattern. Neste MSPCR was used instead of classical MSPCR in order to increase the sensibility and specificity of the method.
Results: The nested MSPCR gave better and clear results as compared with classical and MSMLPA methods. Certain specific conditions for optimization are described.
The Nested MSPCR method proved its efficiency in characterizing the methylation pattern of MGMT gene. The clinical significance of this estimation is linked with the repair capacity of the MGMT enzyme of the tumour damage introduced by classical (alkylating) chemotherapy and radiotherapy. The resistance of Ewing sarcoma tumors was correlated with the MGMT activity and nonmethylated state of its coding gene promoter.

J12.08

Diagnostic panel for testing of germline mutations associated with breast and/or ovarian cancer in Russian population.

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Genetically based breast and / or ovarian cancer is one of the most common forms of family
malignant tumors. Germline mutations in breast cancer are found in 10%, in ovarian cancer in 15% of cases. The routine biochip diagnostic for founder mutations in Russian Federation (185delAG, 300T> G, 4153delA, 4158A> G, 5382insC in BRCA1, 6174delT in BRCA2, 1100delC in CHEK) is commonly used. Additionally, the association of other mutations in NBS1, BLM, KRAS, TP53, PALB2 gene with the higher risk of BC/OC familial cancer has been found in the Slavic population. Also, many researchers have described new clinically relevant mutations in genes BRCA1, BRCA2, CHEK2. To optimize the genetic testing an improved diagnostic panel has been established, including also the following mutations: 2073delA, 3819delGTAAA, 3875delGTCT (BRCA1), 470T> C, IVS2 + 1G> A (CHEK2), R72P, IVS6 + 62G / A (TP53), rs61764370 (KRAS), 172_175delTTGT (PALB2), Q548X (BLM) and 657del5 (NBS1). Analysis of DNA samples of BC/OC patients in has shown the importance of these genetic markers for the Russian population. In addition, searching for new mutations BRCA1/BRCA2 in patients with familial form of BC/OC cancer was performed using the 454 technology (Roche). BRCA1/BRCA2 coding regions were amplified using the BRCA MASTR v2.1 Assay (Multiplicom). Two rare pathogenic mutations (rs80357433, rs80357123) were found in patients with bilateral BC. c.4689C>G mutation (rs80357433) forms a premature stop codon in the BRCA1 gene. The mutations were confirmed by Sanger sequencing. Further investigations using NGS may help in searching of new pathogenic mutations in Russian population.

J12.09

Investigation of the melatonin effect on apoptosis and differentiation in breast cancer stem cells

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Introduction: Cancer is still one of the major health problems. Even though there are significant developments on the anti-cancer treatment, but 5-year survival rates were not significantly improved. In literature, it has been discussed that the main failure of treatment was related to cancer stem cell (CSC) behaviours due to many challenges in the targeted therapies. Melatonin and like chemicals have been used for different diseases. Some studies showed that melatonin is affective on cancer in different ways. However, there is no data about the effect of melatonin on CSCs in the literature. In the present study, we aimed to investigate the effect of melatonin on apoptosis and differentiation in breast CSCs *in vitro*.
Materials and methods: After appropriate treatment time and dose (IC50) were determined by using MTT, MCF7 breast cancer and HEK293 control cells were treated with melatonin. The effects of melatonin on apoptosis, number of CSCs and differentiation were evaluated by flow-cytometry with Annexin-V, CD44+/CD24- markers and MTT, respectively. In order to confirm the FACS results, apoptotic pathway target *BAX* ve *BCL-2* and CSC marker genes (*SOX2, NANOG* and *OCT4*) were analysed by using qPCR.
Results and conclusion: Melatonin increases apoptosis and differentiation in the MCF7 CSCs, but it decreases both in control. This result indicates that the effect of melatonin needs to be studied on the other pathways in order to clarify the therapeutic effect *in vitro* and *in vivo* experiments.
This study was supported by TUBITAK project # 113S478
Key words: Breast cancer, cancer stem cell, melatonin, apoptosis, differentiation

