"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

DOCTORAL SCHOOL

FIELD MEDICINE

CONTRIBUTION OF HIGH-PERFORMANCE IMAGING IN THE DETECTION, CHARACTERISATION AND THERAPEUTIC CONDUCT OF OVARIAN TUMOURS

The Role of Diffusion MRI Sequence in Assessing the Therapeutic Response

PHD THESIS SUMMARY

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MOTIVATION OF THE STUDY

ASSUMPTION

This paper is a retrospective study conducted between May 2014 and March 2016 at the Gynaecology Department of the Central Military University Emergency Hospital on a group of 152 patients who underwent surgery for adnexal tumour pathology.

We analysed the postoperative histopathological/immunohistochemical diagnosis for each of the operated patients and compared the contribution of each of the imaging investigations performed in the detection and characterisation of the formations, as well as their role in the staging of the malignant lesions.

We tracked the sensitivity and specificity of each of the methods, comparing the accuracy of the diagnosis by studying four groups of patients.

Batch A consists of 152 patients examined clinically, biochemically and with transabdominal and transvaginal ultrasonography.

Batch B is represented by the 63 patients for whom the clinical, biochemical and ultrasonographic examination was also supplemented by a computed tomography (CT) scan.

Batch C includes the 76 patients examined clinically, biochemically, ultrasonographically and by magnetic resonance imaging (MRI).

Batch D consists of 34 of the patients who underwent clinical, biochemical, ultrasound and computed tomography examinations in whom the investigations were also supplemented by MRI.

While the ultrasound was the reference technique for all patients in the group with the aim of analysing the morphology of the ovary, especially for localised forms in which the velocity study correlated with age, hormonal status and biochemical markers (CA125 and ROMA score) allowed the diagnosis to be oriented towards benignity or malignancy, for some patients it was necessary to undergo computed tomography (CT) examination and/or magnetic resonance imaging (MRI).

Magnetic resonance imaging has been useful in some cases to confirm the ovarian origin of the lesion, to assess the benign or malignant features necessary to determine the optimal surgical approach pathway, or in advanced formations with extrapelvic extension to better detect small peritoneal deposits.

These investigations allowed more accurate detection of infracentimetric peritoneal extension especially in the absence of ascites.

T2- and T1-weighted sequences were used for the study of anatomy and more accurate tissue characterisation, fat saturation sequences for the detection of components with grainy, haemorrhagic or pure fluidic structure, and diffusion or post-injection sequences of contrast agent (Gadolinium) for the characterisation of tumour content and the detection of intraperitoneal tissue implants.

The diagnostic performance was analysed in relation to the intra- and postoperative results for each individual group.

RESULTS - OVERVIEW OF THE BATCHES STUDIED AND RESEARCH DIRECTIONS

The lesional appearance following the histopathological and immunohistochemical postoperative diagnosis

According to intra- and postoperative results, 114 patients (representing 75%) were diagnosed with benign ovarian lesions and 38 patients (representing 25%) were diagnosed with malignant and borderline formations.

Classification of ovarian tumour formations in the studied group from a histopathological point of view:

A. Epithelial ovarian formations accounted for 68% in the study group and were found in 103 patients, as follows:

- 51 serous lesions, of which 37 benign, 10 malignant and 4 borderline
- 21 mucinous lesions, of which 17 benign, 3 malignant and one borderline
- 16 endometrioid tumour lesions, of which 9 malignant cystadenocarcinoma and 7 endometrial cysts or benign endometrioid cystadenoma
- 4 clear cells tumour lesions, of which 1 benign and 3 malignant
- 5 mixed seromucinous lesions, of which 4 benign and one malignant
- 4 mixed malignant epithelial/mesenchymal lesions - carcinosarcoma
- 2 benign Brenner transitional cell tumours

B. Germinal ovarian tumours accounted for 21% in the study group and were found in 32 patients, as follows:

- 30 mature cystic teratomas
- 1 yolk sac tumour - borderline

- 1 dysgerminoma - malignant

C. Stromal and sex cord tumour formations accounted for 11%, being found in 17 patients, as follows:

- 9 fibromas
- 5 thecoma and fibrothecoma
- 2 virilizing Sertoli tumours
- 1 granulosa cell tumour - malignant

The contribution of imaging investigations to the characterisation of ovarian tumours in the study group and the correlation of these data with the appearance of intra- and postoperative formations

The imaging investigations performed (ultrasound, CT, MRI) were analysed for each of the group of patients. For each type of examination, the frequency of features with increased specificity for ovarian malignant tumour pathology was monitored, which determined the classification of the imaging diagnosis into tumour formations with most likely malignant or benign substrate.

The main imaging features that were considered for formations with a malignant substrate were the following: solid components; endo/exocyst vegetations; wall with irregular thickness and intramural nodules; irregular intratumoral septa with thicknesses over 3 mm; contrast uptake in intratumoral, parietal or septal solid components with curve II/III loading appearance (early contrast uptake of less than or equal to myometrial intensity, persistent in the plateau, or intense early contrast uptake, more pronounced than myometrial and dynamic "wash-out"); size >3-4 cm; diffusion restriction with low ADC index evident on specific MRI acquisitions; peritoneal, mesenteric or omental metastases; ascites; pelvic extension; loco-regional lymph node metastases; distant metastases - extraperitoneal.

In the groups that also included MRI examinations, the assessment of imaging diagnosis for formations with increased likelihood of malignancy was performed in accordance with the O-RADS MRI classification taking into account the presence of criteria for O-RADS MRI 4 and 5.

