Granulosa Cell Tumor of the Ovary: 10 Years Follow-up Data of 65 Patients

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Abstract. *Background: Granulosa cell tumor of the ovary is an uncommon neoplasm. The majority of patients are diagnosed in early stages of disease and overall prognosis is favorable. The stage at time of diagnosis is the only prognostic factor that is unequivocally related to survival. Other prognostic factors have not been well defined and are discussed in the literature controversially. Materials and Methods: In a multi-institutional retrospective study we analyzed all relevant clinical data of patients with histologically proven granulosa cell tumor of the ovary. We applied the Kaplan-Meier method in order to estimate overall survival rates and evaluate prognostic factors. Results: The median follow-up was 75 months (range, 6-315 months). Overall survival was 87% and 76% after 5 and 10 years, respectively. Eighty percent of granulosa cell tumors were diagnosed stage I (FIGO). The survival rate after recurrence was 56.8% after 10 years. Mitotic rate (p=0.003), tumor stage (p<0.001) and residual tumor disease (p<0.001) were associated with a poor prognosis (p<0.001). Age and rupture of the tumor could not be confirmed to be of prognostic value. Conclusion: The results of our study showed that the mitotic index may be a valuable prognostic factor. Complete tumor resection should always be attempted, since residual tumor disease is associated with a poor prognosis. Prospective studies are needed in order to confirm our findings.*

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Rokitansky (1859) was the first to describe granulosa cell tumor of the ovary as a single tumor entity (1). The estimated incidence is between 0.5-1.5/100,000 per year (2-4). Granulosa cell tumors can occur at any age, but are more common after menopause and comprise 2-3% of all ovarian malignancies.

Hormonal secretion is characteristic of these tumors and can lead to meno- and metrorrhagia, postmenopausal bleeding or amenorrhea. A continuous growth of the tumor can cause in other cases non-specific, abdominal symptoms (5).

Approximately 75% of granulosa cell tumors are diagnosed in stage Ia-c (FIGO), 20% represent stage II, 8% stage III and 6% stage IV of tumor disease (5-7). The overall 10-year survival rate is favorable at 75%-90%. Prognosis seems to be strongly associated with tumor stage. Ten-year survival rates are approximately 70-95% for stage I, 55-75% for stage II and 25% -50% for stage III (2, 5-9) .

In contrast to ovarian cancer, relapses are characteristic in granulosa cell tumors of the ovary after a postoperative period of five years.

Complete surgical resection of the tumor is the mainstream of treatment (6-8, 10, 11). It remains to be clarified whether patients with stage I disease benefit from more extensive surgical treatment including total abdominal hysterectomy and bilateral salpingoophorectomy (5, 10, 12, 13). Adjuvant therapy for advanced and recurrent disease has been discussed in various studies, the feasibility of different platinum-containing chemo-therapeutic regimen (14) has been demonstrated in prospective studies (15) and radiotherapy may also represent a treatment option for selected cases (16).

Tumor stage appears to be the most important prognostic factor (2, 9, 17). Other prognostic factors, inconsistently reported (7), include intraperitoneal disease (3, 4, 18), tumor size, patient's age, grade of differentiation, mitotic

Table I. *Patients characteristics.*

Parameter	Value	Number of patients (n)
Age at diagnosis, years (median, range)	53 (3-83)	65
Hormonal status, n (%)	65 (100%)	
Prepubertal	2 (3.1)	
Premenopausal	27 (41.5)	
Postmenopausal	36 (55.4)	65
Partus (median, range)	1 (0-6)	54
Weight, Kg (median, range)	65 (39-116)	44
FIGO-stage, n (%)		65
Ia	38 (58.5)	
Ic	14 (21.5)	
II a	4 (6.2)	
II b	1 (1.5)	
III a	2 (3.1)	
III b	2 (3.1)	
IIIc	2 (3.1)	
IV	2 (3.1)	
Maximal tumor diameter of postoperative tumor mass,		65
n (%)	65 (100%)	
Macroscopic tumor-free	54 (83.1)	
≤2cm	8 (12.3)	
<2cm	2 (3.1)	
no data	1 (1.5)	