J12.10

„Evaluation of BIOMED-2 Molecular Gene Rearrangement Protocols for Clinicopathological Diagnosis of Hodgkin Lymphoma"

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Analysis of molecular clonality was performed by applying BIOMED-2 protocols to evaluate immunoglobulin gene rearrangements patterns in Hodgkin's Lymphoma (HL) cases). We implemented a standard protocol in HL cases, which have been previously suggestion for clonality detection on formalin fixed, paraffin-embedded (FFPE) tissue of non-Hodgkin lymphoma (NHL) patients.
We investigated 50 consecutive FFPE specimens of HL cases, which consisted of 43 cases of cHL and 7 cases of nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL). Positive CD30, CD20, CD15, CD3, LCA and Facsin markers and IGH, IGK, IGH D-J, and IGL monoclonality in cancerous cells were evaluated using immunophenotyping, BIOMED-2 protocols and Heteroduplex analysis method.
Overall, our finding showed 94% (47/50) clear rearrangements in HL cases; consisting of 74% (37/50) in IGH, 70% (35/50) in IGK, 42% (21/50) in IGH D-J and 44% (22/50) in IGL. IGH clonality detection has related to positive CD30, CD15 ($P<0.005$) as well as LCA and Facsin population cells ($P<0.005$). In addition, the relationship between IGK clonality and CD20, CD3-positive population cells ($P<0.005$) were seen as statistically significant.
Analysis of clonal gene rearrangements in IGH and IGK genes using BIOMED-2 protocols could be implemented as a valuable method for increasing sensitivity (94%) and accuracy of HL similarly to NHL.

J12.11

Clinicopathological and genetic characteristics of breast cancer in Bulgarian women

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One in 14 women in Bulgaria will develop breast cancer (BC) during her life (age 75). Despite the advantages in therapy worldwide, prophylactic measurements are the only certain way of handle with this disorder. One of the well-recognized management tool is genetic screening for the main BC susceptibility genes (BRCA1 and 2). There are more than 3000 distinct

mutations in both genes and alterations are two types - point mutations and large genomic rearrangements (LGR).
Each population has specific clinical, histopathological and genetic characteristics of BC. The aim of our study was to investigate them among Bulgarian women with BC.
The total number of patients included in the study (recorded in the Cancer Registry of University Hospital, Pleven) was 176 women with BC, with average age at diagnosis 57 years. On the basis of preliminary selected criteria, 80 women (with average age at diagnosis 50 years) were referred for genetic testing of BRCA1 and BRCA2.
All of them (100 %) were screened for deleterious point mutations - two in BRCA1 (C61G, 5382insC) and three in BRCA2 (6079del4, 9326insA, 9908insA) and 89% for LGR.
The results of our study were: 20 (11%) of women showed familial BC, 21(13%) of them - early onset BC, 20 (13%) had TNBC and only four of them (2%) had bilateral BC. We found only one point mutation among selected patients - 5382insC in BRCA1 in 2, 5% and did not find LGR.
The established data were similar to the reported data for other European populations.

J12.12
Detection of Immunoglobulin IGH Gene Rearrangements on Formalin-Fixed, Paraffin Embedded Tissue in Lymphoid Malignancies

