Chapter 4

Ascitic Fluid in Ovarian Carcinoma – From Pathophysiology to the Treatment

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Abstract

Due to low symptomatology, a lack of screening, and relatively complicated diagnostic procedures of ovarian carcinoma, more and more women are believed to visit their doctors in advanced stage of the disease, complicated with ascitic fluid. There is an increasing evidence that peritoneal cytology is a subjective assessment with certain percentage of false-positive and false-negative results that may cause application of unnecessary chemotherapy or nonapplication of necessary chemotherapy. Maximal cytoreductive surgery followed by intraperitoneal or systemic chemotherapy remains to be the gold standard in preventing ascites. Ascites is not only a symptom of a disease, but a specific microenvironment for formation and mediation of protumorigenic signals that control ovarian cancer progression, proliferation, invasion, anti-apoptosis, chemoresistance and tumor heterogeneity. Acellular cytokines and immunological factors influence ovarian cancer progression and its ability to prevent immune responses of the body and tumor reaction to chemotherapy. Ascites contributes to disease dissemination, changing its course and final outcomes. Management of patients with ascites and ovarian carcinoma is complex and often the goal of the treatment is to target palliative procedures. Multidisciplinary approach is necessary in the management of these patients. Further investigations of new drugs and immunomodulators are needed aiming at prolonged periods between relapses.

Keywords: ovarian carcinoma, ascitic fluid, treatment, cytological findings, immunohistochemical markers

1. Introduction

Ascitic fluid is the presence of large volumes of fluid accumulated in the abdominal cavity. Normally, several liters of peritoneal fluid are produced and it is not accumulated, but

effectively absorbed. This fluid continuously circulates in a clockwise direction helping in the lubrication of intestines.

Malignant ascites accounts for about 10% of all cases of ascites [1]. Causes of nonmalignant ascites are: liver diseases (cirrhosis), congestive heart failure, and occlusion of the inferior vena cava or the hepatic vein occlusion, as well as benign tumors of the genital tract (ovarian fibromas). Malignant ascites are most commonly found with gynecological neoplasms (primarily ovarian and endometrial cancer), gastrointestinal malignancies, and breast cancer. In 15–30% of cases, the ascites is associated with carcinomatosis of the endometrium [2].

According to traditional classification, ascites is divided into exudative and transudative types. Ninety percent of ascitic fluids are transudates resulting from nonmalignant conditions, such as congestive heart failure or liver cirrhosis. Physical characteristics include clear appearance of the fluid with the presence of few cells (acellular) and low albumin level. On the other hand, exudates are most commonly malignant (ovarian carcinoma), with usually cloudy appearance of fluid, increased cellular count, and higher albumin level in comparison to transudates [3].

A new term used to assist in determining such a classification is the serum-ascites albumin gradient (SAAG).

This gradient is defined like the difference between albumin concentration of serum and ascitic fluid. If the gradient is >1.1, it indicates transudates due to portal hypertension, cirrhosis, hepatic congestion, portal vein thrombosis, etc. If SAAG <1.1, it indicates exudates not related to portal hypertension, but mostly malignant etiology (ovarian carcinoma), peritoneal carcinomatosis, chronic peritoneal infection, nephrotic syndrome, or hypoalbuminemia [4].

Besides protein concentrations, ascitic fluid may additionally be analyzed by macroscopic and microscopic testing.

Macroscopic testing means the analysis of appearance and color of ascites. Cloudy physical characteristics indicate the presence of leukocytes, infection, or malignancy. Yellow color is more common in liver diseases, greenish results from the bile, and reddish color may indicate the presence of hemorrhage.

Chemical tests, in addition to albumin concentration, include glucose level concentration (lower with infection), amylase (increased with pancreatitis), and lactate dehydrogenase (increased in carcinomas). If an infection is suspected, Gram stain analyses may be performed, as well as bacterial culture testing, viral testing, and microbacterial testing (tuberculosis).

Microscopic examination is performed if infectious or malignant ascites is suspected. Total cell count or leukocyte counting and differentiation are performed to determine infectious etiology more precisely. If malignant etiology is suspected, the most important thing is to determine the presence or absence of the cells with atypical morphological characteristics or malignant cells.

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2. Pathophysiology

The pathophysiology of malignant ascites is multifactorial and is related to a combination of two basic pathogenic mechanism, increased vascular permeability and obstructed lymphatic drainage.