Out of the total of 32 patients in whom postoperative histopathological and immunohistochemical examinations established the diagnosis of malignant tumours, a group of 24 patients was selected from those who presented for postoperative evaluation at 6 and 12 months. The inclusion criteria were the presence at the time of surgical procedure of

peritoneal metastases previously detected by MRI examination; these were subsequently analysed at follow-up MRI re-evaluations, assessing the appearance especially on the diffusion sequences. In the residual peritoneal deposits after cytoreduction, the diffusion restriction and the ADC value were assessed and compared with the evolution of tumour markers.

Of the total number of patients in the study, 76 underwent magnetic resonance investigation, among them all 38 patients for whom the postoperative histopathological/immunohistochemical diagnosis indicated the presence of malignant or borderline lesions.

Statistical processing of biochemical, histopathological and imaging data

The organisation of the data obtained from the investigation of the 152 cases was performed using descriptive statistical methods, by checking for possible correlations and by univariate analysis (T-test and ANOVA). Logistic modelling and the calculation of the ROC (Receiver Operator Curve) curve was used, which is a graphical representation illustrating the diagnostic ability of a binary classification system, in this study referring to the benign or malignant nature of the tumour according to the ADC value. A significance threshold of $p<0.05$ was used to assess correlations and for univariate analysis. The calculations were performed in EXCEL and Matlab R2015.

Distribution of the nature of tumours by patient age

A first analysis of the incidence of benign and malignant tumour formations was carried out according to the age of the patients. In this classification, the tumour appearance was analysed in the age groups <20 years, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80 and >80.

Graphic representations show that benign tumours have a relatively similar distribution in the middle age groups, with a maximum (35%) in the range of 30-40 years, with only 7% of cases in the under 20 age group and 13% of cases in the over 60 age group.

The distribution of malignant tumours (in which borderline tumours were also considered) shows that over 80% of cases are in the over 40 age group, with a maximum (56%) in the 40-60 age group (Figure 1).

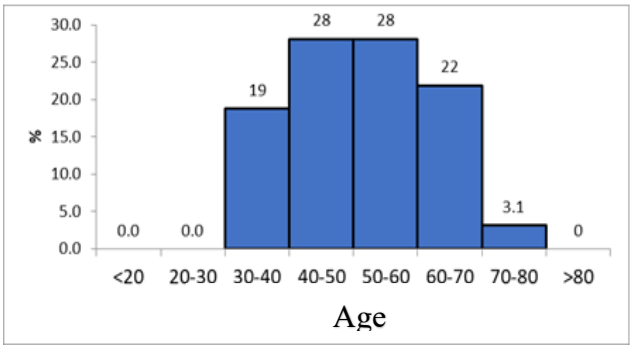

Figure 1. Distribution of malignant tumours by patient age

Correlation of CA125 value with the nature of the tumour (benign, borderline or malignant at the final histopathological analysis)

The variation of the CA125 biochemical assay value for the 152 patients shows a minimum value of 6 U/mL and a maximum value of 2317 U/mL. The mean value is 172 U/mL and the median value is 35.5 U/mL. The median value shows that half of the records are less than 35.5U/mL, with the other half having higher values. The value of the Q3 quartile is 95 U/mL, showing that 75% of the records are below this value. The high value of the mean is due to the presence of very high values in some patients in the study group. This data structure shows that the distribution is far from normal, with the presence of many values above the normal limit. Of the 152 data sets, 6 have values above 1,000 U/mL, representing 4% of the herd.

The instrumental increase in CA125 with increasing malignancy is also evidenced by the median CA125 values for the three types of tumours: 21 U/mL for benign tumours, 174 U/mL for tumours identified as borderline, and 531 U/mL for malignant tumours (figures 2a and 2b)

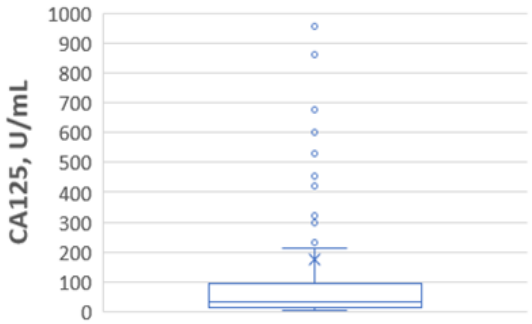

Figure 2a. Distribution of CA125 values the box chart

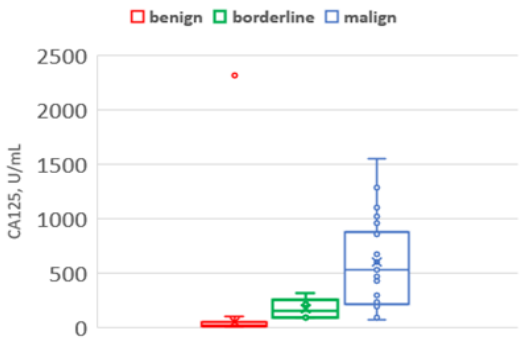

Figure 2b. CA125 index variation according to the nature of the tumor

Analysis of the distribution of ADC value by tumour types

Of the 38 malignant tumours for which MRI was performed, 13 tumours were germinal, 8 stromal and 17 epithelial. Malignant and borderline tumours were mostly epithelial tumours (35). Only 2 malignant tumours were germinal and one stromal. For some of the malignant tumours, diffusion-restricted areas of peritoneal metastases were also measured.

For benign epithelial and germinal tumours, the mean ADC was $1.4*10^{-3}$ mm^2/s, and the lowest values were $1.2*10^{-3}$ mm^2/s. In epithelial malignant tumours, the mean is $1.05*10^{-3}$ mm^2/s, and the highest values slightly exceed $1.2*10^{-3}$ mm^2/s. The mean ADC value in peritoneal lesions is also close to $1*10^{-3}$ mm^2/s, and the distribution of values is similar to that in malignant tumours.

