Gynecological Neoplasms are the Major Cause for Malignant Effusions

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Research

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Abstract

Background: Malignant effusions occur frequently in gynecologic neoplasms and may worsen the prognosis for these patients. Therefore a more detailed analysis for the different cavities is necessary to describe the association between the various histological subtypes and the time related occurrence of malignant effusions in gynecological malignancies.

Methods: Malignant effusion specimens from patients diagnosed at Bayreuth Hospital from June 2013 to December 2018 were reevaluated retrospectively and correlated with the histolgogical subtype of primary tumors and with the clinical follow-up.

Results: 435 patients with malignant effusions were analyzed, including 273 women and 162 men. 54.2% of patients developed malignant effusions in the pleural space in (54.2%) patients, in the peritoneum in (43.9%) patients and in the pericardium in (1.9%). Gynecological malignancies appear most common in (n=147, 34.0%; mean age 67.3 years) patients with predominant occurrence of ovarian carcinoma in malignant abdominal cytology in 75/191 (39.3%) patients, mostly of high-grade serous papillary subtype in 72/75 (96.1%), and only breast cancer in malignant pleural effusions in 49/236 (20.7%), frequently of 39/49 (79.6%) invasive carcinomas of no specific type.

Both involvement of pleural- and peritoneal cavity in 244 female patients with gynecological-, lung- and gastrointestinal neoplasms we obtained in 37 (15.2%) patients, most common in 31/37 (83.78%) gynecological tumors and exclusively of high-grade serous papillary subtype. Malignant ascites occured in patients with lower genital tract tumors in 81/86 (94.2%) within one year after primary diagnosis, whereas breast cancer involves the peritoneum in 2/10 (20%) and the pleural cavity in 11/49 (22.4%) after 12 months.

Conclusions: Gynecological neoplasms were the major cause of malignant effusions in our study. The high-grade serous papillary subtype of lower tract gynecological is most aggressive with predominant occurrence in the peritoneum and exclusive secondary involvement of the pleural cavity. Therefore, an alone/exclusive/sole involvement of the pleural cavity characterize the invasive breast carcinoma of no special type compared to predominant occurrence of the lobular subtype in malignant ascites. Breast cancer showed a statistical significant late occurrence in effusion fluids 12 months after primary diagnosis in contrast to early involvement in gynecological- as well as pulmonary- or gastrointestinal malignancies.

Background

Distant metastatic spread to pleural-, pericardial-, and peritoneal cavities may often occur early in tumor patients, which is important for staging and further oncological treatment [1–7].

In a large United States series of 126.825 hospital admissions for malignant pleural effusions an overbalance of 55.8% female patients is reported and the primary tumors were located in the lung

(37.8%), the breast (15.2%), the hematopoetic system (11.2%), the gastrointestinal (GI) tract (11%) and gynecological (9%), whereas, primary mesothelial neoplasms were observed in approximately 3% [1]. A similar tumor distribution is described for the pericardial cavity [3, 4]. Malignant ascites correlates with diffuse intraperitoneal dissemination of tumor cells, which characterize ovarian cancer and GI neoplasms like gastric, pancreatic, and colon cancer [5–12].

The occurrence of malignant effusions complicates the clinical follow-up and worsens the prognosis for the tumor patients. In contrast to lung cancer, breast cancer is characterized by a late metastatic pattern in malignant pleural effusions, particularly in the main groups of hormone receptor–positive or HER2-receptor–positive patients [13]. The mean period between diagnosis of a primary tumor and the development of malignant pleural effusion has been reported as 41.5 months, with a mean survival time after malignant effusion of 15.7 months [14]. The mean survival time for patients with malignant ascites is less than 20 weeks, and for those with ovarian tumors is 32 weeks [15].

Cytological examination has become the gold standard for detecting tumor cells in effusion fluids in comparison to serological analysis. Ancillary immunostains using the cell block technique may allow a better discrimination between epithelial cells and mesothelial proliferations and helps to detect the phenotype of the tumor cells [16, 17].