Table II. *Chemotherapy regimens.*

Regimen of first-line chemotherapy	n
No chemotherapy	47
Carboplatin/ Cisplatinum +Cyclophosphamid	6
Cyclophosphamid, Methotrexat, + 5-Flououracil	4
Vincristin, Cyclophosphamid + Adriamycin/ Dactinomycin	3
Cyclophosphamid	1
Cisplatinum, Bleomycin and Etoposid	1
Carboplatin and Etoposid	1
Carboplatin + Paclitaxel	1
Actinomycin, Cyclophosphamid +5-Flououracil	1

Figure 1. *Recurrence rate.*

Materials and Methods

A total of 65 patients were included into this study. The study was based on seven hospitals and one outpatient center for gynecologic oncology: Charité University Hospital of Berlin, Campus Virchow (n=27); University Hospital Benjamin Franklin, Berlin (n=17); University Hospital Greifswald (n=9);Oskar-Ziethen-Hospital, Berlin-Lichtenberg (n=4); Hospital Reinkenheide, Bremerhaven (n=3); Achim Hospital (n=3); Outpatient Center Gynecologic Oncology, Berlin (n=2), Germany.

We used the data from the pathological institute of each center in order to identify all the patients with histologically proven diagnosis of granulosa cell tumor of the ovary. Medical notes were reviewed and clinical data extracted. The FIGO classification (Fédération Internationale de Gynécologe et d'Obstétrique) was assigned for each patient.

The clinical status of all patients was updated at the follow-up clinics by telephone and mail. If this was not feasible, we contacted the patient or patient's family directly.

For the discussion of results, a comprehensive literature research was performed by using Medline, Cochrane databases and Embase of the years 1960-2002.

Statistics. We focused on descriptive analysis and the estimation of survival rates. SPSS Software (Version 8.0 1997) was used for all statistical procedures. Normal distribution was confirmed by using histograms, box-plot graphics and the Kolmogorov-Smirnov test. The Chi-square test was applied, when two sample probes were compared for observed and expected frequencies (28). The Student's *t*-test for independent samples was used to compare two independent sample probes with normal distribution. We examined the time interval between the date of the operation and the end of the observation and applied the Kaplan-Meier method to estimate survival rates (29). The Log-rank test was applied to confirm significance. *P*-value of <0.05 indicated statistical significance.

rate and nuclear atypia (19). However, their role as prognostic factors has not been clearly determined, because most of the studies have enrolled only a few patients and only used a short follow-up period (3, 5, 6, 20-26).

In view of these contradictory results, the clinical data of patients with granulosa cell tumors of the ovary was reviewed with the primary objective of determining the prognostic factors and long-term overall survival rate.
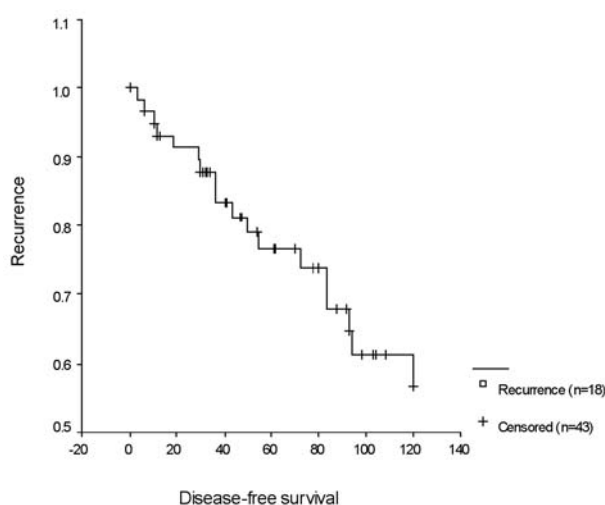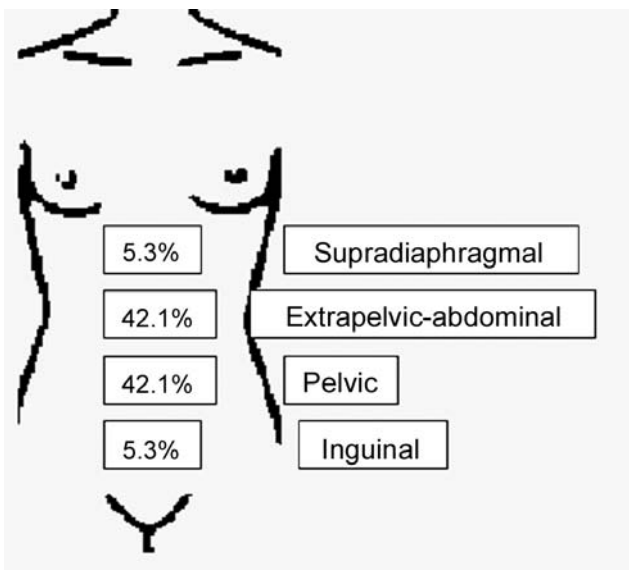
Figure 2. *Localization of recurrent disease (n=18).*