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Human lymphomas are aggressive malignant diseases, which can be categorized based on their B and T cell lineage. B-cell lymphomas form around 90% of the total lymphoma cases, whilst the remnants of malignancies arise from the T cell branch. Lymphomas are mostly characterized as clonal proliferations of specific tumor cells. The detection of malignant lymphomas are extensively investigated by their morphological features, immunohistochemistry and flowcytometric immunophenotyping, but in some cases remain unknown. The BIOMED-2 protocols were used to determine the clonality of IGH gene rearrangements in patients with lymphoma. PCR amplification was performed on FFPE of 50 patients with B-cell lymphoma, which consisted of 11 cases with HLs, 25 cases of B-NHLs and 14 cases of B-LPD (lymphoproliferative disorders) which were diagnosed as unclassifiable lymphoma. The rate of positive clonality was detected in 96% (24/25) of B-NHLs, whereas in 4% (1/25) of cases clonality was showed in a polyclonal pattern. In B-HLs, 82% (9/11) of cases showed clonality and 18% (2/11) of the cases showed polyclonality. (The rate of positive clonality observed was 64.3% (9/14) of cases with B-LPD and in 35.7% (5/14) of cases clonality was not detected in any of immunoglobulin gene family (FR1 , FR2 ,FR3). In groups with DLBCL, clonality was detected in 95% (19/20) of the cases) This makes no sense. In patients diagnosed with FL and MALTs, 100% of cases showed clonality for complete IGH. Our study revealed that Euro Clonality BIOMED-2 protocols could be considered as a valuable and reliable method for clonality detection, especially in IGH analysis.

J12.13
upregulation of stanniocalcin1 gene expression in colorectal cancer

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Introduction: Identification of the genes involved in the carcinogenesis of the colorectal cancer could be useful for identifying of diagnosing biomarkers and improvement of treatment. Stanniocalcin1 is a glycoprotein hormone that is knowp to be involved in various biological function especially calcium hemostasis.Its upregulation has been shown with various cancers in several studies however its main role is not clear in cancer progression. In this study we assessed the expression of STC1 gene in colorectal cancer for the first time in Iran.
Material and methods: Tumor tissues and adjacent tissues were obtained from 48 colorectal carcinoma patients who undergone partial or total colectomy for CRC. The relative expression of STC1 was measured by using quantitative RT-PCR. GAPDH was used as a housekeeping gene. The Relative Expression Statistical Tool (REST) and SPSS software were applied for data analysis.
Results: Relative mRNA levels of STC1 were significantly higher in tumor tissues in comparison with margins (p value =0.025).
Conclusion: Our results showed that STC1 gene expression significantly increases in tumor tissues and therefore, it may be helpful as a molecular biomarker for early diagnosis of CRC.

J12.14
The EGFR mutational status screening in Romanian lung adenocarcinoma patients

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The personalized medicine (tyrosine-kinase inhibitors-TKI) represents an alternative to the advanced lung cancer patient's healthcare. Nowadays, the screening of the EGFR gene (which codifies a protein-kinase), has become a TKI-therapy selection tool. In non-small-cell lung carcinomas, the TKI-therapy response depends, additionally, on hystopatological subtype, the most suitable being adenocarcinoma (ADK).
The study aim was to analysis the EGFR mutational status in ADK patients which makes them susceptible for EGFR TKI-therapy.
DNA was extracted from formalin-fixed paraffin embedded tumor tissues (85 biopsies and 222 resections) from 307 Caucasians patients in different ADK stage (185M:122F, enrolled from December 2013-February 2015). EGFR mutations screening (exons 18-21) was performed by PCR reverse-hybridization (n=144) and ARMS-PCR (n=163).
EGFR mutations were detected in 50 (16,29%) patients (35 with primary and 15 with secondary tumors, mostly TTF-1 positive, tumor cell between 90% - 0,5%, sex distribution of 1M:1.39F, patients age 35-87 year old, average age at screening time-61,17±10,15). The most frequent mutations, which confer sensitivity to TKI therapy, were identified in exons 19 (62%) and 21 (24%). Less frequent were detected mutations in exon 18 (G719S) (6%), and the compound mutation p.E746_A750del/p.L858R (2%). The resistance mutation T790M (exon 20) was detected in 3 cases, in singlet (2%) or doublet condition (4%). The mutation T790M/EGFR-sensitive denotes acquired resistance post TKI-therapy (erlotinib), both high-stage ADK women having a progressive disease evolution.
Our results, in accordance with international data, showed that the EGFR mutational status detected by PCR-based method screening is a sensitive and helpful tool for the clinical decision in the ADK anti-EGFR personalized therapy.