The present large retrospective single center study, including 435 patients, provides an overview of the distribution pattern for malignant tumors in the different cavities with special emphasis on gynecological neoplasms. We suppose that a more detailed analysis of the histological subtypes of gynecological cancer may better characterize the heterogenous metastatic potential of these tumors and in addition we described the time related occurrence of malignant effusions.

Methods

In a retrospective analysis of the period from June 2013 to December 2018, cytological findings for malignant effusion were reevaluated at the Institute of Pathology in Bayreuth Hospital. We were focussed to find correlations between the occurrence of malignant effusions to the different histological subtypes of gynecological malignancies in this collective. Histological probes had been analyzed using Hematotoxylin-Eosin stain and in addition we characterised receptor- and Her2- status of breast cancer patients (Table 1). The results we compared with pulmonary and gastrointestinal neoplasms. For a better overview we summarized a group of other epithelial tumors, which mainly includes urological malignancies and a group of nonepithelial tumors comprising malignant lymphomas, malignant melanomas, malignant mesotheliomas and sarcomas. We correlated our cytological data with previously histological and cytological reports and described a simultane occurrence of malignant effusion from different cavities, if we received the probes within one months. Effusion fluids from the peritoneal cavity includes intraoperative lavage probes in 32 female patients with ovarian carcinoma and 6 with endometrium carcinoma. The specimens had been routinely examined using May–Grünwald–Giemsa

and Papanicolaou staining. Additional immunostaining were carried out using the cell block technique (Table 1).

Table 1
Antibodies used in this study (HIER = Heat-Induced Epitope Retrieval, PIER = Proteolytic-Induced Epitope Retrieval)

Antibody	Clone	Source	Pretreatment	Dilution
Her2neu	CB11	Leica	HIER	Ready to use
ER	6F11	Leica	HIER	1:100
PR	16	Leica	HIER	Ready to use
Ki67	MM1	Leica	HIER	Ready to use
Pax8	Polyclon	Zytomed	HIER	1:25
CDX2	EPR267uy	Zytomed	HIER	Ready to use
TTF1	BG7G3/1	Zytomed	HIER	Ready to use
CK7	RN7	Leica	HIER	Ready to use
Calretinin	CAL6	Leica	HIER	Ready to use
Epithelial Antigen	Ber-EP4	Dako	PIER	1:100

Approval for the retrospective analysis of malignant ascites was received from the Ethics Committee at Friedrich Alexander University, Erlangen (no. 267_19 Bc).

To examine the relationship between occurence of NST (invasive carcinoma of no special type) or lobular breast cancer and pleura(l) effusion or malignant ascites as well as the time related occurence of malignant effusions, odds ratios (OR) were calculated and Fisher‘s exact test was performed. The significance level was set to 0.05. All statistical analysis was performed using the statistical programming language R V3.6.3 [18].

Results

We analyzed cytology specimens of malignant effusions from 435 patients (mean age 68.5 years, range 37–91). In all of 273, the patients were women (62.8%; mean age 68.5 years, range 37–90) and 162 were men (37.2%; mean age 69.4 years, range 38–91). They occurred most frequently in the pleural cavity in 236/435 patients (54.2%, mean age 68.5), in the peritoneal cavity in 191/435 patients (43.9%, mean age 67.7) and in the pericardial cavity in 8/435 patients (1.9%, mean age 61.2). The female predominance is shown always in malignant pleural effusions with 56.4%, in malignant pericardial effusions with 62.5% and especially in malignant abdominal cytology with 70.7 % (Fig. 1).

Gynecological malignancies appears most common in 147/435 (34.0%; mean age 67.3 years) patients, lung cancer in 118/435 (27.1%, mean age 70.6 years) patients, gastrointestinal tumors in 112/435 (25.7%, mean 65.8 years) patients, other epithelial malignancies in 25/435 (5.7%, mean age 70.0 years) patients and nonepithelial tumors in 33/435 (7.5%, mean age 71.2) patients (Fig. 2). Immunohistochemically 59/60 patients patients with breast cancer were characterized for hormone receptor- and Her2 status. We obtained in 49/59 patients a positive receptor- and negative Her2 status, in 6/59 patients both receptor and Her2 positivity, in 2/59 patients hormone receptor negativity combined with Her2 expression and tripple negativity in 2/59 patients.