Benign stromal tumours have a peculiarity: half of them have ADC values below $1*10^{-3}mm^2/s$. Of the 8 benign tumours of this type, 4 are ovarian fibroids for which the ADC value is very low, below $1*10^{-3}mm^2/s$.

For stromal and germinal malignant tumours, no statistical analysis could be performed, as their number was too small (figure 3).

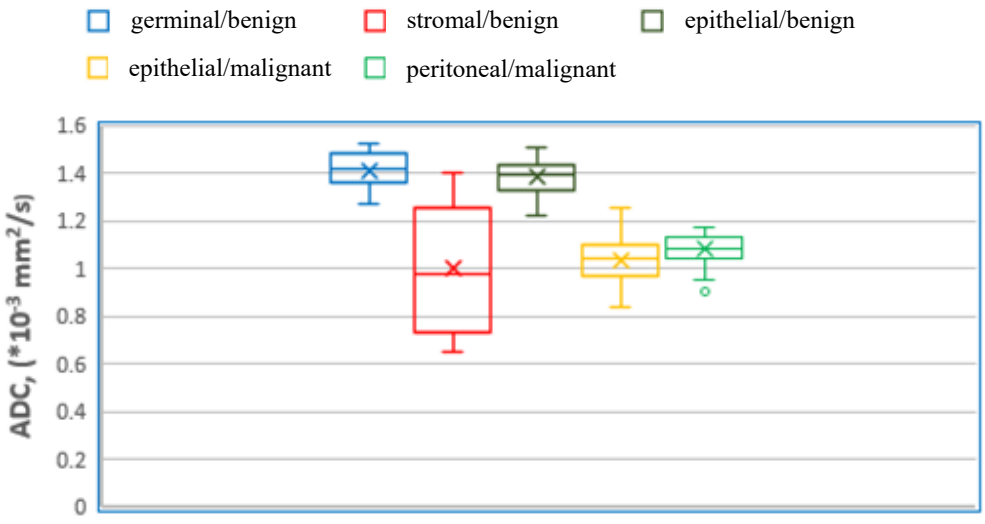

Figure 3. Distribution of intratumoral and peritoneal ADC values depending on the type and nature of the tumor

Analysis of possible correlations of age, ROMA score and ADC index value with benign/malignant tumour

According to the above analysis, the malignant/benign nature of the tumour may depend on several factors, one of which may be the age of the patient. The result of biochemical tests may provide information about the nature of the tumour. However, the most important information comes from the imaging study.

Of the biochemical and imaging tests used to make the diagnosis, we chose the ROMA score (elevated/normal) and the ADC value measured on the MRI investigation, which has lower values in the case of malignant tumours. The analysis of the relative influence of age, ROMA score and ADC value on the nature of the tumour was done by developing a logistic regression model.

Independent variables may be continuous, nominal or ordinal. The ROMA score is a nominal variable with 2 levels, normal and increased (assigned values of 0 and 1 in the model), while the age and the ADC value are continuous variables and can take any real value.

Analysis of the presence of the solid component

Out of the 152 cases investigated, a solid component was identified in 86 of the formations. Only 46% of benign tumours showed solid component, while malignant tumours had a solid component in their entirety (figures 4a,4b,5)

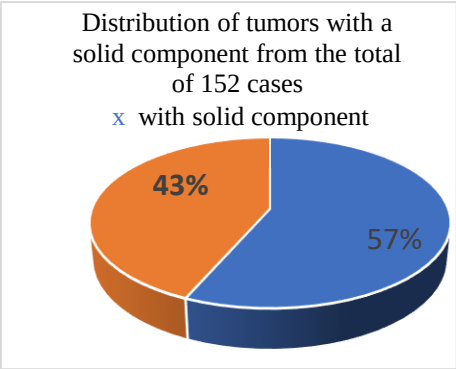

Figure 4a. Distribution of tumors according to the solid component

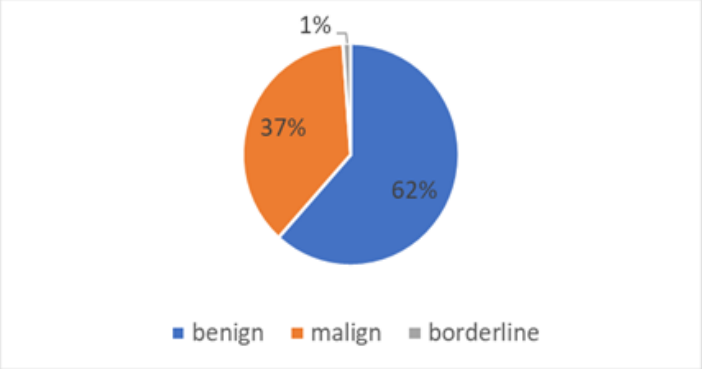

Figure 4b. Distribution according to the nature of the tumor of those with a solid component

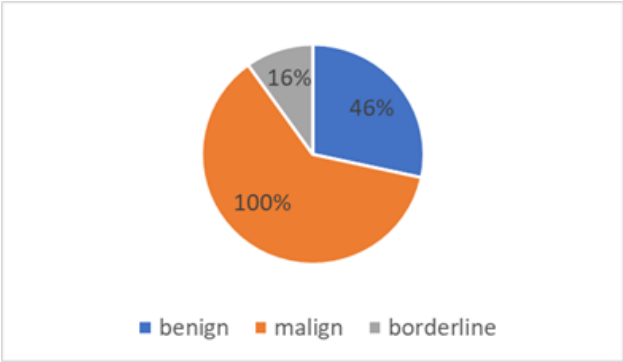

Figure 5. Proportion of tumors with a solid component by tumor type

Analysis of irregular intratumoral septa with thicknesses greater than 3 mm

From the analysis of the 152 ovarian formations, the majority of the cases where these septa had over 3 mm were malignant and borderline tumours. Of the 114 benign tumours, only 30% had intratumoral septa, while in the case of malignant and borderline tumours over 80% had intratumoral septa (figure 6).

