THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Histopathological and molecular pathological prognostic factors in ovarian cancers

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The Examination takes place at the Department of Obstetrics and Gynecology, University of Debrecen , 03.04. 2019. 11:00 AM

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, 03.04.2019. 1:00 PM

Aims and scope

Ovarian cancer is one of the most frequent cause of females' cancerrelated- deaths. Close to 239.000 new cases of ovarian cancer (OC) are diagnosed annually world-wide and this malignancy carries a higher mortality rate (approximately 152.000 each year) than all other female genital cancers combined. Striking geographical differences in its occurrence are noted. OC ranked 5th among the most common lethal cancers in the US in 2014, and its prevalence is known to be unusually high in Eastern- and Central Europe. According to the American Cancer Society in 2017 approximately 22,440 women will be diagnosed with ovarian cancer, and 14,080 women will die of this disease. Epithelial ovarian cancer (EOC) accounts for 90% of all malignant ovarian tumours. The overall prognosis is poor, rate of remission sets only 40–50% of all cases

In advanced stages of epithelial ovarian cancers the 5 year survival rate is only about 27%. According to Hungarian National Healthcare System data, in 2017, 15128 female were diagnosed with OC, ca. 1100 in ovarian cancer. 90% of ovarian cancers are epithelial. Cancer morbidity and mortality shows no diffence in regions of Hungary, neighter can observe better prognostic tendency in 5 year survival survival, which is observed in colorectal cancers.

Primary debulking surgery and platinum-based chemotherapy are the dominant forms of current treatment options. Despite surgery and platinum-based systemic treatment the 5-year survival of these patients is dismal (cca27%). Although age, performance status, histology type, Inter-national Federation of Gynecology and Obstetrics (FIGO) stage and tumor grade are fundamental in determining prognosis of AEOC, there is undisputable need for identifying additional specificmolecular predictive parameters.

Epithelial ovarian cancer (EOC) accounts for 90% of all malignant ovarian tumours. The overall prognosis is poor, rate of remission sets only around half of all cases. Ascites and peritoneal dissemination is a typical and prospective phenomenon is EOCs. Tumor cells detach from the primary neoplasms and easily survive whilst floating in ascites fluid and eventually anchor onto the visceral or parietal peritoneum. Selection of cancer cell subtypes, only those cells which are capable of avoiding detachment-induced anoikis will survive. This pathomechanism is thought to play important role by alterations of the entire adhesion molecule expression profile accompanied by disassembling junctional structures, re-organization of the

cytoskeleton plus re-emerging vimentin expression. The cumulative effects of these alterations are represented by increased motility and proliferation of the tumor cells, by their ability to avoid apoptosis and anoikis, and by the active secretion of matrix metalloproteases. By these surface related changes co-working with active signaltransduction, the tumor cells will be capable to reach other organs surfaces. This is called intraabdominal dissemination – the crutial point of EOC high mortality.

It is a relevant clinical-onco-pathological expectation to find predictive and for a certain degree predictive factors to calculate proper treatment for early progressive tumors with and to determine medication for long term survival patients. The latest oncotherapeutic protocols require prognostic and predictive markers to have the ability to give more individualized and cost/benefit effective treatments and interventions.

Aims and scope

- Our observations are oriented to test expressional profile changes of adhesional molecules and prognostic markers to find molecular predictors (as immunhistochemical markers) of early tumor progression and long term survival.
- We intended to clarify whether the changes of expression patterns of cell membrane associated proteins (E-cadherin and β-catenin), Ki-67 proliferation index and p53 protein are showing differences in EOC's peritoneal dissemination.
- Our goal was to clarify differences in protein profiles of low-grade and high-grade tumors in solid tumors and malignant effusion, as well.
- We intended to test the applicability of cytological microarray (CMA) techniques in analyses of tumor progression and metastasis formation