Five microscopic barriers prevent movement of proteins away from vascular space: capillary endothelium, capillary basement membrane, interstitial stroma, mesothelial basement membrane, and mesothelial cells. In 1922, Putnam described the peritoneal membrane as a living, dynamic membrane through which the electrolytes pass between the peritoneum and serum. The movement of colloid solutions from serum is not clear enough and presents the relative impermeability through intercellular spaces based on Starling's law of osmotic gradient. The exchange of fluid between the plasma and interstitium is based on the hydraulic and osmotic pressure. Oncotic pressure is based on fluid reabsorption from the interstitial space and edema prevention. Macromolecules, proteins and cells that accumulate in the peritoneal cavity may return to the systemic circulation by means of peritoneal lymphatic system and lymphatic stomata to lymphatics that lead to the diaphragm and the thoracic duct [5].

In 1953, Holm and Nielson demonstrated the importance of lymphatic obstruction in pathogenesis of malignant ascites. The basic characteristics of malignant ascites include increased ascitic fluid protein concentration, increase of lactate dehydrogenase, large number of leukocytes, and positive cytology regarding the presence of malignant cells. High protein concentration in the peritoneal cavity results from vascular permeability due to increased vascular endothelial growth factor (VEGF) levels. The concentration of VEGF is significantly higher in malignant ascites than in nonmalignant ascites (cirrhosis). Splanchnic hyperemia and tumor necrosis factor dominate in nonmalignant ascites.

The complete pathogenic mechanism of malignant ascites is still not well understood. The events that are definitely happening and that we are familiar with include an increase of net filtration and accumulation of ascitic fluid resulting from increased capillary permeability, increased surface area for filtration, increased hydraulic pressure difference, and decreased oncotic pressure difference [6].

A two-way permeability of blood vessels is necessary for tissue normal supply with nutrients, gases, minor proteins, and waste removal. It can be basal, acute vascular (a consequence of short exposure to VEGF) and chronic, characteristic of pathological (malignant) angiogenesis.

Apart from the most important aforementioned VEGF that stimulates vascular permeability, other factors responsible for stimulation include basic fibroblast growth factor (bFGF), angiogenin, transforming growth factors (TGF α and β), and interleukin-8. All these factors lead to neovascularization and angiogenesis, starting with endothelium stimulation and resulting in hyperpermeability and degradation of endothelial membrane, followed by migration and proliferation of endothelial cells and the development of new capillaries. VEGF has been identified in ovary tumor cells, with its overexpression reported in ovarian carcinoma.

Neoangiogenesis and an increase of peritoneal blood vessels in size and number result not only in increased permeability but also in increased overall surface area for filtration. The next pathogenic mechanism of malignant ascites is increased hydrostatic pressure difference as a result of minor elevation of portal venous pressure in patients with ovarian cancer (portal veins compression by tumor mass and metastases). On the other hand, the oncotic pressure difference is reduced since the albumins that are responsible for osmotic intravascular pressure (reabsorbs fluid from the interstitial space) degrade into smaller peptides or amino acids (increased production of metalloproteinase).

Of all of these pathogenic mechanisms, it can be concluded that the main cause of ascites is not tumor, but peritoneal surface by indirect action of cytokine mediators (VEGF, etc.).

3. Clinical manifestation and ascites as a prognostic factor

Ascites is the most common symptom in patients with ovarian carcinoma and the reason for visiting a doctor. In 54% of patients with peritoneal carcinomatosis, ascites was the first detectable sign of malignancy [7].

Unfortunately, the presence of ascites most commonly reveals an advanced stage of the disease, since ascites are produced in only 7% in I and II stages of the disease and in 89% in stages III and IV. The amount of ascetic fluid is in correlation with the stage of the disease, for stages I and II its presence is < 0.5 L, but in more than 66% of cases with stages III and IV its presence is > 0.5 L.

More than 2/3 of patients report to their doctors in stages III and IV that when ascites increased abdominal size and abdominal distension, dyspnea, weight gain, lower extremity edema, nausea and vomiting, the phenomenon of fluid wave, and shifting dullness occur. Survival rate in advanced stages of the disease (III and IV) is 5–20% [8].

The presence of ascitic fluid less than 100 ml is without symptoms and impossible to detect gynecologically. In 14% of cases, such as small amounts of ascites are not detected by ultrasound examination either. However, ultrasonography is important not only in detecting ascites but also in its quantification and localization in paracentesis.