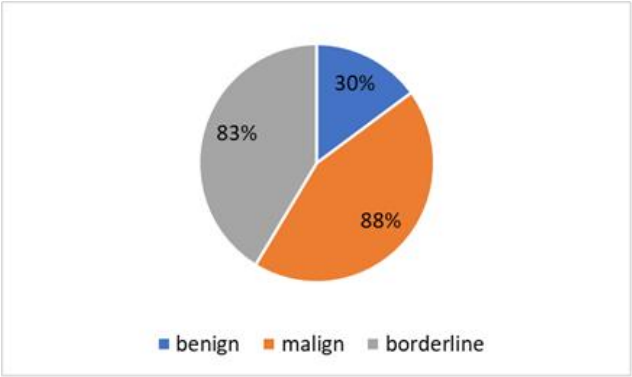

Figure 6. The proportion of tumors within each type (benign, malignant, borderline) showing irregular intratumoral septa measuring more than 3mm.

Contrast uptake analysis of intratumoral solid components

Contrast uptake in solid/parietal/septal components (type I load curve)

Of the total cases investigated, 65 showed this post-contrast load curve.

In the case of benign tumours, this progressive contrast uptake on the dynamic acquisitions performed was encountered in 60 of the formations (52%), while in the case of malignant and borderline tumours it was found in 3 malignant formations and in 2 borderline (representing 10% and 33% of them, respectively) - figures 7a and 7b

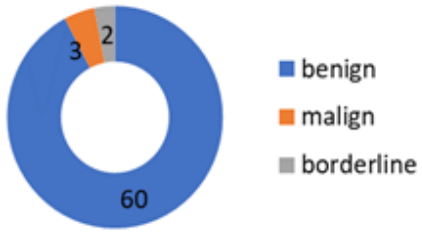

Figure 7a. Distribution of the number of tumors with contrast uptake at the level of solid/parietal/septal components (loading curve type I)

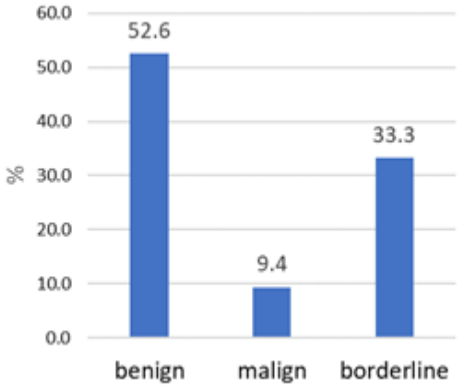

Figure 7b. Proportion of each type of tumor showing contast uptake (type I)

Analysis of contrast uptake data at solid/parietal/septal component level (type II/III load curve)

The contrast uptake with a plateau appearance or with "wash-out" visible on the dynamic acquisitions was found in 26% of the formations examined (in 40 cases).

Distribution by tumour nature shows that 29 malignant tumours (90% of the total) and 4 borderline tumours (66% of the total) showed a type II/III load curve, whereas out of the total of 114 benign tumours this type of curve was seen in 7 cases (representing 6% of the total) - figures 8a and 8b.

All malignant/borderline tumours have a contrast uptake, mainly type II/III, while in benign tumours a small part (6%) has a contrast uptake type II/III, and 41% are without a contrast uptake (figures 9a and 9b).

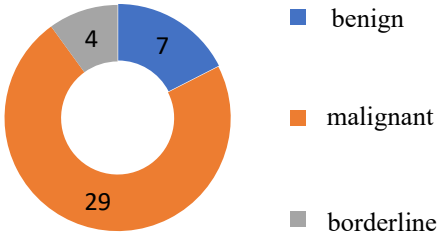

Figure 8a.Distribution of the number of tumors with contrast uptake at the level of solid components (type II/III)

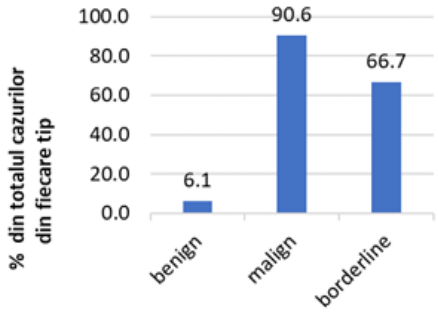

Figure 8b.Proportion of each type of tumor showing contrast uptake (type II/III)