Materials and methods

Advanced epithelial ovarian cancer (AEOC) cases were collected from tissue archives of the Department of Pathology, ClinicalCentre, University of Debrecen, Department of Pathology, Albert Szent-Györgyi Health Centre, University of Szeged, Semmelweis Hospital of Kiskunhalas and Csongrád County Health Care Centre covering the time period of 16 years (1999–2015). The fundamental selection criterion was EOC in advanced clinical stage irrespective of pathological grading. Stages with spread beyond the ovaries were involved: FIGO Ic, FIGO IIc, FIGO IIIa, FIGO IIIb, FIGO IIIc, FIGO 4. 34 cases were FIGO stage III or IV, and 10 cases FIGO stage Ic, or IIc. All cases were selected on the basis of their original histopathology reports. Relevant clinical information was obtained from patients' medical records using the appropriate electronic databases. The mean age was 63 years, all patients had AEOC without additional malignant conditions. Patients whose tumor progressed within twelve months following the introduction ofthe first platinum based therapeutical regimen were assigned "EP [early progressive] cases". Patients surviving at least one hundred months after the primary diagnosis of AEOC comprised the LTS [long term survival] group. Almost all patients had primary platinum-based Taxol-Carboplatin (TC) therapy, or further variations of the following 3protocols: (i) conventional first line cyclophosphamide + cisplatin(CP); (ii) cyclophosphamide + doxorubicin + cisplatin (CAP) or(iii) cyclophosphamide + 4-epi-doxorubicin + cisplatin (CEP). Those patients who had received non-platinum- based primary chemotherapy were excluded. Lack of tumor samples, missing exact OS, incomplete follow up or suboptimal tissue sample (e.g.: only biopsy) were the most common causes for exclusion of patients. Thus, in the end, out of the primarily selected 431 cases, a total of 44 patients represented either "EP" or "LTS" categories, as defined above.

The archives of the Department of Pathology at the University of Debrecen Clinical Center were searched for cases of malignant epithelial ovarian tumors for which tissue samples of the primary tumor or that of a peritoneal deposit (omentum, parietal pelvic peritoneum, abdominal viscera) together with cell blocks of tumorous ascites samples from the same patient were both available. A total of 27 patients met the inclusion criteria. These EOC cases were collected covering the time period of 5 years (2009–2014). All histological sections were reviewed by two pathologists (LT and BN) for confirmation of the initial diagnoses.

New TMA blocks were built. A total of 237+318 cores were utilized all in all 5+7 TMA blocks from the selected 44+27 tumors.

Tissue microarray (TMA) construction.

All tumor samples were fixed in 4% buffered formalin and embedded in paraffin. All histological sections were reviewed by two pathologists (LT and BN) for confirmation of the initial diagnoses. Representative areas within the relevant paraffin blocks were identified by using the corresponding HE stained slides. From these areas 1 mm thick core samples were retrieved using a TMA master (3DHistech Budapest, Hungary) and positioned in the recipient paraffin array block. Three representative cores were obtained from each tumor. If for any reason one or more immunohisto-chemical reactions failed, or either the cores were lost or severely damaged, plus if the cores were non-representative (were necrotic or comprised of dominantly non-neoplastic tissue), new cores were punched from other areas of the original block(s) and a new TMA block was built. A total of 237 cores were utilized in 5 TMA blocks from the selected 44 tumors.

Ascites samples were handled as follows. 50 ml a liquid of ascites fluid were fixed in 10% buffered formalin for 12-24 hours at 4°C, followed by 10 min centrifugation at 2500 rpm. The sediment was mixed into 3% agar gel at 56°C. After solidification at room temperature was complete, the cell-containing agar gel was transferred into routinely used tissue cassettes which allowed further fixation, dehydration and routine tissue processing. Only the “high enough cellularity” samples (high tumour cell density HTCD group N = 22) were used to obtain 2 mm thick cores (3 cores from each) which were adequate for CMA block construction using again the TMA master (3DHistech Budapest, Hungary). The remaining 5 low cellularity samples (low tumour cell density (LTCD) group) were used for IHC analysis as conventional “whole-surface” sections.

Four micron thick sections from the TMA blocks were used forIHC. The slides were deparaffinised and rehydrated following the routine protocols supplied with the antibodies. Endogenous per-oxidase activity was blocked with 0.5% H2O2 for 30 min. Antigen retrieval was accomplished in 10 mM citrate buffer (pH 6.0) in a microwave at 600 W for 5 min. Nonspecific binding was blockedwith 1% BSA for 10 min.

Subsequently, the slides were incubated with the primary antibody: β-catenin (Transduction Laboratories,Lexington KY) clone C19220, 1:100, E-cadherin (Transduction Lab-oratories, Lexington KY) clone 36, 1:100, MIB-1 (Ki-67) (Dako,Glostrup, Denmark) clone, 1:100 and p53 (Labvision, Fremont, CA)clone, 1:100 for 30–60 min, at 37◦C. The slides were incubated with biotinylated rabbit anti-mouse immunoglobulin as the second anti-body and were subsequently treated with streptavidin-peroxidase conjugate for 30 min at 37◦C temperature. DAB was used as chromogen substrate. After counterstaining with haematoxylin, the slides were dehydrated and mounted. Slides without the primary antibody were used as negative controls.

