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GYNECOLOGIC ONCOLOGY

Malignant ascites occurs most often in patients with high-grade serous papillary ovarian cancer at initial diagnosis: a retrospective analysis of 191 women treated at Bayreuth Hospital, 2006–2015

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Abstract

Background Malignant ascites often develops in patients with ovarian cancer, but there is a lack of more detailed characterization of the different histological subtypes.

Methods Ascites specimens from patients with ovarian cancer who were treated at Bayreuth Hospital from 2006 to 2015, with follow-up until December 2016, were reevaluated retrospectively.

Results A total of 191 women (mean age 64 years, range 48–79) were included, of whom 180 (94.2%) had carcinoma, three (1.6%) had malignant mixed müllerian tumors (MMMTs), four (2.1%) had sex cord–stromal tumors (SCSTs), three (1.6%) had germ cell tumors (GCTs), and one (0.5%) had a sarcoma. The carcinoma group comprised 134 (70.1%) patients with high-grade serous papillary ovarian cancer, 17 (8.9%) with low-grade serous papillary ovarian cancer, 10 (5.3%) with mucinous carcinomas, nine (4.7%) with endometrioid carcinomas, six (3.1%) with clear cell carcinomas, and four (2.1%) with neuroendocrine tumors. The latter group consisted of two patients with mixed neuroendocrine–nonneuroendocrine tumors (MiNENs), one with only a small cell carcinoma (SCCO), and one with a mucinous carcinoid. The noncarcinomatous group of eight patients (4.2%) included three (1.6%) with Sertoli–Leydig cell tumor and mature cystic teratoma (MCT), one (0.5%) with a granulosa cell tumor, and one with a leiomyosarcoma. A statistically significant difference in the proportion of patients with malignant ascites was observed, at 17.7% (3/17) in those with low-grade serous papillary ovarian cancer and 91.8% (123/134) in those with high-grade serous papillary ovarian carcinomas. In both patients with MiNEN, the glandular tumor cell component was found in the ascites. Tumor cells were found in the ascitic fluid in 50% (5/10) of patients with mucinous ovarian carcinomas, 16.7% (1/6) of those with clear cell carcinomas, and 33.3% (1/3) of those with MMMTs. The two patients (2/3; 66.7%) with neoplastic squamous cell components in MCT and the only patient with a granulosa cell tumor in the SCST group (1/4; 25%) had malignant cell populations in the ascites, whereas patients with endometrioid cell carcinoma and leiomyosarcoma lacked tumor cells in the ascites. The malignant ascites was detected at the initial diagnosis in all 138 (100%) patients with ovarian neoplasms.

Conclusions High-grade serous papillary ovarian cancer was the main histological subtype most frequently found in ascites fluid in this series. The significant difference ($P < 0.00001$) in the malignancy rate in comparison with low-grade serous papillary carcinoma confirms the histological distinction between the two entities. Initial evidence of ovarian cancer in ascites fluid allows correct primary diagnosis in cytology specimens and is important for staging and prognosis.

Keywords Malignant ascites · Ovarian tumors · Histological subtypes

Introduction

The incidence of ovarian cancer in Western countries has remained fairly constant over the past 30 years and has slightly decreased in Germany, with 7250 newly diagnosed patients in 2014 [1]. Approximately, 70–75% of the patients are in stages III and IV at the time of diagnosis,

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with a 5-year overall survival rate of 38% in Germany. Ovarian cancer is thus the most lethal type of gynecological malignancy. Ovarian neoplasms are a heterogeneous group, including epithelial neoplasms, germ cell tumors, sex cord–stromal tumors (SCSTs), mesenchymal tumors, and hematological tumors [1–5].

Epithelial neoplasms are the type of ovarian cancer most often diagnosed, in 90–95% of cases in published studies and in our own group's experience in everyday practice [2, 6]. The updated WHO classification distinguishes in the epithelial group between serous carcinoma, mucinous carcinoma, seromucinous carcinoma, endometrioid carcinoma, clear cell carcinoma, Brenner tumor, and undifferentiated carcinoma [6]. Malignant ascites is assessed as part of tumor staging and is an independent prognostic factor [1, 7, 8].