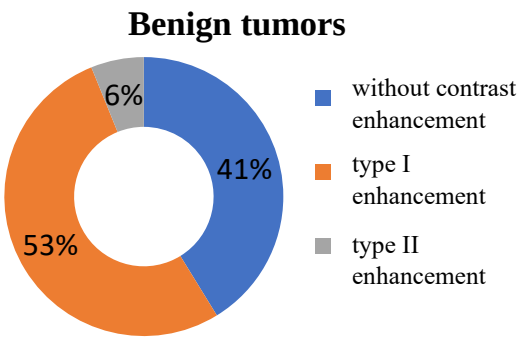

Figure 9a. Proportion of contrast uptake in benign tumors

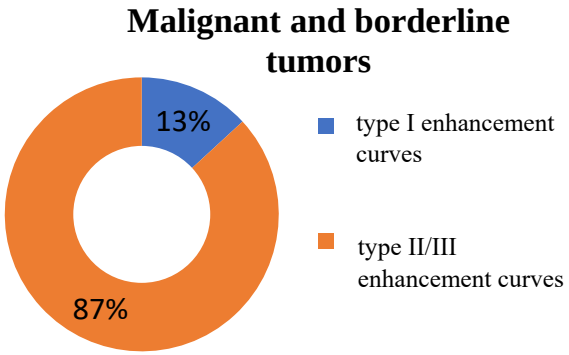

Figura 9b. Proportion of contrast uptake in malignant and borderline tumors

Tumour size analysis

Tumour size over 4 cm was recorded in all 38 malignant or borderline tumours and in less than two thirds of benign tumours (73 out of 114) - figures 10a and 10b.

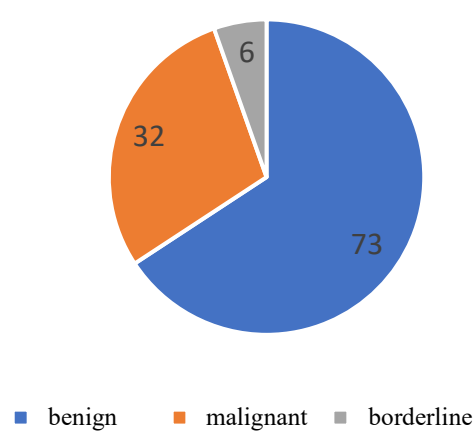

Figure 10a. Distribution of the number of tumors larger than 4cm in size

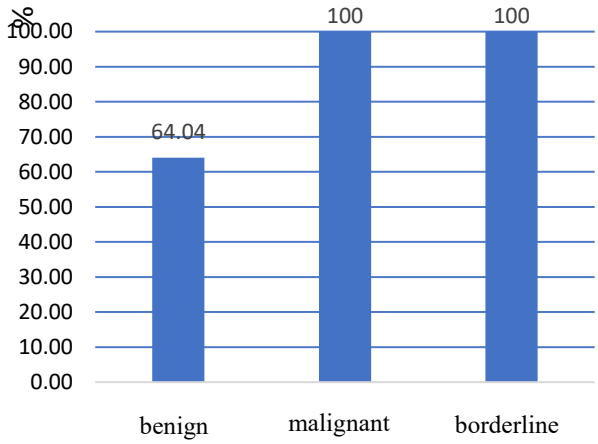

Figure 10b. Proportion (%) of each tumor type >4cm in size

Study of the presence of ascites

Of the cases studied, 84% did not have ascites. It has been associated with most malignant tumour formations (75% of them - in 24 out of 32), in none of the borderline tumours and in a single case of benign tumour (figure 11).

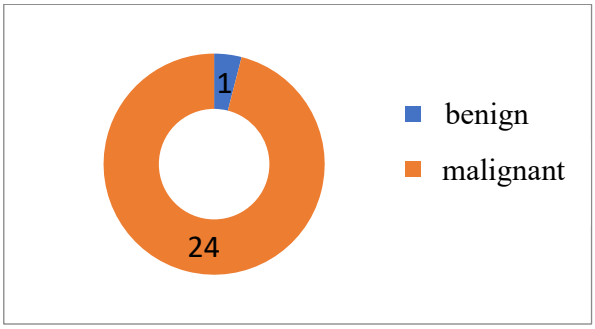

Figure 11. Distribution of the number of tumors presenting ascites

Analysis of loco-regional lymph node metastases

A total of 38 tumours out of the 152 cases showed loco-regional lymph node metastases. Of these, the majority are malignant and borderline tumours (74% of this group). Of the total benign tumours, only 8.8% has associated loco-regional lymph node hypertrophy.

Analysis of cases with macroscopic peritoneal metastases

Macroscopic peritoneal metastases have been seen only in malignant tumours, with 81% of malignant tumours having this appearance.

Analysis of pelvic parietal/contiguous organ extension

The majority of malignant tumours (65%) and one third of borderline tumours showed pelvic parietal/contiguous organ extension. Of the benign tumours, only one showed this appearance, which is less than 1% (figures 12a and 12b).

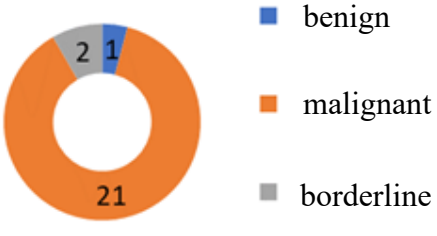

Figure 12a. Distribution of the number of tumors with pelvic extension

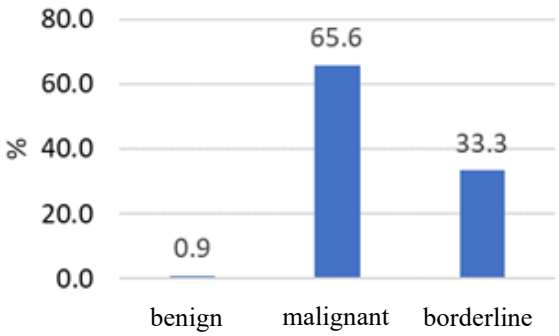

Figure 12b. Proportion of occurrence of parietal pelvic extension according to the nature of the tumor

Distant metastases

These cases in which distant metastases, as opposed to peritoneal metastases, have been found in 50% of malignant tumours and have not been highlighted in benign or borderline formations.