IHC reactions were recorded and digitalized by Mirax slidescanner. Evaluation of slides were made on digitalized slides. LTCD groups' slides were evaluated in usual analogue system.

Evaluation

Survival cases: Membranous and nuclear β-catenin expression (IHC "decoration") was evaluated separately. Those cases in which only <10% "decorated" ('stained', i.e., positive) cells were observed were classified as negative. If the decorated cells' number was >10% of all cells, the sample scored positive. Only membranous E-cadherin IHC-reaction was regarded as relevant and those cases scored pos-itive in which the decorated cells' number exceeded 10% of all the cells. The 10% cut-off value was applied for Ki-67 and p53 nuclear reactivity as well.

Solid tumor vs. ascites cases: Nuclear and cell membrane decoration for β-catenin were assessed separately. For E-cadherin only membrane-localized decoration was valued as positive, while for p53 and Ki-67 only nuclear reactivity meant a positive score. In each positive case the actual percentage of positively decorated tumor cells was determined. We determined the range of IHC positivity, and used no cut-off values.

Statistical analysis:

Differences involving classical and molecular features betweenthe LTS and EP groups were analyzed with Kaplan–Meier test torecognize statistical significance. Multivariate logistic regression analysis helped to detect independent factor(s) that might haveinfluenced clinical outcome, namely long-term OS and/or PFS.

The IBM SPSS 24 software (specifically Mann-Whitney-Wilcoxon test) was utilized for comparative evaluation of the results which have been collected from primary tumors and ascites samples, and also Spearman correlations were calculated.

Results

Accordig to prognostic study the median age of patients which was 63 years (95% CI; 52.1–57.4). The majority of the tumors were serous carcinomas (70.5%). Other histological types were endometrioid (6.8%), mucinous (9.1%), and dedifferentiated carcinomas (13.6%). Further special histotypes (E.g., clear cell carcinoma or malignant Bernner-tumour) were not encountered. Twenty-two patients (50%) had optimal tumor debulking surgery representing the most effective tumor volume reduction. The majority (72.7%) of carcinomas was in FIGO stage III. FIGO stage I and II C comprised 18.2%, and 4.5%, respectively. Within the group of FIGO stage III, stage IIIC dominated (61.3%), while FIGO stage IIIA and IIIB were represented by 2.3% and 9.1%, respectively. Only 4.5% of all tumors comprised the FIGO stage IV group. Histological grade I and grade II tumors were collectively grouped (total number 23) as “low-grade tumors” (52.3%). The number of grade III lesions was 21, which were classified as high-grade tumors” (47.7%). We identified 14 patients (32%) with early progression (EP) and 17 patients (39%) belonged to long term survivors (LTS).

IHC results

P53: Detection of p53 reactivity. In low-grade [LG] tumors nuclear expression of p53 was found in 11/23 (47.8%). The same reaction was positive in 14/21 (66.7%) in high-grade [HG] carcinomas. In the samples from optimal tumor debulking 10/22 (45.4%) showed p53 nuclear expression, while in cases of suboptimal debulking 15 cases (68.1%) had p53 expression. In serous tumors p53 nuclear expression was detected in 18 cases (58%), in non-serous phenotypes 7 cases (53%) proved positive with this antibody. In patients older than 65 years 65% (13 patients) expressed nuclear p53, while in those below the age of 65 years, nuclear expression of p53 was detected in 50% (12 patients).

Ki-67: The Ki-67 proliferation marker was expressed in 10/23 cases (43%) in LG tumors and 14/21 (66.7%) in HG tumors. In 9 samples (40.9%) showed Ki-67 nuclear expression from optimal tumor debulking, while 15 cases (68.1%) from suboptimal debulking specimens displayed Ki-67 expression. In serous tumors Ki-67 nuclear expression was detected in 17 cases (54.8%), in non-serous phenotypes 7 cases (53.8%) were positive. In patients over 65 years thirteen cases (43.3%) expressed

nuclear Ki-67, while the younger patient group 11 cases (45.8%) showed specific nuclear Ki-67 decoration.