Figure 3. *Survival after recurrence.*

Figure 4. *Overall survival after 120 months.*

Results

Patient characteristics. A total of 65 patients with histologically proven granulosa tumor of the ovary were included in this study. The median year of diagnosis of the patients was 1992 (range, 1968-2000). Median follow-up was 75 months (range, 6-315 months). The median age at diagnosis was 53 years (range, 3-83 years). Three pediatric patients (4.5%) between 3 and 16 years were included (Table I).

All patients underwent primary surgery. In only one case was the tumor classified as being inoperable during the explorative laparotomy (FIGO stage IV). Generally, an abdominal hysterectomy and bilateral adnectomy were performed (n=42). In 5 cases hysterectomy had been performed earlier due to benign diseases, so only adnectomy was undertaken. To preserve the fertilization a unilateral adnectomy was performed in 10 cases of FIGO stage I. Other surgical procedures were performed infrequently: omentectomy (n=21), appendectomy (n=9), lymphadenectomy (n=7) and bowel resection (n=2).

Eighty percent (n=52) of all patients were diagnosed in stage I; 7.7% stage II; 9.2% stage III and 3.1% stage IV. A total of 18 patients (28%) received adjuvant chemotherapy, which contained different platinum-based combinations in 9 cases (Table II). Nine out of these 18 patients were in FIGO-stage I and 9 in stage II-IV. Eight different protocols of chemotherapy were used in this cohort. A total of 8 (12.3%) patients received postoperative radiotherapy, in 3 cases for an simultaneous adenocarcinoma of the uterus. In 3 cases an irradiation according to an after-loading technique and in 5 cases a percutanous irradiation was applied.
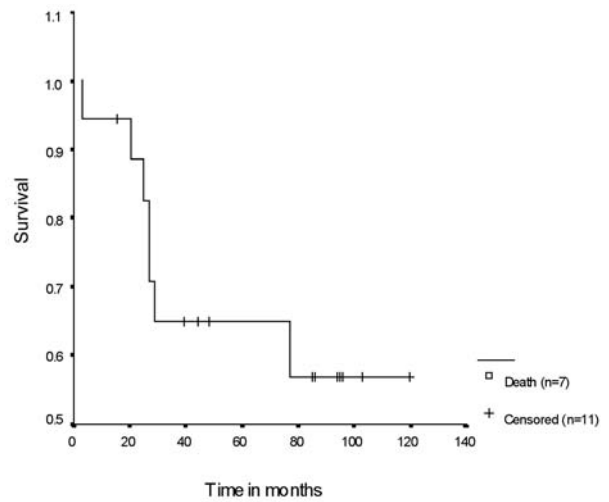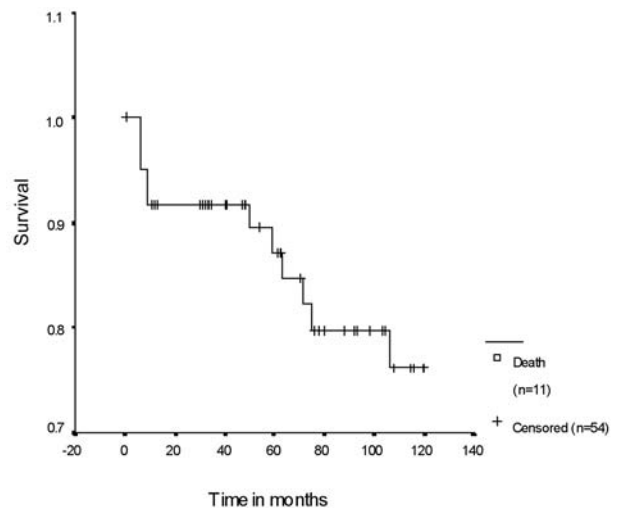
The average tumor size (largest diameter) of stage I (n=47) and stage II-IV (n=11) was 10.3 cm (0.6-27 cm) and 12 cm (3.5-28 cm), respectively. This difference was not significant (*p*=0.44).