Calculation of the sensitivity and specificity of MRI and CT investigations performed in the study group

Evaluation of sensitivity and specificity of MRI examination

Of the batch of 76 cases investigated by MRI (ultrasound + MRI and ultrasound + CT + MRI) as well, the number of positive cases (malignant/borderline tumours) diagnosed with MRI was 35, and following post-interventional histopathological examination the number of confirmed tumour formations of this type was 38. Benign cases diagnosed by MRI were 41 while the final histopathological test confirmed 38. Among the semiological MRI criteria with high significance in assessing the malignancy of tumour formations, the appearance on the diffusion sequences with DWI hypersignal and decreased ADC index in solid parietal or intratumoral structures had a particular weight. This was also supported by the presence of other particular imaging characteristics of malignant formations, particularly in the differentiation of malignant formations from benign stromal formations with fibromatous appearance.

Tumours diagnosed as borderline on the histopathological investigation were considered malignant tumours for the purposes of this study.

Assessment of sensitivity and specificity of CT examination

Of the group of 63 patients in whom a CT investigation was performed (ultrasound + CT, ultrasound + CT + MRI), the number of positive cases (malignant tumours) diagnosed by CT were 36, and in the final histopathological examination the cases confirmed as malignant are 33. The benign cases diagnosed by CT are 27, while the final histopathological test confirmed 30.

Analysis of the data shows that the imaging investigation has high specificity and sensitivity.

Analysis of the values of the parameters recorded in the postoperative follow-up period at 6 and 12 months

In 24 patients with malignant tumours, the results of the investigations were recorded 6 and 12 months after the surgery, respectively. Biochemical investigations (CA125 values) and ADC values from MRI investigation are analysed compared to baseline values (before the surgery).

ADC values had a significant increase in the first 6 months, on average by $0.18*10^{-3}$ mm2/s, but insignificant in the following 6 months (average $-0.02*10^{-3}mm^2/s$).

After analysing the distribution of the initial intratumoral ADC values, at 6 months and 12 months after the surgery, there was an increase in the average values, but also in the minimum values during the follow-up period.

Comparison of ADC values measured after 6 and 12 months with ADC values at peritoneal metastases measured at the time of diagnosis shows a clear improvement in these values after 6 months, which is maintained after 12 months in all but less than 20% of cases.

The mean and median ADC induction in peritoneal lesions measured at 6 months and 12 months after surgery increased significantly from the baseline. The distribution of ADC values after 12 months shows that there are several ADC values lower than those recorded at the 6-month assessment, indicating that these cases may not have had a favourable evolution in the postoperative period at 6-12 months.

Another important indicator in the diagnosis was considered the serum level of CA125 that was measured during the follow-up period, at 6 and 12 months. The variation of CA125 indicator after 6 and 12 months shows a decrease in the mean and the maximum values.

The study of possible correlations between age, ADC and CA125 values at baseline, after 6 months and after 12 months was done by calculating the Pearson correlation coefficient.

DISCUSSION AND CONCLUSIONS

1. Distribution of tumour formations in the study group in relation to the age of the patients

The benign tumour formations had a maximum distribution in the age range 30-40 years (35%), being found in only 7% at the ages below 20% and 13% at the ages over 60 years.

The distribution of malignant tumours (in which borderline tumours were also considered) showed that over 80% of cases were found in the age group over 40 years, with a maximum of 56% in the age group 40-60 years.

The ratio between the number of malignant and benign tumours is low until the age of 40 and increases with age, peaking in the age group 50-60 years when the frequency of malignant tumours reaches the same level as benign tumours.

2. The lesional appearance of the tumour formations in the study group following the postoperative histopathological and immunohistochemical diagnosis

75% of the formations were represented by benign ovarian lesions and 25% by malignant or borderline formations.

From a histopathological point of view, 68% of the ovarian tumour formations were epithelial, 21% germinal and 11% stromal and sex cord tumour formations.

The most common malignant and borderline formations were found in epithelial lesions and accounted for 33.9% of them. Malignant and borderline formations were less common in germinal (only 6.25%) or stromal and sex cord tumour histological types (5.88%).

Of the malignant and borderline ovarian tumour formations in the study group (38), epithelial tumours accounted for 92.1%, of which the most common histopathological subtype was serous tumours (40%).

3. Correlation of CA125 data in relation to the result of the histopathological examination of the tumours in the study group

The variation in the value of the biochemical test CA125 for the 152 patients showed a minimum value of 6 U/mL and a maximum value of 2317 U/mL, with a mean value of 172

U/mL, but the median value shows that half of the records are less than 35,5 U/mL. Of the 152 records, 6 have values above 1000 U/mL.

The correlation of CA125 data with the nature of the tumour was performed by evaluating the Spearman coefficient, the value obtained was 0.74 with a significance $p=2\cdot10^{-26}$. This shows that there is a very good correlation between the C125 value and the nature of the tumour (the likelihood of lesions being malignant increasing by the CA125 value). The instrumental increase in CA125 value with increasing malignancy is also evidenced by the median CA125 values for the 3 types of tumours: 21 U/mL for benign tumours, 174 U/mL for tumours identified as borderline, and 531 U/mL for malignant tumours.

The age correlation of the CA125 value was, however, very weak, the Sperman correlation coefficient having a value of 0.26 at a level of significance $p=8\cdot10^{-4}$

4. The contribution of high-performance imaging investigations to the differentiation of benign from malignant or borderline tumour formations in order to establish the therapeutic conduct.