96/147 (65.3%) of the gynecological tumors exhibit malignant abdominal cytology, 49/147 (33.3%) malignant pleural effusion and 2/147 (1.4%) pericardial effusion. The 96 female patients with malignant abdominal cytology encompass 75 (78.9%) ovarian carcinomas, 1 (1.1%) tubal carcinoma, 10 (10.5%) breast cancers and always 10 (10.5%) patients with endometrium cancer. High-grade serous papillary subtype occurs in 72 patients, mucinous carcinoma in 2 patients and malignant mixed Müllerian tumor (MMMT) in 1 patient with ovarian cancer (Fig. 3). The tubal carcinoma expose high-grade serous papillary subtype. The lobular carcinoma of breast cancer we obtained in 8 patients and the invasive carcinoma of no special type (NST) in 2 patients (Fig. 4). Endometrium cancer encompass each 5 patients with high-grade serous papillary subtype and MMMT. Combined with 83 GI tumors we diagnosed in 179 /196 (93;2%) of or patients with malignant ascites these main tumor types. Alltogether we analyzed 25 patients with other epithelial tumors like gynecologic, pulmonary and gastrointestinal malignancies and 33 nonepithelial tumors as shown in Fig. 5.

25/75 (33%) patients with ovarian carcinoma showed an additional malignant pleural effusion, simultaneously in 17 patients and after a mean time of 25.8 months in 8 patients. Both 1/1 (100%) patient with tubal carcinoma and 1/10 (10%) patient with endometrium cancer expose simultaneously a malignant pleura effusion. All of these 27 patients were of the high-grade serous papillary subtype and in cause of this clinico-cytological correlation we could exclude an alone pleural involvement from tumors of the lower genital tract. The overall rate of secondary pleural involvement from lower genital tract tumors amounts 27/86 (31.4%) and is higher compared to 2/33 (6.1%) for female patients with GI tumors.

From the 49 breast patients with malignant pleural effusion were 39 (79.6%) of NST subtype (Fig. 6), 6 (12.2%) a lobular carcinomas, 1 (2.04%) a neuroendocrine carcinoma, 1 (2.0 %) inflammatory carcinoma, 1 (2.0 %) an oncocytic carcinoma and 1 an (2.0 %) phylloides tumor. As shown in Fig. 7 lung cancer occurs most common in malignant pleura effusion, however if we compared only female patients we detected a slight overbalance of breast cancer in 49 patients compared to 48 patients with lung cancer. The two female patients with malignant pericardial effusion showed always in one patients the NST subtype of breast cancer and cervical cancer, whereas the remaing 6 patients had lung cancer. Fisher‘s exact test showed a statistically significant increase of malignant pleura effusion compared to malignant ascites for the NST subtype of breast cancer ($P < 0.001$; OR = 17.33; 95%-CI: 3.567–84.235).

Breast cancer exhibit in malignant pleura effusions in 11/49 (22.4%) female patients within 12 months after primary diagnosis compared to 39/48 (81.2%) of female lung cancer patients and in 15/17 (88.2%) female patients with GI tumors (Fig. 8). In malignant abdominal cytology we detected breast cancer in 2/10 (20%) patients within 12 months, ovarian carcinoma in 74/75 (98.7%), tubal carcinoma in 1/1 (100%), endometrium cancer in 6/10 (60%) and GI tumors in 32/33 (97%, Fig. 9). Fisher‘s exact test showed that a late occurrence of breast cancer compared to other gynecological malignancies was statistically significant ($P < 0.001$) with a very high odds ratio (OR = 68.18; 95%-CI: 21.29-219.27).

Discussion

Gynecological cancers occurs most frequently in 34% of our patients with malignant effusions including lavage probes for ovarian tumors. These findings becomes importance, because they results from a single center, which exclude an unproportional influence of any clinical section on the tumor distribution in comparison to various other studies [2, 3, 4, 7, 8, 11, 15, 19–23]. Further leads the predominance of gynecological tumors to an overbalance of female patients in malignant effusions and required both from clinical as well as from immunohistochemical viewpoint a sex specific data analysis [1].