J12.15
Discordance of HER2 status in primary breast carcinomas and distant metastatic sites

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Background: Assessment of human epidermal growth factor receptor 2 (HER2) status in patients with breast carcinoma (BC) is commonly performed using neoplastic tissue from the primary tumor. There are few data regarding the HER-2 status in the corresponding distant metastases. Several papers have shown that HER2 status may be different in metastatic lesions when compared with the primary tumor, and this discrepancy is more frequently found in distant metastases than in locoregional ones.
Methods: HER-2 status in 47 patients with a primary breast tumour (at different time of therapy stages) and at least one distant metastatic (bone, brain, lung, liver, or other) lesion was analysed by immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH).
Results: The overall concordance rate for HER2 was 91.48%. Thirty-four cases were concordantly HER2-negative in primary BC and distal metastases, nine cases were HER2-positive in both primary and metastatic tumors, and 4 cases were discordantly HER2-positive in the primary BC and HER2-negative in the metastases.
Conclusion: Simultaneous determination of HER2 in BC and corresponding distant metastases is not mandatory, but may influence the therapeutic management. Discordance in HER2 status may be found not only between primary BC and its metastases, but also between consecutive relapses of the same tumor.
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J12.16
Hypermethylation of KISS1 and EDNRB promoters as predictors of disease progression in patients affected with sporadic colorectal cancer

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PS-21-020
The influence of intra-abdominal hypertension on the morphological status of internal organs
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Objective: It is known that an increase of intra-abdominal pressure has a negative effect on the function of the gastrointestinal tract, respiratory, cardiovascular and urinary systems.
Method: It was an experimental research: male rats of the same age, weight, diet ($n = 100$). Among them: a control group ($n = 10$) - intact animals without affecting; comparison group ($n = 90$) - animals, which was artificially created by intra-abdominal hypertension of different degrees (15, 25, 35 mm Hg) and different exposure times (3, 12, 24 h). The method of creation of intra-abdominal hypertension - pneumoperitoneum.
Results: We made a histological examination of tissue of kidneys, liver, intestines, myocardium and lung. We got these results: lung - perivascular edema, focal hemorrhage, atelectasis foci; myocardium - fragmentation of cardiomyocytes with ischemic area, vascular congestion, focal and extensive hemorrhage in the myocardium; liver - dystrophy of hepatocytes, congestion of segments central vein; kidney - dystrophy of renal tubular epithelium, perivascular hemorrhage, congestion of the capillaries. Pathological changes in the intestine were not identified.
Conclusion: The degree of these changes depends on time and level of intra-abdominal hypertension.

PS-21-021
Trousseau's syndrome associated with lung adenocarcinoma presented as acute myocardial infarction
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Objective: Trousseau's syndrome (TS) may be encountered in a form of diverse and polymorphic spectrum of thrombotic disorders in setting of malignant disease. We suspected that TS was an underlying cause of acute myocardial infarction (AMI) in a 49-year-old man with low cardiovascular risk and suspicious lung infiltration.
Method: We represent a case of 49-year-old man with radiologically detected abnormal 15 mm shadow in right lung hilum who suddenly developed AMI. Four days later, and before diagnostic bronchoscopy, the patient died, and clinical autopsy was performed.
Results: Post mortem results revealed poorly differentiated lung adenocarcinoma in advanced stage. Blood clots were found in medium and small branches of coronary blood vessels not only in the field of myocardial infarction, but also in surrounding non-necrotic muscle. In addition to massive AMI, ischemic infarcts were found in kidney and spleen. Occlusive thrombi and thromboemboli were found in veins and arteries of medium and small caliber in visceral organs, and in venous plexuses of the pelvis.
Conclusion: Although TS is not rare, the presentation with AMI is very seldom encountered in clinical practice. For patients without clinical evidence of atherosclerosis, hypercoagulability associated with cancer as underlying cause of AMI should be considered and investigated.