The main imaging characteristics that were analysed in the ovarian tumour formations in order to differentiate between malignancy and benignancy were the following:
- tumour size >3-4cm
- solid components
- endo/exocyst vegetations and irregular intratumoral septa with a thickness of over 3mm
- walls with irregular thickness and intramural nodules
- the contrast uptake at the level of intratumoral, parietal or septal solid components with the assessment of the load curve (type II/III curves, with significance for malignancy represented by early contrast uptake of less than or equal to the myometrium intensity, persistent on the plateau, or early contrast uptake more intense than the myometrium intensity and with wash-out on dynamic acquisitions).
- the pathological diffusion restriction seen on specific MRI acquisitions, with DWI hypersignal associated with low ADC index
- the presence of peritoneal, mesenteric or omental metastases.
- the presence of ascites
- pelvic tumour extension
- loco-regional lymph node metastasis
- the presence of distant (extraperitoneal) metastases

- Tumour size analysis

Tumour size of over 4 cm was found in all of the 32 malignant tumours, in 6 borderline tumours and in almost two thirds of the benign tumours (73 out of 114). The copious dimensions found in patients diagnosed with malignant tumours may be due to non-specific symptomatology at the onset and late presentation at the gynaecological examination, which causes a long delay in diagnosis, with ovarian masses being most frequently discovered incidentally during a routine consultation.

- Intratumoral solid component analysis

57% of the tumour formations of the patients in the study had a solid intratumoral component. Of these, all of the malignant tumours analysed and 16% of the borderline tumours had a solid component structure, while only 46% of the benign tumours showed this feature.

- Intratumoral septa analysis

The presence of irregular intratumoral septa with thicknesses of more than 3 mm was found in more than 80% of malignant and borderline tumours and in only 30% of benign tumours.

- Contrast uptake analysis in tumour solid/parietal/septal components

Of the benign formations, only 59% showed contrast uptake (53% with a type I progressive load curve and only 6% with a type II plateau load curve), with the remaining 41% having no contrast uptake.

All malignant or borderline tumour formations showed contrast uptake, the type II/III load curve being found in over 80% of them.

- Analysis of the ADC value information in the solid components of the ovarian tumour formations assessed by MRI

Of the study group, 76 patients were investigated preoperatively and by MRI. The role of the diffusion MRI sequence was analysed by assessing the ADC index within the intratumoral solid component and macroscopic peritoneal metastases.

Significant differences in ADC values were appreciated between patients with malignant ovarian disease and those with benign conditions. The group of patients with borderline tumour formations did not differ significantly from the other two groups. The

ADC values recorded in the group of borderline ovarian lesions were close to the values in the group of malignant lesions but such low ADC values were also found in some benign fibromatous tumours, and the mean ADC values in the group of lesions considered to be benign cannot be clearly distinguished from the ADC values found in borderline lesions.

The analysis of ADC values for malignant tumours could only be performed for epithelial tumours since the number of germinal and stromal formations was very low in the patients enrolled in the study.

The mean ADC values in epithelial malignant tumour formations were $1.05*10^{-3}mm^2/s$, which is also close to the mean value found in their peritoneal metastases ($1*10^{-3}mm^2/s$).

For benign epithelial and germinal lesions, the mean ADC values were $1.4*10^{-3}mm^2/s$, a value that differs significantly from that found in malignant lesions.

The ADC analysis confirmed the peculiarity of benign stromal tumours to present a decreased ADC index, half of their ADC values being below $1*10^{-3}mm^2/s$.

- Correlations between patient age, ROMA score and ADC index value in MRI sequences, in relation to the benign/malignant nature of the tumour.

The analysis of the influence of these factors on the nature of the tumour was performed by developing a logistic regression model in the algorithm of which the variables of age, ROME score and ADC index value were entered.

The resulting regression coefficients were insignificant ($p>0.05$) for ROMA score and age ($p=0.91$ and 0.063, respectively) and significant ($p<0.05$) for ADC value ($p=0.0032$).

To correlate the probability of identifying tumour malignancy according to the ADC value, the ROC (Characteristic Operator Receiver) curve was used to plot the true positive rate (TPR) in relation to the false positive rate (FPR) rate at different ADC variability values by analysing the area under the ROC curve (AUC). The value obtained was 0.89, representing a value characteristic of a good classification model, leading to the assessment of the ADC value as having a high accuracy in assessing the malignancy of the ovarian lesions analysed.

- The presence of ascites

84% of the cases studied had no ascites and only 16% had associated ascites.

Ascites was present in 75% of malignant tumours (in 24 out of 32 cases), in none of the borderline tumours, and in a single case of benign tumour.

- Analysis of macroscopic loco-regional and peritoneal lymph node metastases

Of the 38 tumour formations that had loco-regional lymph node metastases, 74% were due to malignant and borderline tumours.

In 8.8% of all benign tumour formations, reactive loco-regional lymph node hypertrophies were found. Macroscopic (over 2 cm) peritoneal metastases were only seen in malignant tumours and were associated with them in 81% of the cases.

- Pelvic parietal/contiguous organ extension

Pelvic parietal or contiguous organ extension was observed in about 65% of malignant tumour formations, in one third of borderline tumours and only in one case of benign tumour. The latter was assessed sonographically and CT as a tumour formation with malignant features, intraoperatively associated with endometriosis and confirmed histopathologically as a benign mucinous-type tumour formation.

- Assessment of distant metastases

Computed tomography and magnetic resonance imaging were particularly useful in assessing metastases and preoperative staging of ovarian disease, in addition to ultrasound.

Of the malignant tumours, 50% had distant metastases, which are not found in borderline or benign tumours.

5. Assessment of postoperative evolution by analysing the ADC index at the level of peritoneal residual deposits and the values of the serological marker CA125.