Malignant ascites accounts for approximately 10–15% of cases of intra-abdominal fluid production and is the second most common cause of ascites after congestive failure [9–11]. Intraperitoneal tumor spread, with the development of malignant ascites followed by gastric, pancreatic, and colon cancer, is observed in 73.5% of patients with ovarian cancer [11, 12]. The progression of ovarian tumors is characterized by diffuse intraperitoneal tumor cell dissemination and this represents an important aspect of tumor staging. Almost 75% of the patients are initially diagnosed at the advanced stages III and IV, which explains the poorer prognosis for patients with ovarian malignancies in comparison with other gynecological tumors [3–5]. The overall mean survival from the time of diagnosis in patients with malignant ascites is approximately 20 weeks, while for patients with ovarian cancer it is 32 weeks [13]. An association between malignant ascites and high-grade serous papillary carcinoma has been reported in a few large series [14, 15]. Cytological tumor cell patterns for other histological entities have mainly been described in small series and case reports [16–26].

The present study is a retrospective analysis from a single center in Bayreuth, Germany, of patients with ovarian tumors who were treated for malignant ascites in accordance with the histological subtypes.

Materials and methods

The histological and ascites specimens for 191 patients with ovarian tumors who were treated at Bayreuth Hospital from 2006 to 2015, with a follow-up period extending up to December 2016, were reevaluated. The carcinoma group included all invasive tumors, but borderline lesions were excluded.

Statistical analysis

A Chi-squared test was used to compare the increase in malignant ascites fluids observed between low-grade and high-grade serous papillary ovarian carcinomas. The difference was found to be significant at $P < 0.05$ [27].

Results

The study included 191 patients with a mean age of 64 years (range 48–79). Most of the patients ($n = 180$, 94.2%) had carcinoma; three (1.6%) had malignant mixed müllerian tumors (MMMTs); and eight (4.2%) had noncarcinomatous tumors. In the carcinoma group, 134 (70.1%) patients had high-grade serous papillary carcinoma, 17 (8.9%) had low-grade serous papillary ovarian cancer, 10 (5.3%) had mucinous carcinoma, nine (4.7%) had endometrioid carcinoma, six (3.1%) had clear cell carcinoma, and four (2.1%) had neuroendocrine tumors. The group with neuroendocrine tumors included two patients with mixed neuroendocrine–nonneuroendocrine (MiNEN) tumors, one patient with small cell carcinoma, and one with a mucinous carcinoid. Four patients (2.1%) had sex cord–stromal tumors (SCSTs), including three Sertoli–Leydig cell tumors and one granulosa cell tumor. The germ cell neoplasms consisted of three (1.6%) teratomas; neoplastic squamous cell carcinoma components were found in two of the three teratomas. Finally, one patient (0.5%) had a leiomyosarcoma. The patients' mean ages relative to the subtypes are shown in Table 1.

Malignant ascites was found most often in patients with high-grade serous papillary ovarian carcinoma (123/134, 91.8%). This is significantly higher in comparison with low-grade serous papillary carcinomas (3/17, 17.7%; $P < 0.00001$). Tumor cells were found in the ascites fluid in five of the 10 patients with mucinous carcinoma (50%), in

Table 1 Mean age in 191 women with ovarian cancer treated in Bayreuth from 2006 to 2015 (years)

Total	
High-grade serous papillary ovarian carcinoma	66
Low-grade serous papillary ovarian carcinoma	60
Mucinous ovarian carcinoma	56
Endometrioid ovarian carcinoma	65
Clear cell ovarian carcinoma	66
Neuroendocrine tumors	66
Malignant müllerian mixed tumors	77
Sex cord–stromal tumors	51
Germ cell tumors	48
Leiomyosarcoma	79

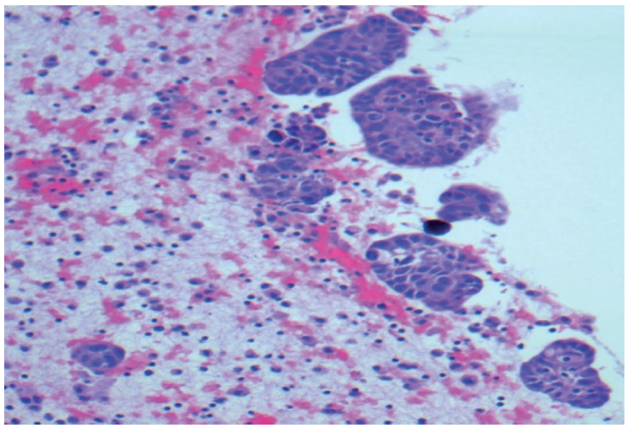

Fig. 1 Ascitic fluid with high-grade serous papillary ovarian carcinoma and psammoma bodies (hematoxylin–eosin cell block, original magnification × 20)