Most (65.3%) of all gynecologic malignancies we diagnosed in the peritoneal cavity and in 71.1% of female patients with malignant abdominal cytology we observed gynecological neoplasms. It is widely accepted in the literature that ovarian carcinoma is the prototype of dissiminated peritoneal spread in malignant ascites [5, 6, 12, 24–27]. In our previous studies on ovarian cancer we described the highest malignancy rate, at 85.7%, the earliest occurrence, and a predominance of the high-grade papillary subtype in patients with malignant abdominal cytology [10]. The correlation between malignant abdominal cytology and high-grade serous papillary subtype we could extent in the present study on endometrium carcinomas. These findings underline the discrimination between non aggressive type 1 endometrium cancer with lacking occurrence of malignant ascites in our study from aggressive type 2 endometrium cancer with appearance of malignant ascites in high-grade serous papillary subtype and also MMMT [28, 29]. Moreover, we obtained in tumors from the lower genital tract the highest rate of 31.4% for secondary pleural involvement compared to 6.1% for female patients with GI tumors. Therefore is the knowledge of previous findings for all patients necessary, which exclude in our study an alone pleural involvement for ovarian carcinomas. These finding is remarkable because ovarian carcinoma achieves in various other studies the third or fourths most common epithelial tumor of malignant pleura effusions [12, 24, 25]. Further it may affect the dayly diagnostic practice, because in both involvement of peritoneal and pleural involvement a gynecological malignancy is more probably, whereas GI tumors showed a predominant peritoneal or an infrequently pleural involvement. The exclusive involvement of peritoneal and pleural cavity by high-grade serous papillary subtype highlights the aggressive potential of this subtype and should be noted at initial diagnosis for continous follow-up controls.

Malignant ascites from gynecological tumors include in 10.5% patients with breast cancer, which showed a lobular subtype in 80% with a characteristic diffuse pattern in effusion fluids and is in agreemet with literature data [30, 31]. In contrast to other gynecolocigal and gi malignancies appears malignant ascites in breast cancer patients only in 20% within 12 months, compared to 60% in endometrium cancer, 98.7% in ovarian carcinoma and 97% in female patients with gastrointestinal tumors. These late metastatic potential in patients with breast cancer should be correlated with a positive receptor state for this patients, which we also obtained in 90% of our patients [13, 32–35].

Second most frequent gynecological neoplasms were found in 33.3 % of malignant pleura effusions after patients with lung cancer [12, 14]. As mentioned above reduced our cytological clinical correlation the occurrence of malignant pleura effusions in patients with gynecological neoplasms to breast cancer and if we compared only female patients we received a slight overbalance of 49 patients with breast cancer to 48 patients with lung cancer. In contrast to malignant ascites the most often occurring subtype of NST carcinomas predominates in malignant pleura effusion. Similar to malignant ascites they obtained only in 22.4% of the patients within 12 months after primary diagnosis compared to 81.2% for female lung cancer patients and 88.2% in female patients with GI tumors [33, 35]. These time associated occurrence of breast cancer in malignant pleural effusion may help at first in dayly diagnostic practice to discriminate lung from breast carcinoma and could further prove by immunostains.

Only 1.4% of the malignant effusions we could detect in the pericardium with female predominance and similar tumor distribution as in the pleural cavity, which is in agreement with literature data [12, 36, 37, 38]. Also similar clinical symptoms, such as dyspnea, cough and chest pain characterize patients both with pleural and pericardial effusions [19, 37]. Patients with malignant pericardial effusion were 7.3 years younger than patients with malignant pleura effusions and the effusion fluid is extremely bloody because of cavitary and intralymphatic tumor spread [4]. We diagnosed only 1 patient with breast cancer and 1 patient with cervix carcinoma and both patients showed an involvement of the pericardium within 12 months. These major findings correlated with literature data, however, the number of patients is low [12, 37, 38].