E-cadherin: Membranous E-cadherin reactivity. In LG tumors we found expression of E-cadherin in 17 cases (73.9%), while 14 cases (80.9%) were positive from the HG tumor group. From the optimal tumor debulking series 16 samples (72.7%) showed E-cadherin expression, while this result was positive in 18 cases (81.8%) from the suboptimal debulking specimens. In serous tumors E-cadherin expression was detected in 25 cases (80.6%), in non-serous phenotypes 9 cases (69.2%) presented the same result. In patients over 65 years of age 17 cases (85.0%) expressed membranous E-cadherin, while in individuals below age 65, membranous expression of E-cadherin was detected in 17 cases (70.8%).

β-catenin: Membranous β-catenin decoration. In LG tumors we found membranous expression of -catenin in 18/23 cases (78.2%), and 15/21 patients' samples (71.4%) from the HG group displayed the same positivity. In cases of optimal tumor debulking 17/22 samples (77.2%) showed -catenin membranous expression, while this result was observed in 16 cases (72.7%) of suboptimal debulking series. In serous tumors β-catenin membranous expression was detected in 25 cases (80.6%), in non-serous phenotypes 8 cases (61.5%) showed this IHC pattern. In patients over 65 years 14 cases (70.0%) expressed membranous β-catenin, while in 19 cases (79.1%) from younger individuals was membranous expression of β-catenin detected. Nuclear β-catenin IHC positivity. In LG tumors we found nuclear expression of β-catenin in 3/23 cases (13.0%), and in HG tumors 3/21 (14.2%) tumors showed this decoration. In cases of optimal tumor debulking 4/22 samples (18.2%) showed nuclear β-catenin reactivity, while from the series of suboptimal debulking 2 cases (9.1%) nuclear positivity indicated β-catenin transposition. In serous tumors β-catenin nuclear expression was detected in 1 cases (3.2%), in non-serous phenotypes 5 cases (38.4%) were similarly decorated. In patients, over 65 years 4 cases (20.0%) expressed -catenin in the cell nuclei, while in younger individuals nuclear β-catenin expression was detected in 2 cases (8.3%).

β-catenin: Nuclear β-catenin expression was detected in a total of 6 (13.6%) of all cases. In all of them nuclear positivity was accompanied by synchronous membranous β-catenin reactivity. Solely membranous β-catenin expression was detectable in 33

(75%) of all cases. E-cadherin expression was positive in 34 patients (77.2%). High Ki-67 labeling index was detected in 24 cases (54.5%) and p53 nuclear positivity was observed in 25 cases (56.8%).

Comparison of the putative impact of the features characterizedby IHC as well as that of the clinical parameters on OS and PFS of the EP and LTS patients was evaluated applying univariate and multivariate statistical analyses.

OS: Univariate analysis indicated that serous histological type has a potentially negative impact on outcome when compared to different histological categories (68.03 mo. vs. 117.01 mo.;**p = 0.025**). Similar conclusion was reached with regard to suboptimal debulking, that resulted in significantly shorter OS (57.48 mo.vs 105.36 mo.; **p = 0.003**) both with univariate- and with multivari-ate (0.325; **p = 0.005**) analysis. There was no statistically significant association between OS and age-, tumor grade- or tumor stage.Nuclear β-catenin expression was only detected in LTS patient's group (146,67 mo. vs. 71,84 mo;**p=0.041**) while this reaction was negative in the EP patient'sgroup (0/27). Positivity of the p53 IHCreaction did show an impact on OS when compared to p53 negative cases (70.40 mo. vs. 99.80 mo.), however, this difference was not statistically significant (***p = 0.057***). None of the other parameters, namely, membranous β-catenin staining, E-cadherin- or Ki-67expression appeared to have significant prognostic value

PFS: As expected if tumor debulking is suboptimal (i.e., thereis residual tumor mass) that has a significant negative impacton PFS compared to radical tumor removal (14.00 mo vs. 42.93mo. respectively; **p=0.001**) both with univariate analysis and with multivariate analysis (0,329; **p=0.002**). No statistically significant correlation between PFS/age, PFS/histopathological cell type,PFS/tumor grade- or tumor stage was found. Patients with high Ki-67 index had shorter PFS than those patients with low KI-67 (26 mo. vs. 61.95 mo.; **p= 0.039**) with univariate analysis. It is of note that despite of early progression, adequate response to platinum based therapy was observed in 3 cases which resultedin favorable lengthening of OS to more than 100 months.In 3 of the 6 cases characterized by nuclear β-catenin expression we observed relapse of the disease over 12 months. One of these patients had suboptimal primary tumor debulking. In these cases platinum re-induction therapy was performed with success – the patient OS attained our limit.