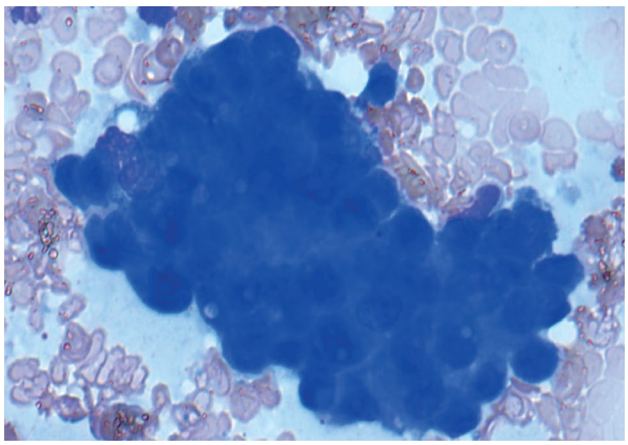

Fig. 2 Ascitic fluid with low-grade serous papillary ovarian cancer (May–Grünwald–Giemsa smear, original magnification × 40)

none of the patients with endometrioid carcinoma, and in one of the six patients with clear cell carcinoma (16.7%). Two of the four patients with neuroendocrine tumors (50%) had malignant ascites, but a glandular tumor cell component was detectable in both patients with MiNEN. Malignant ascites was noted in three of the six patients with germ cell neoplasms (50%), in both patients with teratoma with a neoplastic squamous cell carcinoma component, and in one patient with MMMT. In the SCST group, only the patient with the granulosa cell tumor (1/4, 25%) had tumor cells in the ascitic fluid and the patient with leiomyosarcoma did not have any tumor cells in the ascites.

Malignant ascites was the initial finding compared with histology in all 138 patients. The various histological subtypes are illustrated in Figs. 1, 2, 3, 4, 5, 6, 7 and 8.

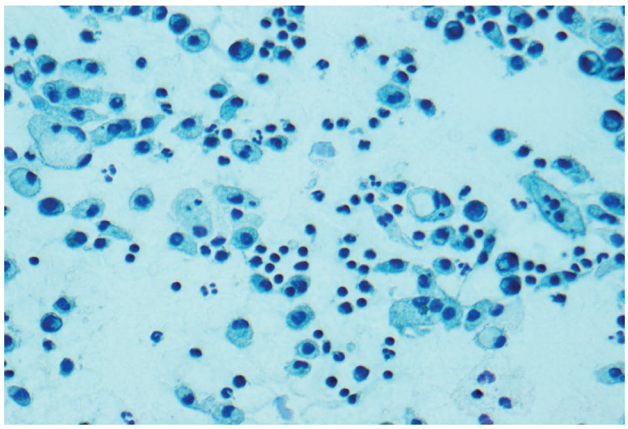

Fig. 3 Ascitic fluid with mucinous ovarian carcinoma (Papanicolaou, original magnification × 20)

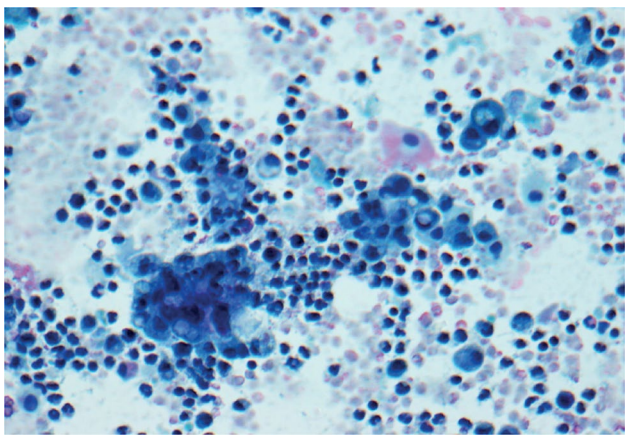

Fig. 4 Ascitic fluid with ovarian clear cell carcinoma (Papanicolaou, original magnification × 10)