Hematological neoplasms were the most common nonepithelial tumor in malignant effusions in our study, occuring in 3.4% of the patients with female predominance in 66.6%. In agreement with the findings in the literature 80% of them were located in the pleura and 20% in the peritoneum [39–41]. Immunohistochemically, B-cell lymphomas were represented in 86.7% and high grade subtype in 66.6% of the patients. The cytological impact of these findings is the diffuse tumor cell pattern for malignant lymphomas in differential diagnosis to lobular breast carcinoma and all other diffuse enddifferentiated carcinomas, which require applications of further immonstains.

Strengths of the present study are the large number of patients included. Limitation of the study is its retrospective single center design and the fact that the effusion fluids from the peritoneal cavity includes intraoperative lavage probes.

Conclusion

Malignant effusion fluid is a pattern of distant tumor metastasis and therefore becomes important for cancer staging. This retrospective study shows a topographical association between lung and breast cancers with pleural and pericardial effusions, and between ovarian and gastrointestinal cancers with malignant intraabdominal cytology. Gynecological malignancies were the main cause of malignant effusions in this study with predominant presence of ovarian carcinoma in malignant intraabdominal cytology and breast cancer in malignant pleural effusion. High-grade serous papillary carcinomas were the most aggressive subtype in d appears exclusively subsequent in malignant pleura effusions. An alone occurrence of breast cancer we obtained in malignant pleural effusions. NST subtype of breast cancer predominantly involved pleural cavity while the lobular subtype was found most commonly in the peritoneal cavity. Both in malignant pleural effusions and malignant abdominal cytology we diagnosed lower gynecological tumors, lung and gastrointestinal cancer most frequently within 12 months after primary diagnosis, whereas only breast cancer metastasis later.

List Of Abbrevations

GI gastrointestinal

HER2 human epidermal growth factor receptor 2

NST invasive carcinoma of no special type

MMMT malignant mixed Müllerian tumor

OR odds ratios

PAP Papanicolaou

Declarations

Ethics approval and consent to participate

Approval for the retrospective analysis of malignant ascites was received from the Ethics Committee at Friedrich Alexander University, Erlangen (no. 267_19 Bc).

Consent for publication

not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JK: project development, data collection, data analysis, manuscript writing; CLS: data collection, data analysis; WS: data analysis, manuscript editing; SN: data collection, data analysis; AO: data collection, data analysis; CS: data collection, data analysis; WA: statistical analysis; MV: project development, manuscript editing; JL: project development, manuscript editing.

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Figures

Fig. 1

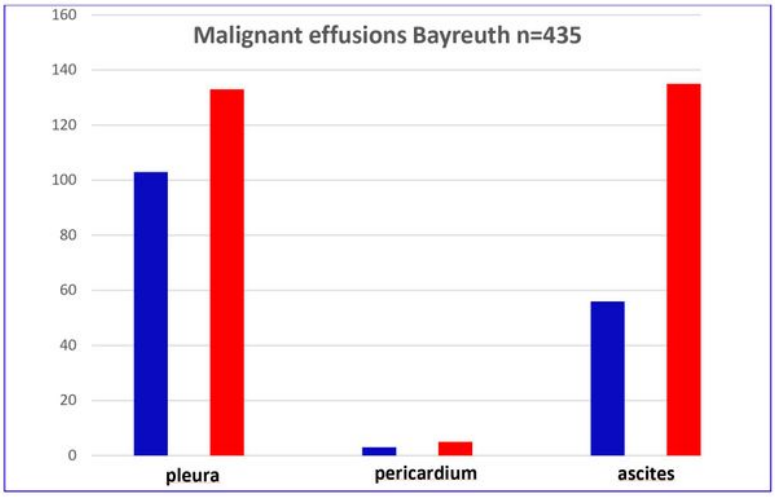

Figure 1

Gender distribution of malignant effusions in Bayreuth Hospital (blue=male, red=female)