Results of observations: malignant effisions and solid tumors.

Accordig to our solid tumor and ascites study the total number of cases included in the study was 27, out of these 78% (21) represented primary OC, and the remaining samples had been removed from metastatic foci localized on peritoneal surfaces of the omentum, abdominal viscera or pelvic wall. Tumors had been graded prior to the study-selection: 75% (18) tumors were high grade [HG] and 25% (9) were low grade [LG] neoplasms. The higher stages (FIGO II-IV) were lumped together as group representing peritoneal dissemination. CMA blocks were constructed from 22 ascites samples with high cellularity (HCTD group) and from five samples with low cellularity traditional sections were used for immunohistochemistry (IHC). The results of IHC reactions were evaluated by digital image analysis.

IHC results from solid tumors

p53 protein expression as shown by IHC positivity was rather variable: range 0-100%, mean: 45.56%. Ki-67 positivity also covered a broad range (1-68%), mean: 19.08%. E-cadherin IHC positivity varied between 0-91% (mean: 31.4%), while membranous β-catenin expression occurred in 40-100% (mean: 82.19%) without any case of nuclear expression thereof.

IHC reactivity profile of ascitic tumor cells

The range of p53 positivity was similar to that of solid tumors (0-100%), however the mean value in the ascites series was considerably lower: 32.76%. Results of the Ki-67 IHC reaction on ascitic cells also differed from that of solid tumors and varied between 1-83% (mean: 25.72%). In the ascetic samples E-cadherin expression was detectable in a diversified representation (0-92%), mean: 39.52%. Nuclear β-catenin positivity was not observed in this series either, whilst the mean value for membranous decoration was 58.77%, covering a range of 0-100%.

Significantly higher number of p53 positive cells were detected in primary tumors than in ascitic cells (45.56 vs 32.76, **p=0.001**). Although on average the proliferation marker Ki-67 decorated more ascitic cells than cells in solid tumors, this difference was not statistically significant. (25.72% vs. 19.08%, p=0.101). E-cadherin expression was

more abundant in ascitic cells than in primary tumor cells, however, this difference was not significant, either. (39.52% vs. 31.40%, p=0.294). Ascitic tumor cells' membranous β-catenin expression was significantly lower than that of cells from primary tumors. (82.19 vs 58.77% **p=0.006**).

To test the hypothesis that grade and stage is influenced by the level of expression of the IHC markers analyzed we set out to compare IHC results as a function of these variables. Histopathological grade LG primary tumors' cells average p53 expression was 24.89%, while in HG tumors this value was 58.06%, this difference was statistically significant (**p=0,039**). Similarly significant (**p=0,004**) difference characterized Ki-67 decoration that occurred in only 6.22% of LG primary tumors, but was seen in 25.11% of HG neoplasms. E-cadherin was detectable in 33.75% in LG tumors and this value was not markedly different from the 30.44% labelling observed in HG tumors. β-catenin expression was seen in 78.67% of LG tumorous cells, also quite similar to the value detected in HG tumors (81.89%). Expression profiles of the 4 markers in ascitic cells were not significantly coupled with grades, although the tendencies of differences (i. e., lower p53, higher Ki-67 expression as well as increased E-cadherin and decreased β-catenin expression in ascitic cells compared to primary tumors) which characterized the lumped data prevailed in both high and low grade samples. Correlations between tumor stage and IHC marker-expression E-cadherin expression was lower (27.45%) in more widespread tumors (advanced stages) than in rather confined tumors (44.83 % in early stages), although the difference was statistically not significant. Likewise, the value portraying membranous β-catenin expression in early stage-cases (86%) was not significantly higher than that observed in more advanced tumors (79.33%). There seems to be an elevated p53 and Ki-67 expression in more advanced cases but interpretation of these observations deserve caution due to small sample numbers and also because more advanced tumors tend to be of higher grades.