PS-21-022
Adult extrarenal nephroblastoma arising in a retroperitoneal mature teratoma
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Objective: Nephroblastoma is a frequent tumour in children but rare in adults. We report an even rarer case of an adult extrarenal nephroblastoma developed in a retroperitoneal mature teratoma, with speculated metastatic gonadal origin.
Method: A 44-year-old man with a 5-month history of intermittent colicky low back pain underwent radiologic examination that revealed a large right-sided retroperitoneal cystic-solid mass. Surgical resection was performed. Grossly, a 17 cm, well circumscribed, multilocular, cystic tumour filled with green-tan fluid and containing a 6 cm solid nodular area was identified.
Results: On pathology, the solid area revealed the classic triphasic pattern of nephroblastoma (blastema, stroma and epithelial glandular structures). The cystic spaces were covered by fibrin or lined by squamous epithelium and foreign body giant cells. Immunohistochemically, blastema cells were focally positive for WT-1 and vimentin, stroma for vimentin and epithelial structures for cytokeratins AE1/3. The diagnosis of nephroblastoma arising in a setting of mature teratoma was made. Urological examination was advised, which showed a small scarred calcified area in the right testis.
Conclusion: The few reported cases of adult extrarenal nephroblastomas in teratomas developed in metastatic sites of gonadal teratomas. Literature search did not reveal cases of adult nephroblastoma in primary retroperitoneal teratoma.

PS-21-023
Primary extra-gastrointestinal stromal tumour of the retroperitoneum: Case report
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Objective: Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract and typically express c-kit/CD117. Rarely neoplasms with similar pathologic features are found outside gastrointestinal tract (omentum, mesentery, retroperitoneum) and are called extra-gastrointestinal stromal tumours (EGISTs). Only 58 cases of primary retroperitoneal EGISTs have been reported. We herein report an additional case of this rare entity.
Method: A 19-year-old female presented with lower abdominal pain. Pre-operative radiological evaluation with ultrasonography and computed tomography revealed a 3 × 3.8 cm retroperitoneal heterogeneous solid mass located near the left common iliac artery. She underwent surgical removal of the tumour.
Results: On gross examination, we identified an encapsulated tumour 5 × 4 × 2.5 cm and the frozen section was "negative for malignancy". Microscopically, the neoplastic cells were proliferating spindle cells, with mitotic rate of 0–1/50hpf. Immunohistochemistry revealed strong positive staining for c-kit and CD34 and the diagnosis of GIST was confirmed. Pathologic diagnosis was GIST of low malignancy potential according to Fletcher classification. The patient had uncomplicated postoperative course and did not receive adjuvant tyrosine-kinase inhibitor therapy. At 2- years follow-up she remains disease-free.
Conclusion: Primary EGISTs of the retroperitoneum are extremely rare. Immunohistochemistry for c-kit may help in the differential diagnosis of EGIST from other mesenchymal tumours.

PS-21-024
Incidence and morphological characteristics of the gastroenteropancreatic neuroendocrine tumours, diagnosed and confirmed for one year in UMHAT Dr. Georgi Stranski, Pleven
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Objective: Over 90 % of neuroendocrine tumours (NETs) in Bulgaria were reported to arise in the gastrointestinal tract. Our objective was to