Of the patients diagnosed with ovarian malignancies, MRI investigation was also used for 24 patients to monitor the post-treatment evolution at 6- and 12-months follow-ups, respectively. Biochemical investigations and ADC values were analysed in comparison with baseline values (prior to intervention).

The ADC values showed a significant increase in the first 6 months (on average by $0.18*10^{-3}mm^2/s$) but insignificant in the following 6 months. The variation of the ADC index

values in the controls 6 and 12 months after the intervention was also analysed in relation to the age of the patients, without a statistically significant correlation with it.

Comparison of ADC values measured at 6 and 12 months with ADC values at peritoneal deposits measured at the time of diagnosis showed a clear improvement in these values at 6 months, which was maintained in about 80% of cases at controls at 12 months. The remaining 20% of the patients evaluated had lower ADC values compared to the previous ones, suggesting an unfavourable evolution in the post-operative period between 6-12 months.

Another important indicator in the diagnosis was considered the serum level of CA125 which was measured during the follow-up period, at 6 and 12 months.

The correlation of the ADC index and the CA125 titre was performed by calculating the Pearson correlation coefficient, both for the pre-operative initial stage and at the 6 and 12 months post-operative controls respectively, resulting in no correlation at the initial stage between the 2 parameters and a moderately decreasing correlation at 6 months and strongly decreasing at 12 months. A decrease in CA125 was thus observed with the increase of the ADC index, the linear dependence being more pronounced at the 12-month investigation.

6. Assessment of the sensitivity and specificity of MRI and CT investigations in characterising and evaluating the post-treatment evolution of ovarian tumour lesions.

Of the sample of 76 cases investigated by MRI examination (groups of patients evaluated by ultrasound and MRI or ultrasound, CT and MRI), the number of cases identified as positive for malignant tumour formations was 35 in relation to the post-interventional histopathological examination that established the diagnosis of malignancy in 38 of the cases analysed (borderline tumours being considered to belong to the malignant tumour group).

The cases assessed by MRI as benign were 41, with post-interventional histopathological examination establishing the diagnosis of benignity in only 38 of them.

The value of the ADC index at the level of solid tumour components was of particular value in assessing the MRI diagnosis, although in two cases of benign fibromatous tumour formations the low value of the ADC index led to the appearance of the two false positive results.

At the same time, some of the tumour formations, especially the borderline ones, with non-specific semiological characteristics for a formation with definite malignant features, led to the appearance of another 5 false negative results.

The analysis of the confusion matrix for the results of the MRI investigation showed a sensitivity of 87%, a specificity of 95% and an accuracy of 91% for the assessment of the malignant nature of ovarian masses.

Of the sample of 63 cases investigated by CT examination (groups of patients evaluated by ultrasound and MRI or ultrasound, CT and MRI), the number of cases identified as positive for malignant tumour formations was 36 in relation to the post-interventional histopathological examination that established the diagnosis of malignancy in 33 of the cases analysed.

The cases assessed by MRI as benign were 27, with post-interventional histopathological examination establishing the diagnosis of benignity in only 30 of them.

The confusion matrix for assessing the sensitivity and specificity of the CT investigation in assessing the malignancy of ovarian tumour formations showed a sensitivity of 91%, with a specificity of 80% and an accuracy of 85%.

The CT evaluation has been particularly beneficial in bulky tumours with distant extension by assessing metastases in other organs, the existence of associated comorbidities in order to optimise therapeutic conduct.

The semiological assessment criteria were overall similar to those used in the other imaging investigations, but without being able to benefit from the particular value as a potential tumour biomarker represented by the MRI diffusion sequence.

7. Magnetic resonance imaging assessment in the study was a high-performance investigation due to the multiple sequences available for the characterisation of tissue structures in order to differentiate the components of tumour formations, with increased specificity in the assessment of malignancy.

The multiple sequences that can be used for the analysis and differentiation of tissue structures with optimal appreciation of lipomatous, cystic, hematic or various stages of haemoglobin degradation, in conjunction with the value of the diffusion sequences, can be effective investigational alternatives in patients with allergies or impaired renal function when the administration of contrast agents for tumour characterisation is contraindicated.

Through the possibility of multiplanar acquisitions, a superior assessment of tumour masses was ensured, with a good appreciation of organ membership and anatomical relationships, and through the diffusion sequences and the characterization of the post-

contrast load curves, a significant increase in sensitivity was noted in the determination of the malignancy with particular importance for choosing the optimal therapeutic conduct.

Tumour areas with increased signal on diffusion sequences and low absolute diffusion index (ADC) represent structures with increased cellularity consistent with tumorigenicity.

The increase in the post-therapeutic ADC index in residual tumour masses signifies a favourable course of the disease, being considered as a biomarker for the dynamic assessment of the therapeutic response in oncological diseases. The increase in this index correlated in most cases with the reduction in the titre of tumour serological markers.

At the same time, the low ADC index value had increased sensitivity in the assessment of lymph node hypertrophies, which are suspected of metastasis regardless of size.

Some low ADC index values could not always be correlated with the malignancy, as other factors such as extracellular fibrosis, the shape and size of the intercellular spaces could influence its value and some formations, especially of the fibromatous ones, although benign, showed a decreased ADC index value. For these cases, other imaging characteristics (especially the type of contrast uptake) and some clinical-biological parameters have guided the diagnosis.

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1. Yolk sac tumor in a 20 year old patient - Romanian Journal of Military Medicine Vol. CXX No.3/2017, Clinical Practice pag 56-59 (chapter 8.2.3)
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2. Demon-Meigs syndrome - Diagnosis and therapeutic conduct - Romanian Journal of Military Medicine Vol. CXXIV No.1/2021, Varia pag 84-88
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