ABSTRACT

PURPOSE: To analyze the role of the grade of the tumor as a prognostic factor for women with early epithelial ovarian cancer

MATERIAL AND METHODS: For the purpose of the research, a cohort of 254 female patients with ovarian cancer (stage I- II) was investigated for a 12 year period (2000- 2012). All of the patients were surgically staged, and have histopathology result for morphology type and degree of differentiation (grade) of the tumor.

For the purpose of our research we used descriptive analysis, Variation analysis, Correlative analysis, Graphic analysis, Kaplan – Mayer analysis, Chi – square – analysis.

RESULTS: In multivariate analysis with eighteen others potential factors the tumor grade proved to be an independent prognostic factor for overall- and progression free survival of female patients with early epithelial ovarian cancer along with age, stage and tumor markers.

CONCLUSIONS:
1. The tumor grade is a reliable predictor of survival for patients with early epithelial ovarian cancer.
2. There is a point the grading system to consist of only two grades. It allows us to quickly distinguish the patients at higher risk from those at relatively low risk, which can reflect in the aggressiveness of the treatment.
3. Because of the definite early recurrence of disease patients with high- grade ovarian tumors that survived more than five years, we can consider being cured.

Keywords: epithelial ovarian cancer, survival, prognosis, tumor grade, prognostic factor,

INTRODUCTION

Widespread opinion is that ovarian cancer shows no early symptoms and so it is commonly late diagnosed. That is why the early detection through improvement of diagnostic and screening methods is one of the main directions of the contemporary tendencies in oncology. As there is a significant difference of survival between the early and the advance stages of EOC, we have focused our attention on studying prognostic factors for early stages of epithelial ovarian cancer (EOC I – II stage).

Grade of the tumor is one of the most important prognostic factors, taken under consideration when it comes to the survival of female patients with early EOC.

OBJECTIVE

To analyze the role of the grade of the tumor as a prognostic factor for women with early epithelial ovarian cancer.

MATERIALS AND METHODS

The medical records of 254 female patients with ovarian cancer (stage I- II) were investigated for the purpose of the research. All women are surgically treated and staged during the period 2000 – 2005. The time of the post-operative exploration was 12 years (2000- 2012). All of the patient have histopathological result for morphology type and degree of differentiation (grade) of the tumor.

We created an investigation paper form, which we used to collect the information that we imported in a table manner and processed with statistical package MedCalc 12.2.1.0.

The information has been collected, using investigation paper form, which we preliminarily created than imported in a table manner and processed with statistical package MedCalc 12.2.1.0. We used Descriptive analysis, Correlative analysis, Variation analysis, Graphic analysis, Kaplan – Mayer analysis, Covariate analysis, Chi – square – analysis.

RESULTS:

Corresponding to the including criteria were 215 of 254 female patients. The other 39 patients were removed from the research because of: insufficient data (n = 17), the non-epithelial origin of the tumor (n=15), and reason of death, other than the investigated disease (n=7). Out of 215 patients with early epithelial ovarian cancer, 121 are with grade I, 67 – with grade II and 27 with grade III of their tumors. The highest mortality rate has the group with grade III tumors – 66.7% (n = 18 of 27); next is the group with grade II tumors – 40% (n = 27 of 67) and last – the group with grade I tumors – 12.4% (n=15 of 121). The average
overall survival of women with grade I tumors is 108 months, with grade II tumors – 80 months, and with grade III tumors – 38 months.

Some contemporary researchers are sharing the opinion that the grading system for epithelial ovarian cancer should consist of only two grades: high grade - and low-grade tumors (the two-tier system) [1]. Others are using a four grade system, with IV being classified as undifferentiated [2].

However, all the patients of our research were graded by the still official three – grade system, so that is how we divided the cases:

1. Well differentiated tumors (Grade I)
2. Moderately differentiated tumors (Grade II)
3. Poorly differentiated tumors (Grade III)

The correlation between the grading system and the vital status we represent through two categories called alive and deceased listed in Table 1.

Table 1. Grading and vital status of the patients.

<table>
<thead>
<tr>
<th>Vital status</th>
<th>Grade</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Alive</td>
<td>106</td>
<td>40</td>
</tr>
<tr>
<td>Deceased</td>
<td>15</td>
<td>27</td>
</tr>
</tbody>
</table>

155 (72,1%)
60 (27,9%)
215

Out of 215 patients with early epithelial ovarian cancer, 121 are with grade I, 67 – with grade II and 27 with grade III of their tumors.

Of 121 patients with well-differentiated epithelial ovarian cancer, 15 women (12.4%) have died until the end of the period.

27 of 67 women (40%) with moderately differentiated tumors have deceased during the 13 years period.

Of 27 patients with low differentiated ovarian tumor at the end of the follow-up period died 18 (66.7%).

According to our data the highest mortality rate has the group with grade III tumors – 66.7% (n = 18 of 27); next is the group with grade II tumors – 40% (n = 27 of 67) and last – the group with grade I tumors – 12.4% (n=15 of 121).

The overall survival of the groups with different grade of differentiation is shown on figure 1.