Fig. 2

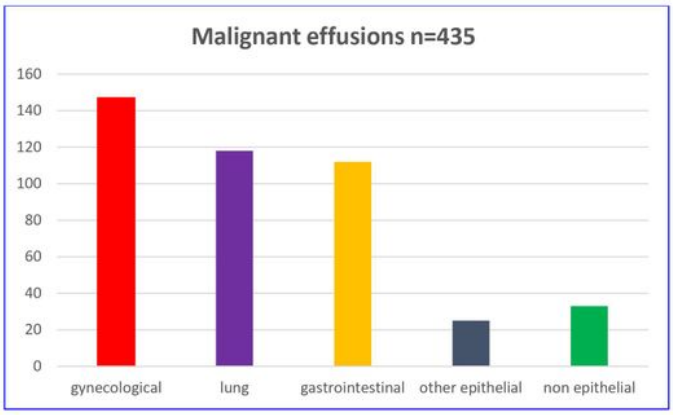

Figure 2

Tumor origin of malignant effusions in Bayreuth Hospital

Fig. 3

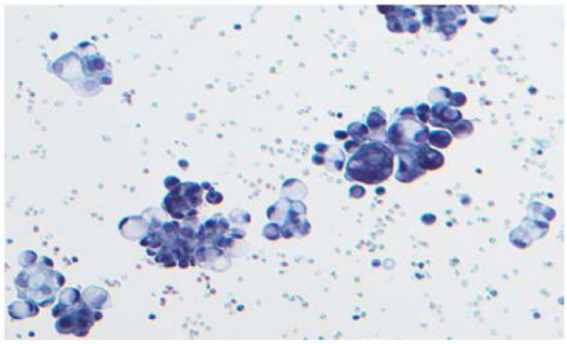

Figure 3

Neoplastic papillary proliferation of a high grade serous papillary ovarian carcinoma in ascitic fluid, PAP 20x

Fig 4

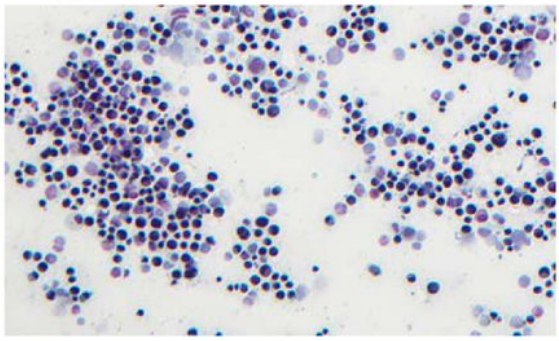

Figure 4

Neoplastic diffuse proliferation of lobular breast carcinoma in ascitic fluid, PAP 20x

Fig. 5

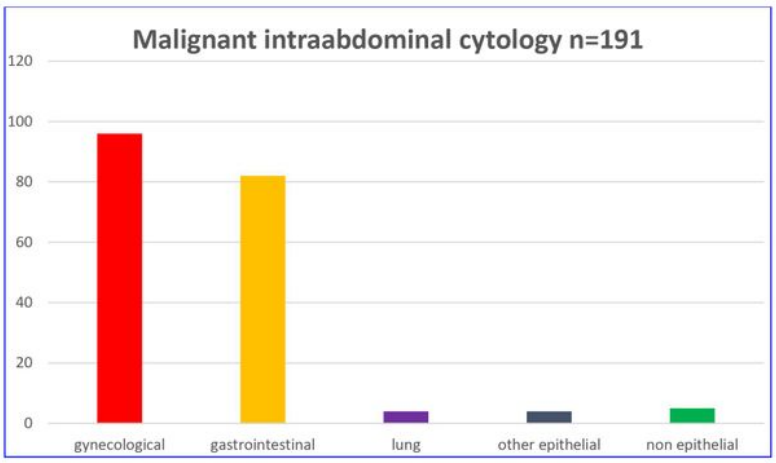

Figure 5

Tumor origin of malignant intraabdominal fluid in Bayreuth Hospital

Fig. 6

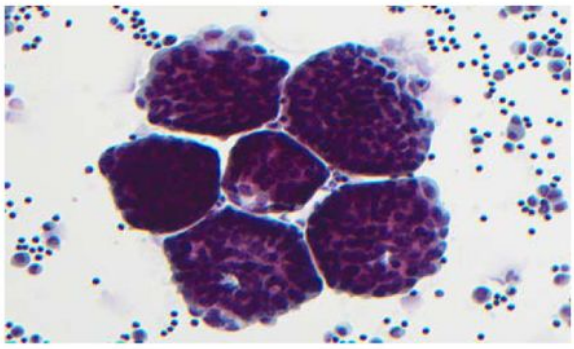

Figure 6

Neoplastic balloon like proliferation of NST breast cancer in pleural fluid, PAP 40x