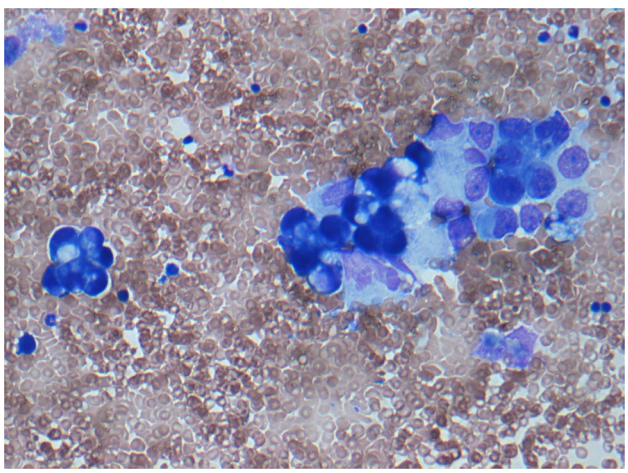

Fig. 5 Bloody ascitic fluid with the glandular component of a mixed neuroendocrine–nonneuroendocrine tumor (May–Grünwald–Giemsa, original magnification × 40)

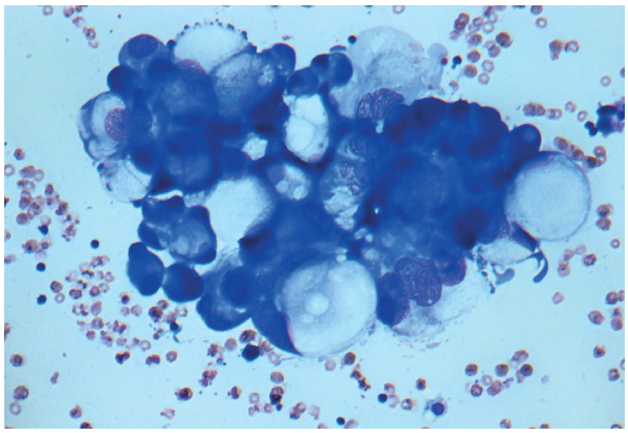

Fig. 6 Ascitic fluid from the glandular component of a malignant müllerian mixed tumor (May–Grünwald–Giemsa, original magnification × 50)

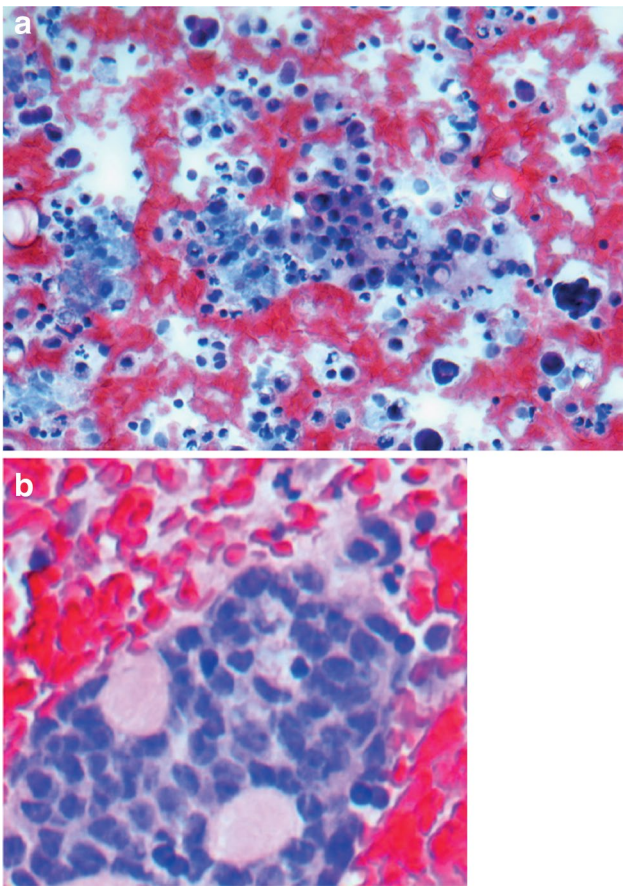

Fig. 7 **a** Bloody ascitic fluid with a malignant granulosa cell tumor (Papanicolaou, original magnification × 20). **b** Bloody ascitic fluid with typical Call–Exner bodies from a granulosa cell tumor (Papanicolaou, original magnification × 60)