Fig. 1. Tumor grade and overall survival
The differences in the curves are obvious and indicative of overall survival according to the degree of differentiation. The differences of the curves are significant and show the expected dependence of the overall survival of patients with epithelial ovarian cancer, stage I–II on the grade of differentiation of their tumors.

The average overall survival of women with grade I tumors is 108 months, with grade II tumors – 80 months, and with grade III tumors – 38 months.

**Progression free survival**

In the contemporary oncology, the quality of life, i.e. progression free survival is equally, if not more, cherished than the simple duration of life, i.e. overall survival. The progression free survival of the three groups of patients is illustrated in figure 2.

**Fig. 2.** Grade and progression free survival

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**Official data:**

Recurrence of cancer appeared in 12.4% of the patients with Grade I tumors (n=15 of 121), in 41% of the patients with Grade II tumors (n=28 of 67) and in 66.7% of the women with Grade III tumors (18 of 27(p<0.0001)).

**Five years survival**

The five years survival of the three groups of patients is as it follows: *Grade I - 91%* (n= 110 of 121), *Grade II – 70.1%* (n=47 of 67) and *Grade III – 33.3%* (n=9 of 27).

Five years progression free survival of the same groups are - *Grade I – 92%* (n=111 of 121), *Grade II – 66%* (n=44.2 of 67), *Grade III - 15%* (n=4 of 27).

**Table 2.** Coefficients and Standard Errors

<table>
<thead>
<tr>
<th>Covariate</th>
<th>B</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor grade II</td>
<td>1.3813</td>
<td>0.3232</td>
</tr>
<tr>
<td>Tumor grade III</td>
<td>2.2584</td>
<td>0.3528</td>
</tr>
<tr>
<td>Significance level</td>
<td>P &lt; 0.0001</td>
<td>18</td>
</tr>
</tbody>
</table>

All of the deceased patients with poor-differentiated tumors received relapses and died until the fifth postoperative year. One third of the patients of the same group that survived the five years period were alive to the end of the investigated period.

In regard to the overall- and progression free survival of women with early epithelial ovarian cancer the patients with low differentiated carcinoma represent a high-risk group (p<0.0001).

We used Cox – proportional regression to estimate the hazard of death ratio for the different groups, as shown on table 2. The control group here was naturally the grade I- group.
The hazard of death is nearly 4 times higher for the patients with moderately differentiated and almost 10 times higher for the group with poorly differentiated, compared to control group (women with the highly differentiated ovarian tumors).

If, as some of the authors suggest (Minal J. et al. 2015), we divide the patients into only two grade groups, for example, Group A (Grade I tumors) and Group B (Grade II + Grade III tumors), they still have a significant difference of the Kaplan – Mayer curves of overall survival (figure 3). The curve of the patients from B- group descends much more rapidly and reaches lower (down to 50% overall survival) than the A-group curve (around 88% overall survival).

**Fig. 3.** Grade and overall survival - 2 groups.

The hazard of death of Group B (Grade II+ Grade III) is approximately 7.5 times higher than Group A (Grade I).

**DISCUSSION**
In 2001 Vergote et al. refer to the tumor grade: “Degree of differentiation, the most powerful prognostic indicator in stage I ovarian cancer .......” [3] The significance of the degree of differentiation was confirmed by the results in our research for stage I as well as for stage II epithelial ovarian cancer. The tumor grade was loaded for statistical calculation along with eighteen others potential prognostic factors for multivariate analysis, and it proved to be an independent prognostic factor for overall- and progression free survival of female patients with early epithelial ovarian cancer. Other independent prognostic factors were age, stage and tumor markers. Stage and grade were...
found more significant factors by other researchers like George D. Malkasian Jr. et al., 1984, comparing them to the histologic type [4].

Even though we are investigating patients in the early stage of epithelial ovarian cancer, we can see from the statistical results high mortality rates for Grade II (40%) and for Grade III (66.7%).

In May 2018 Nasioudis D et al. are investigating 1242 women with non-clear cell epithelial ovarian cancer apparently confined to the ovary, stratified by tumor grade. They make a conclusion: “Regional LN metastasis in apparent stage I low-grade mucinous and endometrioid ovarian tumors is infrequent.”[5] In our research, we haven’t excluded the clear cell carcinomas, but we have similar results for both I and II stage epithelial ovarian cancer. We also found that in regard to the overall- and progression free survival of women with early epithelial ovarian cancer, the patients with low differentiated carcinoma represent a high-risk group (p<0.0001).

Despite that, the 5-year survival is not as indicative time frame, as it used to be it still can serve a purpose. Because all of the deceased patients with poor-differentiated tumors received early relapses and died until the fifth post-operative year, the patients of the same group that survived the five years period we could consider as cured, which is true for 1/3 of the patients with Grade III in our research.

CONCLUSION

The tumor grade is a reliable predictor of survival for patients with early epithelial ovarian cancer. It can be used in combination with other independent factors for even more effective prognosis.

There is a point the grading system to consist of only two grades. It allows us to quickly distinguish the patients at higher risk from those at relatively low risk, which can reflect in the aggressiveness of the treatment.

Because of the definite early recurrence of disease patients with high-grade ovarian tumors that survived more than five years, we can consider being cured.

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