Recurrence. Eighteen patients experienced a relapse of the malignant disease. The average disease-free survival for this subgroup was 67 months; the median was 55 months (range, 3-221 months). The estimated 10-year recurrence rate was 43% (Figure 1).

Recurrence was predominantly located intraperitoneally. Distant metastasis was generally rare (Figure 2). Pulmonary and skeletal metastasis occurred in one patient. Only one patient presented with recurrent disease in the inguinal

Table III. *5- and 10- year survival rates*

Stage (FIGO)	n	Five years	Ten years
I	52	95%	87%
II	5	75%	75%
III	6	40%	20%
IV	2	50%	0%

Figure 5. *Survival stage I versus stage II-IV (p<0.0001).*

region. Paraaortal or retroperitoneal lymph node disease was confirmed in one case, a retroperitoneal lymphonodectomy, however, was only performed in 2 patients with recurrence. Six patients were operated due to relapse and 7 patients received 5 chemotherapy. In a subgroup of 5 patients, an irradiation of the relapsed tumor was applied.

The 10-year survival rate after tumor recurrence was 56.8% and did not fall below the median survival. The average time of survival was 82 months (Figure 3).

Overall survival. The estimated overall survival after 5 and 10 years was 87% and 76%, respectively (Figure 4).

Age. We could not confirm any significant difference of survival rates between patients younger than 50 years and those older than 50 years ($p=0.45$).

Tumor rupture. In 59 cases the surgical report indicated whether the tumor had ruptured or remained intact. Tumor rupture occurred in 28 cases; descriptions such as "disintegration", "rupture" or "deliberate drainage" of the tumor were used. The data was insufficient to pinpoint exactly the cause of rupture: the tumor may have ruptured before or during surgery. An extremely fragile consistency was observed in 4 cases and the tumor tissue disintegrated during the procedure. In only 2 cases were the results of cytological examinations of peritoneal fluid documented. We could not find any significant difference between survival rates of patients with and without tumor rupture ($p=0.25$).

Tumor stage. Survival rates after 10 years were 87.2%, 75%, 20% and 0% for stage I, II, III and IV, respectively (Table III).We compared the survival rate of patients with early stage (FIGO I) and advanced stage (FIGO II-IV) disease, to clarify the association between stage and prognosis (Figure 2). The estimated, average survival (median survival had not been reached) was 113 months for stage I tumors and 67 months for advanced stage tumors (II-IV). The Log-rank test confirmed significance for these differences ($p<0.001$) (Figure 5).
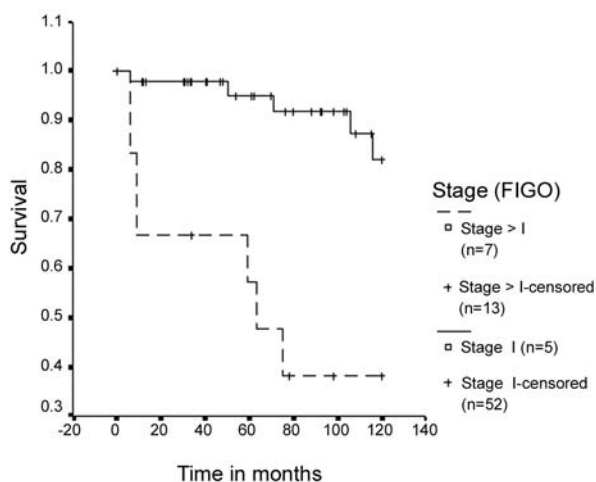
Mitotic rate. We obtained information about the mitotic rate from the histopathological reports of 37 patients. We distinguished between "high" and "low" mitotic rate. Mitotic figures HPF (High Power Field) of 5/10 or above, or the simple description "high" were interpreted as high mitotic rates. Descriptions such as "moderate" or "low" mitotic rates were interpreted as low (Table IV). We analyzed the differences between the mitotic rates of patients with early stage tumors (FIGO I) and advanced stage disease (FIGO II-IV). Pearson's and Spearman's analysis revealed a correlation of 0.47 ($p=0.003$) (Table IV).