Fig. 7

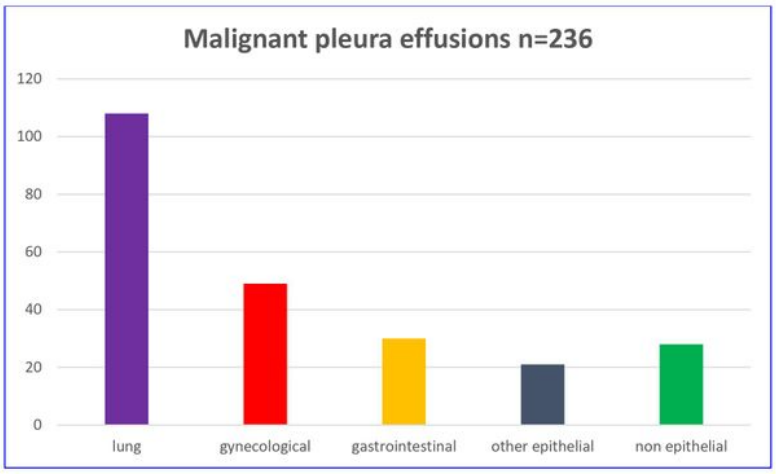

Figure 7

Tumor origin of malignant pleural effusions in Bayreuth hospital

Fig. 8

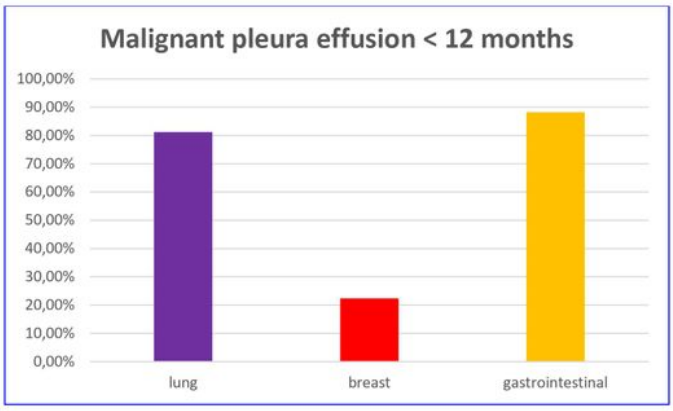

Figure 8

Time related occurrence of malignant pleural effusions in Bayreuth Hospital

Fig. 9

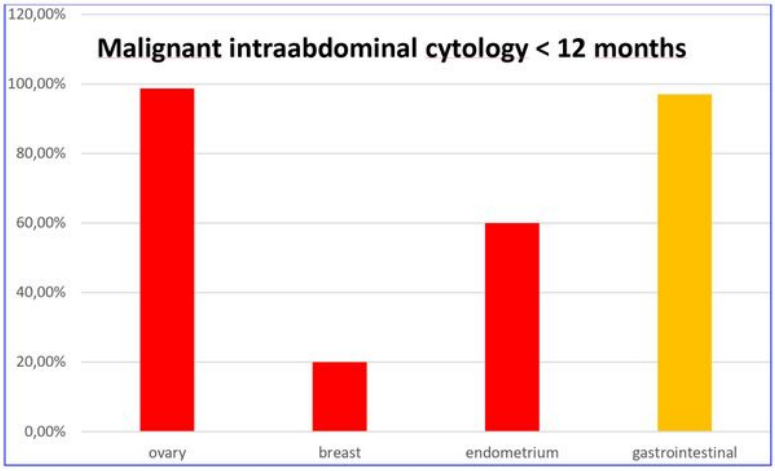

Figure 9

Time related occurrence of malignant abdominal cytology in Bayreuth Hospital