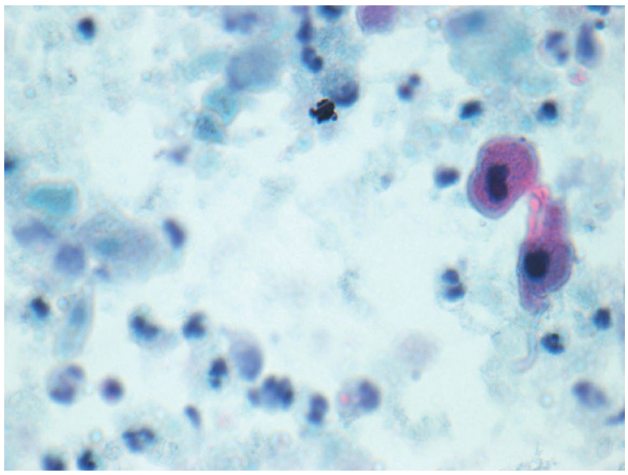

Fig. 8 Ascitic fluid with a malignant squamous cell component from a mature cystic teratoma (May–Grünwald–Giemsa, original magnification × 40)

Discussion

Cytological evidence of tumor cells in the ascitic fluid is the gold standard for diagnosing peritoneal carcinomatosis, in comparison with the physiological examination, radiological techniques, and chemical analysis [28]. The sensitivity of peritoneal cytology ranges from 56 to 97%, with specificity rates of up to 93.61% [29]. Although a serological increase in the protein concentration and lactate dehydrogenase, as well as a low serum–ascites albumin gradient, may be suspicious for a malignant effusion, an infectious or inflammatory cause cannot be excluded [8]. In addition, tumor markers such as cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), and alpha fetoprotein are also lower in comparison with the cytological data [30]. The most common biomarker for diagnosis and treatment monitoring of ovarian cancer, CA-125, is associated with the advanced stages III and IV, and only 56–60% of the patients with early stages are found to have increased levels of the antigen [30]. Unfortunately, benign lesions such as endometriosis, endosalpingiosis, and peritoneal proliferation may also be associated with increased CA-125 levels, so that the findings can be misinterpreted as showing malignancy [28].

Peritoneal washing and ascites puncture are the two methods used to detect tumor cells in the effusions, with minimal risk for patients. Peritoneal washing samples were obtained from all 150 patients who underwent surgical interventions, and ascites puncture was done in the other 41 patients. Independently of the method used, all patients with ovarian neoplasms were found to have tumor cells in the ascitic fluid initially. This remarkably high 100% rate may have been achieved because borderline tumors, which occur in 7–15% of patients or up to 29% in a large study in Norway [31, 32],

were excluded. However, the data emphasize the diagnostic importance of peritoneal washing as a standard examination for patients with ovarian tumors. The method has been included in the International Federation of Gynecology and Obstetrics (FIGO) staging system since 1975 [33, 34].

The surgical management may also benefit from an initial cytological diagnosis of ovarian cancer. In the present series, 112 patients with high-grade serous papillary ovarian cancer underwent surgical resection. In 52 of these patients (46.4%), advanced resection of small-bowel and large-bowel segments was required, and nine patients (8%) underwent a second operation on segments of the colon. It is possible that a small proportion of them may initially have undergone surgery with the indication of colon cancer, so that an accurate primary diagnosis of ovarian cancer in the ascites puncture might help avoid unnecessary resection of colon segments. An initial finding of tumor cells in the ascites fluid is very specific for ovarian malignancies and helps distinguish these patients from those with colon cancer. Only a few cases of the latter were observed, most commonly with cancer originating in the appendix with primary malignant ascites and a low malignancy rate of approximately 7% (unpublished data).

Ovarian neoplasms are the most frequent malignancy identified in ascites fluid [9, 10]. An analysis of 143 malignant ascites effusions in our own department identified ovarian cancer in 56 patients (35.5%), always with carcinomas, followed by pancreatic cancer in 26 (16.5%) and gastric cancer in 25 (15.8%) [11]. The specific biology of ovarian cancer, with primary peritoneal dissemination, in comparison with other types of malignancy, is the reason for this predominance. In ascitic fluid, serous carcinomas as the major histological subtype showed a predominantly papillary pattern, with small areas with a single cell pattern in 132/134 carcinomas, most often with psammoma bodies. Only two of 135 high-grade serous papillary carcinomas showed only diffuse tumor cell spread.