Tumor size and mitotic rate. The average tumor size (largest diameter) for tumors with high mitotic rates (n=9) was 12.1cm (range, 6-20 cm) and for tumors with low mitotic rates (n=27) it was 10.5 cm (range, 1.3-24 cm). This difference of 1.6 cm was not significant ($p=0.44$).

Survival and mitotic rate. Application of the Kaplan-Meier method revealed a significant difference, when we compared the time of survival for low and a high mitotic counts ($p<0.001$). Every patient with a low mitotic rate has survived 120 months, in contrast to only 20% of patients with a high mitotic rate (Figure 6).

Survival and postoperative residual tumor mass. Overall, 54 patients did not have any postoperative macroscopic residual tumor mass. In 10 cases complete tumor extirpation was not possible. In comparison survival was significantly worse for patients with postoperative residual disease ($p<0.001$) (Figure 7).

Furthermore, we analyzed the survival rate for those patients who were positive for all three risk factors: residual

Table IV. *Mitotic rate.*

	Frequency (n)	Percentage
Low mitotic rate	27	41.5%
High mitotic rate	10	15.4%
No information	28	43%
Total	65	100%

disease, stage and high mitotic rate. Only 3 patients carried all 3 risk factors. The median survival in this group was 9 months (range, 6-9). The survival in comparison with those patients who carried less than 3 risk factors was significantly worse ($p < 0.001$).

Discussion

In this study we analysed the clinical data of 65 patients with a granulosa cell tumor of the ovary. General clinical characteristics including age distribution and tumor stage were in coherence with findings reported in previous studies (2-5, 7-9).

The median follow-up period for 65 patients was 75 months (range, 6-315). This is significantly longer than in other recent studies. The follow-up in a study published by Pecorelli *et al.* was only 38 months (30). Granulosa cell tumors are well known for late recurrence, therefore long-time follow-up is necessary in order to obtain reliable data regarding the clinical course of the disease. In our study recurrent disease occurred after an average of 69 months, the median interval being 60 months (range 3-221). Other studies reported an average disease-free survival of 5 to 10 years (4, 5, 18, 27). The longest recurrence-free interval in our study was 18 years. Hines *et al.* reported a patient with recurrent disease 37 years after initial diagnosis (27); other reports about recurrence 10-30 years after diagnosis have been published (11, 31-35). As a clinical consequence, lifelong follow-up for all patients with granulosa cell tumors is warranted and should not end after five years. The overall recurrence rate was 43% after 10 years and appeared to be higher than in other studies. Other authors reported recurrence rates of 9-18.9% up to 40-60% , but often other sex-cord stromal tumors were included and the follow-up period was quite short in these studies (3, 5, 8).

We could confirm the generally favorable prognosis of granulosa cell tumors of the ovary; the overall survival rate was 87% and 76 % after 5 and 10 years, respectively. Eighty percent of all tumors were diagnosed at an early stage, but prognosis was significantly poorer for patients with advanced tumors with 10-year survival rates of 20% and 0% in stage III and IV, respectively, similar to ovarian cancer (despite its
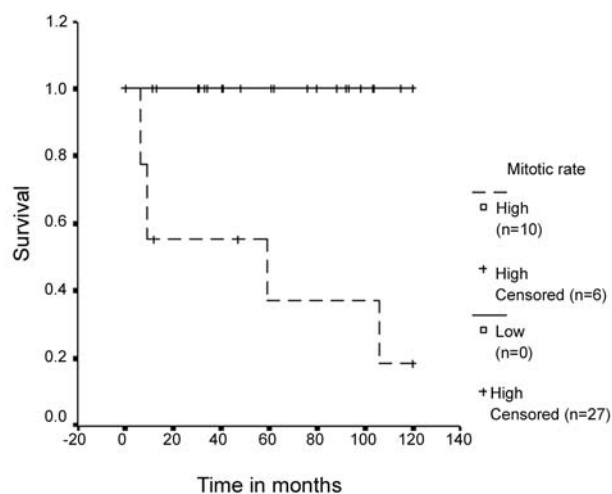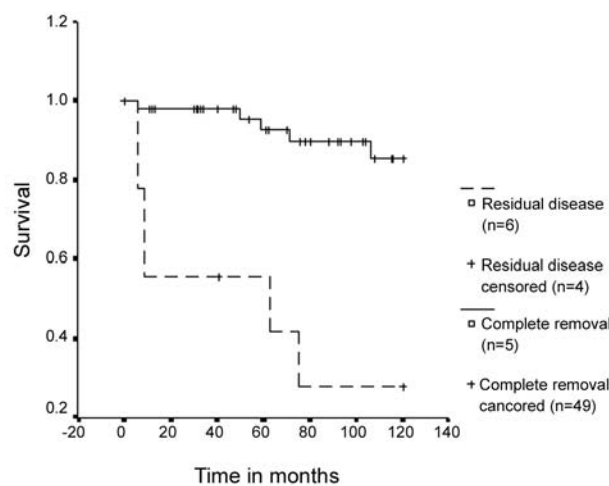