study the incidence and morphological characteristics of the gastroenteropancreatic NETs, diagnosed for 1 year.
Method: The present retrospective study explores the incidence and morphological characteristics of the gastroenteropancreatic NETs, diagnosed and confirmed for 1 year period (during 2014) in UMHAT "Dr. Georgi Stranski", Pleven.
Results: Seven cases of gastroenteropancreatic NETs were diagnosed and treated for the studied period. Most common primary sites were: pancreas in 4 (57.14 %) cases and 2 in colon (28.57 %) cases. According to the morphological criteria, 2 (28.57 %) were well differentiated NETs, 3 (42.86 %) were moderately differentiated, and 2 (28.57 %) were poorly differentiated NETs. One of them was mixed adenoneuroendocrine carcinoma. All cases demonstrated immunoexpression of Chromogranin A and Synaptophysin in adition to the distinct neuroendocrine morphology. Distant site metastasis were observed in 5 (71.43 %) cases.
Conclusion: According to our results, most of the gastroenteropancreatic NETs were well and moderately differentiated. A considerable number of patients had distant metastasis at the time of diagnosis. The expression of Chromogranin A and Synaptophysin supported the morphological diagnosis of gastroenteropancreatic NET.

PS-21-027
Dantrolene variable hepatic toxicity related to oral and intravenous long term administration
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Objective: Dantrolene sodium is a muscle relaxant used in therapy of spasticity and malignant hyperthermia, because of its wery well delimited peripherall action on skeletal muscle. Its major inconvenient is still related to hepatic injury. Our study try to identify a possible relationship between dantrolene way of administration and the degree of hepatic injury, as an useful step towards the most appropriate therapeutic decision.
Method: 21 male Wistar rats were randomly assigned in three groups, control group/oral administered dantrolene group/intravenous administered dantrolene group, for 3 weeks. 5 mg/kg body weight of dantrolene, in a volume of 0,3–0,5 ml/100 g weight, in a suspension of saline solution with 0,5 % carboxymethyl cellulose was given once a day.Samples of hepatic tissue were prelevated and processed for the microscopic exam.
Results: The two groups of rats which received dantrolene presented large susceptibility for hepatic alterations; hepatic steatosis, signs of acute hepatitis revealing the toxicity of dantrolene.
Conclusion: Long term dantrolene administration requires a clinical and laboratory monitoring of the liver functions, together with individualization of doses, in order to obtain the optimal response with minimal hepatic injuries.

PS-21-028
Electro-hyperthermia induced programmed cell death in a colorectal cancer allograft
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Objective: The electric field and the concomitant heat of <42oC, generated by modulated electro-hyperthermia (mEHT), can selectively target malignant tumours due their elevated glycolysis (Warburg effect), ion concentration and conductivity compared to normal tissues. mEHT has been used as a complementary to radio- and chemotherapy. We earlier showed in immunocompromised mice that mEHT can provoke apoptosis and may promote immune cell infiltration in colorectal cancer xenografts. Here we tested the mEHT related damage, stress and immune response in cancer allografts in immunocompetent mice.
Method: We implanted Colon-26 carcinoma allografts in Balb/C mice. After mEHT treatment we used immunohistochemistry on fixed samples for detect AIF, BAX, caspase-3, HMGB1 proteins and CD3+ cells.
Results: mEHT resulted in progressive tumour damage compared to controls. The cell death response was accompanied increase of activated caspase-3 levels, without significant translocation from mitochondria into nuclei of apoptosis-inducing factor (AIF), or accumulation of Bcl-2-associated X protein (BAX) in mitochondria. Stress-associated release of HMGB1 protein and increased number of CD3 positive T cells were also observed. Additional i.p. administration of a CD8+ T-cell promoting agent resulted in a systemic tumour destruction.
Conclusion: mEHT can induce caspase-dependent programmed cell death and stress-associated release of HMGB1, which may support T cell mediated tumour immunity.