Comparisons between cells from primary, metastatic and ascitic tumor cells

Expression of p53 protein increased, although not significantly in metastatic tumors when compared to those from primary tumors (66.3% vs 41.47%). Non-significant decrease of the Ki-67 labeling index (LI=16%) was detected in metastatic neoplastic foci when contrasted with LI determined in primary tumors (LI=19.61%). E-cadherin expression levels were moderately lower (28.6%) in metastatic cell populations than

those in primary tumors (32.14%). This difference was rather augmented when comparisons were made within the early stage tumor group, while the variance turns non-significant in advanced stages (44.8%, 27.06% vs. 28.6%). The IHC scores that indicate β-catenin expression decrease from 82% (primary) to 76.67% (metastatic) and this decline is consistent irrespective of tumor stage. Ascitic cells express less mutant p53 protein compared to cells from primary tumors (28.95% vs 41.48%), the same reduction is detectable when comparing ascitic cells to cells from metastatic foci (48% vs 66.33%). Note that these differences are statistically not significant. There is a synchronous increase in proliferative activity in ascitic cells which is indicated by the augmented Ki-67 LI values (primary tumor vs. ascetic tumor cells, 19.62 vs. 25.65%; metastasis vs. ascetic tumor cells, 16.0% vs. 26.0%, respectively. Ascitic cells express more E-cadherin than primary tumor cells (42.1% vs 32.14%) and less β-catenin: 55.19% in ascitic cells and 82% in primary tumor cells. Adhesion molecules' expression values (% of labelled cells) of metastatic tumor cells and of ascitic tumor cells were almost identical, the differences were within observational error limits. For E-cadherin the values were 28.6% (metastatic) and 26.5% (ascitic); for β-catenin 76.67% (metastatic) and 73.8% (ascitic).

Result summary

Solid tumors and ascites cells p53 and Ki-67 expression showed correlation with tumor grade. P53 and Ki-67 expression elevated in high-grade primary tumor cells and ascites cells. Slightly decreased E-cadherin and moderately elevated β-catenin expression was detected in high-grade tumors. Ascites tumor cell E-cadherin expression elevated and membranous β-catenin expression decreased in both low-grade and high-grade cases compared to that in primary tumors. Expression of E-cadherin in ascites intensifies, that is specific to ovarian cancer cells. Meanwhile β-catenin membranous expression shows marked decrease. Expressional profile of metastatic tumours and ascites tumour cells presented similar level of decrease and ascites tumour cells had significantly lower p53 and elevated Ki-67 expressional activity.

Concusions of the study

- ✓ Nuclear β-catenin is a predictive marker of long term survival and for a certain degree predicts platinum sensitivity
- ✓ Proliferation marker Ki-67 is an unfavorable predictor of early progression
- ✓ Cell adhesional molecule E-cadherin has no effect on OS or PFS - according to our study – but plays important role in ascites transmitted intraabdominal tumor progression with intensifying membranous expression in ascites
- ✓ Cell membrane associated β-catenin protein expression decreases in malignant intraabdominal effusion, particularly in tumors with early stage
- ✓ Elevated protein p53 expression is tipical in high-grade solid EOCs and malignant peritoneal effusion, as well
- ✓ Ki-67 nuclear expression intensified in ascitic tumor cells compared to solid tumors
- ✓ Cytology microarray is exclusively suitable method to compare malignant effusions with solid tumors.

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List of publications related to the dissertation

1. Tóth, L., **Nagy, B.**, Méhes, G., László, E., Molnár, P. P., Póka, R., Hernádi, Z.: Cell adhesion molecule profiles, proliferation activity and p53 expression in advanced epithelial ovarian cancer induced malignant ascites-Correlation of tissue microarray and cytology microarray. *Pathol. Res. Pract. 214* (7), 978-985, 2018.
   DOI: http://dx.doi.org/10.1016/j.prp.2018.05.014
   IF: 1.466 (2017)
2. **Nagy, B.**, Tóth, L., Molnár, P. P., Méhes, G., Thurzó, L., Póka, R., Hernádi, Z.: Nuclear-catenin positivity as a predictive marker of long-term survival in advanced epithelial ovarian cancer. *Pathol. Res. Pract. 213*, 915-921, 2017.
   IF: 1.466

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List of other publications

3. Dajnoki, Z., Béke, G., Mócsai, G., Kapitány, A., Gáspár, K., Hajdu, K., Emri, G., **Nagy, B.**, Kovács, I., Beke, L., Dezső, B., Szegedi, A.: Immune-mediated Skin Inflammation is Similar in Severe Atopic Dermatitis Patients With or Without Filaggrin Mutation.
Acta Derm.-Venereol. 96 (5), 645-650, 2016.
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