Figure 6. *Survival and mitotic rate.*

Figure 7. *Survival and postoperative residual tumour mass.*

different tumor biology) (Table V). Thus tumor stage has been confirmed to be of prognostic significance (8).

Complete surgical resection is the mainstay of treatment (6-8, 10, 11). It remains to be clarified whether patients with stage I disease benefit from more extensive surgical treatment, including total abdominal hysterectomy and bilateral salpingoophorectomy (5, 10, 12, 13). As we described previously, repeated debulking procedures can contribute to medium- and long-term survival with good symptom control in patients with recurrent disease in selected cases (11). Residual tumor disease was clearly associated with a poor prognosis in our study ($p < 0.002$). Complete tumor removal should always be attempted as primary treatment and a multidisciplinary procedure should be considered for advanced stages.

Table V. *Five year survival and stage (FIGO).*

Stage	Granulosa cell tumor	Epithelial ovarian cancer
I	70-95%	85%
II	55%	62%
III	40%	18%
IV	10%	8%

From different studies [2; 4; 5; 7-9; 36]

A total of 25 patients received systemic chemotherapy, whereby 18 were applied as primary adjuvant treatment and 6 as treatment of relapse. The value of systemic chemotherapy in granulosa cell tumors of the ovary is discussed controversially in the literature. Some authors recommend polychemotherapy containing cisplatinum, vinblastin and bleomycin for patients with advanced stage or relapse (10,14,30).The superiority of adjuvant chemotherapy to surgery alone has not been confirmed in a randomised trial. Due to the lack of data the optimal platinum-based regimen is also still unknown. To date, an adjuvant chemotherapy for patients with completely (macroscopic) removed granulosa cell tumor of the ovary is not obligatory (37).

An average tumor diameter of 10.6 cm in our study indicated a delayed diagnosis; however, 80% of all patients were diagnosed in FIGO stage I. Interestingly, the tumor sizes of early stage tumors and advanced stage tumors only differed marginally. A more aggressive biological behavior of advanced stage tumors may be the reason for early infiltration and is not based on the tumor diameter. Therefore, the tumor diameter is not a valid prognostic factor for granulosa cell tumors of the ovary. In this context the fact that the mitotic rate was related to tumor stage ($p < 0.005$) and prognosis ($p < 0.001$) may play a more important role. We obtained these clear results despite the fact that the histological reports came from different pathologists and were not standardized.

Björkholm *et al.* (2,6, 21) retrospectively analyzed the clinical data of 54 patients. Five-year survival was 100% in the group of patients with a low mitotic index ≤4/10 HPF (High-power field). The 5-year survival rate of patients with a mitotic index of 5-9/10 HPF was 80%, median survival was nine years. The prognosis of patients with a mitotic index of 10/10 HPF was poor and all these patients died within 4 years. Miller *et al.* (38) compared 19 patients with recurrent tumor disease and 51 patients without disease. The mitotic rate was higher in the group with recurrence. A recent study published by Fujimoto *et al.* (39) compared disease-free survival of 27 patients. They distinguished between a mitotic index of ≤3/10 HPF and ≥4/10 HPF, their results were also significant ($p < 0.0005$).

Other histopathological prognostic factors, including ploidy and S-phase fraction, have been investigated in recent years (24, 25). Molecular biological markers such as p53 increasingly attract attention (19). So far none of these markers have become established as relevant prognostic factors in day to day clinical routine and should be investigated in prospective studies.

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