PS-21-029
Structural changes in the tissues for transplantation after sterilization with gamma and electron beam radiation
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Objective: Sterilization is an important step in the preparation of biological material for transplantation. The aim of the study is to compare morphological changes in three types of biological tissues induced by different doses of gama and electron beam radiation.
Method: Frozen biological tissues (porcine skin xenografts, human skin allografts and human amnion) were irradiated with different doses of gamma rays (12.5, 20, 35, 50 kGy) and electron beam (15, 25, 50 kGy). After melting the specimens were fixed by formalin, processed by routine paraffin technique and stained with hematoxylin and eosin, alcian blue at pH 2.5, orcein, periodic acid Schiff reaction, phosphotungstic acid hematoxylin, Sirius red and silver impregnation.
Results: The basic staining showed vacuolar cytoplasmic degeneration of epidermal cells by the lowest doses of gamma and electron beam radiation. There was damage of fine elastic fibers in the xenografts dermis at the dose of 25 kGy of both radiation types. Disintegration of epithelial basement membrane was induced by the dose of 15 kGy of electron beam radiation. Disintegration of the fine collagen fibers in the papillary dermis was induced by the lowest dose of electron beam and by the highest dose of gamma radiation.
Conclusion: Irradiation by both, gama rays and the electron beam, causes similar changes on cells and extracellular matrix, with singnificant damage of the basement membrane and of elastic and fine collagen fibers in the papillary dermis, the last caused already by lowest dose electron beam radiation. Supported by VEGA 1/0297/14.

PS-21-030
Modulated Electro-hyperthermia (mEHT) of allografted colorectal cancer: Does modulation make any difference?
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Objective: Modulated electro-hyperthermia (mEHT) can be complementary to radio- or chemotherapy in clinical oncology. We earlier showed that amplitude modulated radiofrequency (13.56 MHz) current of mEHT can be enriched in cancer cells to elevate heat and induce programmed cells death without harming adjacent non-malignant tissues. The effect of modulation, chosen to fit the time-fractal fluctuation in fractal electrophysiology, was studied in EHT treatment.

PS-09-028

Immunohistochemical expression of p53 and BRCA1 in high grade endometrial carcinoma

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Objective: Identification of tumours with BRCA dysfunction has therapeutic and prognostic implications proven for breast and ovarian but still debatable for uterine carcinoma. The aim of this study is to evaluate the expression of p53- and BRCA1-proteins, detected by immunohistochemistry, in high grade endometrial in comparison with high grade serous ovarian carcinomas (HGSOC).
Method: The investigation was performed on 13 cases of endometrial carcinoma with serous and non-serous G3 morphology and 13 age-matched cases of HGSOC using monoclonal anti-p53 and BRCA1 antibodies. Two of the uterine cases - one with serous and one case with mixed histology (serous and G3 endometrioid) had history for previous breast carcinoma.
Results: All 13 HGSOC and 5 out 13 endometrial cancers showed p53 overexpression. Twelve of thirteen ovarian carcinomas revealed no expression of BRCA1 and therefore are suspicious for BRCA1-mutations. In the uterine group the same pattern was observed only in the two cases with previous breast carcinoma which were p53 positive.
Conclusion: Combination of serous morphology, p53 overexpression and history for previous or synchronous breast cancer or HGSOC could be included as criteria for stratification of patients with endometrial carcinoma suspicious for BRCA1-mutations and suitable for genetic testing.

PS-09-029

Primary strumal carcinoid of the ovary as an uncommon form of ovarian teratoma: A case report

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Objective: Strumal carcinoid (SC) is a rare variant of ovarian teratoma, characterized by an intimate mixture of thyroid tissue and carcinoid structures in a variable proportion. Primary ovarian carcinoids form 5 % of ovarian teratomas and 0, 5–1, 7 % of all carcinoid tumours.
Results: Case Description: We present a case of strumal carcinoid occurring in 45-year-old woman. The pacient with short history of constipation underwent an unilateral salpingo-oophorectomy for cystic tumour of the left ovary detected by the ultrasonography. Histopathological analysis of the tumour mass revealed SC of typical morphology. The woman subsequently underwent abdominal hysteradnexectomy and omentectomy without residual tumour structures. No subsequent therapy was indicated. Currently, the patient has no signs of relaps.
Conclusion: Primary ovarian carcinoid tumours represent a group of ovarian monodermal teratomas, occuring in middle-aged or older women. Most patients are asymptomatic or may have unspecific symptoms of abdominal distention, a minority has carcinoid syndrom or a constipation. These tumours are classified into five groups according to their histological patterns: insular, trabecular, mucinous, strumal and mixed. Only few cases have malignant course. SC, when confined to the ovary, is almost always benign.