A statistically significant difference in the rate of malignant ascites, at 17.6% for low-grade serous carcinomas and 91.7% for high-grade carcinomas, was observed in the present study—underlining the different biology of the two entities. Histologically, low-grade serous carcinomas are characterized by small atypical nuclei, no increase in mitotic activity, an absence of necrosis and hemorrhage, and at the molecular level by a high frequency of mutations in the *KRAS* and *BRAF* genes and no *TP53* mutations: these represent what is known as type I serous carcinoma, which originates in serous borderline tumors. In contrast, high-grade serous carcinoma or type II carcinoma shows atypical nuclei, increased mitotic count, necrosis and hemorrhage in solid areas, and *TP53* mutations in nearly all tumors; it may originate from a serous carcinoma in situ in the fallopian tube [35, 36]. The cytological findings may, therefore, help verify the histological diagnosis and allow better discrimination between the two entities.

Interestingly, the glandular component of MiNEN tumors was also found in the ascites fluid. Both these cases were reclassified after reevaluation of the tumor cell population in ascites fluid, since the characteristic small cell pattern with nuclear molding of enlarged tumor cells and only sparse cytoplasm was not found. However, only neoplastic papillary proliferations were detected and the histology was, therefore, reevaluated, identifying a small papillary component in approximately 10% of the tumor in both cases—emphasizing the finding that most neuroendocrine neoplasms in the genital tract may be associated with other neoplasms and only rarely occur in a pure form [37]. In a report of two cases of ovarian small cell carcinoma in the ascitic fluid, loose clusters with a predominantly single cell pattern were reported. It may be of importance that the patients were 28 and 30 years old and had hypercalcemia [17]. Similarly, in the present study the patient who only had small cell carcinoma was 44 years old and had hypercalcemia, whereas the two patients with MiNEN were 77 and 79 years old, respectively, possibly representing the pulmonary type of small cell component. This rare neuroendocrine differentiation is a feature of undifferentiation in predominantly younger patients with associated hypercalcemia and may be a germ cell neoplasm or a hereditary condition [38, 39]. Carcinoid tumors may also be associated with germ cell neoplasms [6]. In addition, two cases of gastrointestinal MiNEN tumor with only glandular tumor cell spread to ascitic fluid were observed in the present series with malignant ascites [11].

The second most frequent malignant tumor in ascitic fluid in the present series was mucinous ovarian carcinoma. This carcinoma frequently occurs unilaterally, is often larger than 13 cm with typical gelatinous cysts, originates from borderline lesions, and is diagnosed at FIGO stage I in up to 80.6% of cases [40]. Malignant ascites was found in five of 10 patients (50%) with a glandular intestinal pattern—in four of them with a few foci of papillary tumor cell spread and in one patient only with an incoherent single cell pattern. The mucinous tumor component is more difficult to identify in comparison with histological specimens and this is sometimes difficult to distinguish from gastric and pancreatic cancer due to slightly reduced *PAX2* and *PAX8* reactivity and a lack of *WT1* expression in mucinous ovarian cancer [41–44]. In patients with pseudomyxoma peritonei, mucinous ovarian cancer is the second most frequent cause in 28.57% of cases, after appendix and colorectal cancers [45].

Endometrioid carcinoma was the third most frequent type of cancer found in the present study at 4.7%. This type of carcinoma often occurs unilaterally, without extracapsular spread at the initial diagnosis, and it is associated with a better prognosis, with a 5-year survival rate of 78% in stage I patients. This would be the most probable explanation for

the lack of malignant ascites in the present series, a finding that is in agreement with most of the literature reports. The different histological patterns are better characterized in the uterus, but there may be evidence that a microcystic, elongated, and fragmented cell pattern in combination with clear cell features is associated with a poorer prognosis in ovarian tumors as well, and that there is an association with Lynch syndrome if mismatch repair proteins are lost [46, 47]. In contrast, a report of a series in Scotland described ovarian endometrioid carcinoma in 29% of cases, with ascites formation in 47% (122/270) of these patients [48]. On the other hand, endometrioid cancer of the uterus was found in the ascitic fluid in 1% of our own series, a rate that has also been reported by others [11, 49].

Ovarian clear cell carcinoma occurred in 3.1% of the patients in the present series and is characterized by glycogen-rich cytoplasm in the tumor cells. Like endometrioid cancer, these tumors most often grow unilaterally, are associated with endometriosis, and show mutations in *ARID1A* and *PIK3CA* as well *PTEN* deletions at the molecular level [50]. The poorer prognosis in comparison with endometrioid cancer is due to resistance to platinum-based chemotherapy in the advanced stages of the tumor [50]. The single patient with malignant ascites in the present study had papillary tumor cell clusters, only slight clear cell cytoplasm, and moderate nuclear atypia [25, 51]. The clear cell morphology can be highlighted by napsin A or hepatocyte nuclear factor-1β (HNF-1β) immunostaining as in renal cell cancer and extracellular hyaline material has also been described in the literature as characteristic of clear cell ovarian carcinoma [52–54].