CT scans have an important role in detection and are potent in showing peritoneal carcinomatosis, omental involvement, and peritoneal ischemia. Paracentesis, laparoscopy, and laparotomy assist in final determination of the amount, biochemical, and cytological origin of ascitic fluid, as well as primary localization of tumor that caused the production of ascitic fluid (immunohistochemistry and markers).

Ascites is a grave prognostic marker. The presence of malignant ascites in malignomas of other location (pancreas, stomach, large intestine, breasts) is a poor prognostic parameter, with survival rate of 7–13 weeks from the time of detection. In ovarian carcinoma, survival rate is longest, more than 19 weeks. Unfavorable prognostic parameter is depressed serum albumin, as well as depressed serum ascites albumin (transudate) [9].

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4. Cytology, biochemistry, and immunohistochemistry of ascitic fluid

The first report on peritoneal fluid cytology aimed at detecting subclinical metastases was published in 1950. FIGO introduced peritoneal washing cytology in staging of ovarian carcinoma in 1973. Positive cytological finding is important for substaging of I and II stages of the disease (I and II c stages) and is an important predictive prognostic and recurrence factor. However, more and more studies show that morphologic examination of cytological samples, associated with therapeutic and prognostic implications, is not a diagnostic tool with high sensitivity. Malignant cells may be few in number and hardly recognized among numerous mesothelial cells and macrophages. On the other hand, mesothelial cells exhibiting reactive changes (with enlarged hyperchromatic nuclei and cytoplasmic alterations) may be misinterpreted as neoplastic cells, thus resulting in stage upgrading and unnecessary chemotherapy.

Reactive mesothelial cells - enlarged, with dense cytoplasm, enlarged nucleus with nucleolus, may be vacuolated, or contain cellular windows. Endosalpingiosis displays organized clusters with uniform and scant basophilic cytoplasm cells, the nucleus with normal membrane, a fine chromatin, and small nucleoli. Endometriosis, as another diagnostic error, shows the presence of round cells arranged in three-dimensional clusters and layers, round and bean-shaped nucleus with fine chromatin, and scant and vacuolated cytoplasm. The most sensitive finding in endometriosis is the presence of macrophages with hemosiderin.

For all of these reasons, peritoneal cytology may be false positive in even 4.5% of cases. On the other hand, the false-negative rate is high and accounts for more than 20%. The factors that are responsible for such a false-negative rate may include poor distribution of washings, infrequent exfoliation of cells, and interpretive errors [10].

Cytological manifestation of serous carcinoma presents single cells or poorly cohesive irregular cell clusters, with large pleomorphic nucleus and prominent nucleolus. Cytological manifestation of endometrioid carcinoma shows three-dimensional cluster of cells with large eccentric and pleomorphic nucleus, coarse chromatin, prominent nucleolus, and abundant cytoplasm.

One of our study showed reliability and limitations of cytological analysis of ascites in ovarian carcinoma. The experimental group was composed of 76 cytological findings obtained from patients diagnosed with ovarian carcinoma, whereas the control group included 94 cytological findings of benign ovarian tumors and ascites in liver cirrhosis. **Table 1** shows distribution of false-negative cytological findings of ascitic fluid with respect to the histological type of tumor. **Table 2** shows distribution of false-positive peritoneal cytological findings with respect to the cause and histological type of tumor. In that study, it was concluded that peritoneal cytology of ascitic fluid is highly specific (93.61%) but it has a relatively low sensitivity (68.92%). In 30.02%, peritoneal cytology had false-negative results, and in 6.38%, it showed false-positive results [11].

The sensitivity of peritoneal cytology according to literature data is as low as 50–60% and as high as 97%, depending on the study, the stage of the disease, and the involvement of the peritoneum [12].

Histological type	Total number of histological type	Number of negative cytological findings	Percentage of false-negative findings
Serous	54	15	27.77
Mucinous	6	2	33.33
Endometrioid	4	3	77
Clear cell	6	2	33.33
Anaplastic	4	1	25
Granulocellular	2	0	0
Total	76	23	30.2

Table 1. Distribution of false-negative cytological findings of ascitic fluid with respect to the histological type of tumor.

In patients with stage Ic and ruptured capsule, cytology is positive in 75% and with peritoneal involvement in 94% cases [13]. Cytology sensitivity in peritoneal involvement is 82.9% and specificity 98.1% [14]. Some other authors found in their studies that the sensitivity of total validity of cytology to be somewhat lower than 60% with almost 100% specificity [15].