PS-09-031

Impaired endometrial receptivity in infertile patients with external genital endometriosis

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Objective: To study the morphological and molecular substrate of impaired endometrial receptivity in fertile patients with external genital endometriosis who enter an assisted reproductive technology program.
Method: 140 infertile patients, including 50 women with grade 1-2 external genital endometriosis (a study group), 44 with endometrioid ovarian cysts (a comparison group), and 54 with tuboperitoneal factor of infertility (control group) were examined. All the patients underwent aspiration pipelle endometrial biopsy on 6–8 days following ovulation. Serial paraffin-embedded sections were used to determine the count of pinopodia and the expression of leukemia inhibitory factor (LIF), HOXA10, glycodelin A, integrin avβ3, and aromatase in the superficial epithelium, glandular epithelium, and endometrial stroma.
Results: The patients with external genital endometriosis had significantly lower pinopodium counts ($p < 0.05$), decreased expression of LIF, HOXA10, integrin avβ3, and glycodelin A in the superficial epithelium and a significantly increased expression of aromatase in the superficial epithelium, glands, and endometrial stroma cjmparing with control ($p < 0.05$). The highest expression of aromatase was seen in patients with endometrioid ovarian cysts.
Conclusion: Changed endometrial receptivity may be one of the leading causes of infertility and lower efficiency of the assisted reproductive technology program in patients with external genital endometriosis.

PS-09-032

Transitional cell carcinoma of the endometrium: A case report

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Objective: Endometrial transitional cell carcinoma (TCC) is a rare tumour with a few cases reported in the available literature. We present a case of endometrial transitional cell carcinoma in a 43 years old patient presented with profuse bleeding. After curettage and diagnosis of TCC was made, the patient underwent operation.
Method: The operative material contained the uterus with both adnexa. The uterus (720 gr weight) contained an intracavitary, polypoid mass which infiltrated the whole myometrium, serosa and the left ovary. The tissue specimens were fixed in 10 % buffered formalin and embedded in paraffin. Immunostainings with CK7, CK20, Vimentin, Estrogen receptor, Progesteron receptor and Thrombomodulin were made.
Results: Microscopically, the tumour was composed of solid sheets and tightly packed papillary structures with thin fibrovascular cores lined by many layers of transitional cells showing moderate to severe atypia. The neoplastic cells were positive only for CK7 and Vimentin. The patient had FIGO stage III A. Pulmonary and liver metastases occurred after the chemotherapy and the patient passed away 11 months after diagnosis.
Conclusion: TCC is a distinct type of endometrial carcinoma which has to be recognized. It broadens the spectrum of endometrial neoplasms.

PS-09-033

Sertoli - Leydig cell tumour with heterologous elements

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Objective: Ovarian Sertoli-Leydig cell tumour of intermediate differentiation with heterologous elements is a rare ovarian tumour that belongs to the group of sex cord stromal tumours. This tumour affects mainly young women, with an incidence of less than 0,5 % of ovarian tumours. We present a case of unilateral ovarian tumour in a 34-year old patient.
Method: The tissue sections were conventionally fixed, embedded, stained with HeEo and immunostained with Calretinin, Inhibin, CK7, CK20, Vimentin, CD99 and Synaptophysin.
Results: Gross examination of the pathologic specimen showed an ovarian mass with a diameter of 14 cm, with smooth intact external surface. The cut section revealed solid tumour with cystic areas filled