MMMT and carcinosarcoma of the ovary occur in 1–4% of patients, with clinical symptoms similar to those of patients with epithelial neoplasms, but the prognosis is inferior in comparison with the large group of serous malignancies [55, 56]. These tumors contain both a malignant epithelial and a mesenchymal component, which can also be identified in ascitic fluid by an increased Ki-67 proliferation rate and matrix metalloproteinase-7 expression in the epithelial cells in comparison with mesenchymal tumor cells [21]. The present study only included one patient with malignant ascitic fluid with a predominantly undifferentiated epithelial component. Unfortunately, a cell block for better characterization of the different tumor cell components was not available.

The small group of nonepithelial ovarian tumors in the present series included a 2.1% rate of SCST tumors, consisting of three patients with Sertoli–Leydig cell tumors and only one patient with granulosa cell tumor, which was the only sex cord–stromal tumor with malignant ascites effusion. Larger series have reported a rate of approximately 1.2% for sex cord–stromal tumors, with granulosa cell tumors predominating in 90% of cases, best characterized clinically and cytologically by *FOXL2* mutations at the molecular level [26, 57, 58]. In agreement with the literature findings, the patient in the present study had naked nuclei, Call–Exner bodies, and metachromatic stroma [26]. The patient with a malignant granulosa cell tumor was followed up for a 9-year period, with three recurrences after 3, 6, and 8 years, and tumor cells were always detected in the ascitic fluid. These follow-up data confirm that the lesion's biological behavior is that of a low-grade malignant tumor [58]. Only one case report has described the occurrence of a Sertoli–Leydig cell tumor in ascitic fluid [16].

Mature cystic teratoma (MCT) was the only germ cell neoplasm noted among the ovarian tumors, occurring in three patients in this study (1.6%). This finding is in agreement with larger series, which have reported a wide age distribution of these lesions between 2 and 80 years and preferential occurrence in patients of reproductive age, with only 5% of the tumors occurring in postmenopausal women [6, 59, 60]. Malignant transformation may develop in 1–2% of cases, more often in patients over 45 years of age with tumors more than 10 cm in diameter, and most commonly with squamous cell carcinoma developing in 80% of cases [61]. Both the patients with MCT with transformation to squamous cell carcinoma in this study had malignant ascites, with a typical single cell pattern of polymorphous tumor cells with dyskeratinization. This is remarkable in comparison with the low rate of malignant effusions in primary squamous cell carcinomas from different sites of origin [11]. The development of adenocarcinoma and melanoma in ascitic fluid has also been reported with MCTs [23]. Other germ cell neoplasms such as dysgerminoma, yolk sac tumor, mixed germ cell tumor, and embryonal carcinoma only occur rarely in younger women and also produce malignant ascites fluid, as has been described in case reports [18, 22].

Overall, the rate of nonepithelial ovarian tumors in this single-center study was only 4.2%, so that more detailed analysis of these is not possible. The series also included one patient with leiomyosarcoma without malignant ascites. One case report has described an angiosarcoma in a patient with ascites and increased numbers of Burkitt lymphomas with peritoneal spread and ascites formation have been reported in patients with ovarian tumors in Africa [20, 62, 63].

The major conclusion of the present study is thus the observation that there is a significantly higher frequency of malignant ascites in patients with high-grade serous papillary ovarian cancer, in comparison with patients with low-grade carcinoma. This is of diagnostic importance, since the malignant ascites is an initial finding in these patients. Furthermore, a primary cytological analysis of ascitic fluid allows a better discrimination from gastrointestinal neoplasms, especially from appendix carcinomas, which often shows a peritoneal spread. The evidence of tumor cells in the

ascitic fluid may indicate additional intraperitoneal chemotherapy and is important for follow-up and prognosis.

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Author contributions JK project development, data collection, data analysis, manuscript writing; CLS data collection, data analysis; BM data collection, manuscript writing; WS data analysis, manuscript editing; AO data collection; JL project development, manuscript editing; AA project development, manuscript editing; MV project development, manuscript editing.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

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