Upon the completion of the treatment, the results of secondary cytology are an important and independent prognostic marker that highly correlates with optimal effects of surgical treatment, recurrence, and overall survival rate. Thus, in positive secondary cytology, survival rate is 13–32 months, and in negative >48 months [16].

In order to improve total validity of peritoneal cytology, as well as cervical cytology, immunohistochemical and biochemical biomarkers are found to be useful. Among other things, the concentration of alkaline phosphatase level (in malignant ascites it is > 350 mg/dl), lactate dehydrogenase, fibronectin, telomerase, as well as tumor markers CA – 125, CEA, p53, and β-HCG plays an important role.

Histological type	Total number of histological type	Number of positive cytological findings	Percentage of false-positive findings
Fibroma	9	0	0
Dermoid	11	0	0
Endometrioma	13	2	15.38
Serous	39	2	5.12
Mucinous	20	2	10
Liver cirrhosis	2	0	0
Total	94	6	6.38

Table 2. Distribution of false-positive peritoneal cytology findings with respect to the cause and histological type of tumor.

There is also a specific group of panel antibodies, primarily MOC-31 and Ber-EP4, highly effective in distinguishing mesothelial from cancerous cells. This differentiation may be supported by separation of antibodies into adherent cells (AD) (mesothelial and mesenchymal) and nonadherent (NAD) cells [17].

Telomerase has been the most tested biomarker lately. It is an enzyme essential for normal replication of chromosomes and constant growth of cancer cells (via telomere). In most somatic cells, telomerase activity is not expressed. On the other hand, in almost 100% of ovarian carcinoma, increased expression of telomerase activity has been proved. A special importance of the role of telomerase activity is in predicting the recurrence of the disease and in the post-treatment follow-up it is aimed at the detection of early recurrence. Contrary to 24–54% of cases with diagnosed residual disease, cytology, and second-look surgery negative, telomerase was found to be almost 100% positive [18]. The main limitation of this telomerase (TRAP) assay in wide clinical application is the rate of false-positive results in dermoid tumors and in some inflammatory processes.

Moreover, a recent study by Zhu et al. explored the values of tumor markers in serum and ascites for identifying and diagnosing malignant ascites by analyzing the clinical data of patients diagnosed with ascites; their findings suggested that compared to a single index, combined detection of tumor markers in the serum and ascites will significantly improve diagnostic sensitivity and specificity [19].

5. Ascites as a prognostic marker

Malignant ascites is a sign associated with malignant disease. The presence of ascitic fluid in ovarian cancer plays a major, even a key role in further progression of the malignant disease. The spread of ovarian cancer and the occurrence of peritoneal and abdominal metastases depend on ascitic fluid.

Specific cellular and acellular components of ascites provide tumor-friendly microenvironment, which not only promotes tumor cell growth and motility but also inhibits the positive response of chemotherapy, thus directly promoting chemoresistance in tumor cells [20, 21].

Available literature data on the disease progression and recurrence prove that metastases and recurrences may be prevented or reduced if the tumor is removed before being exposed to ascites and before tumor cells invade the peritoneum. Thus, for stage I disease, if the tumor is encapsulated and confined to the ovary, without ascites and without positive peritoneal washing, substage Ia, the recurrence rate accounts for 29%, but for the same stage I, substage Ic, with ascites and peritoneal washing positive for malignant cells, the recurrence rate expected is 59% [22].

Understanding the pathology of formation and reabsorption of ascites is necessary for demonstrating its impact on the disease progression and occurrence of metastases. Two thirds of the peritoneal fluid is reabsorbed by the lymphatic channels and reaches the diaphragm and the right subclavian vein by the negative intrathoracic pressure. Physiological factors that stimulate this flow are gravity, diaphragmatic pressure, organ mobility, and recesses formed

by key anatomical structures [23]. There are three most common sites of ascites reabsorption and ovarian cancer metastasis, including the greater omentum, right subphrenic region, and pouch of Douglas, areas which have easy access to ascites [24].

On the other hand, the disease recurrence is almost always associated with the development of ascites. The most common and almost only therapeutic approach in the treatment of recurrences is chemotherapy. Chemoresistance and poor response to chemotherapy, often driven by the presence of ascites, directly correlate with survival rate and the disease recurrence. In chemoresistant tumors, a 5-year survival rate is less than 27% [25]. Thus, ascites indirectly affects a malignant disease prognosis, both by forming a specific microenvironment promoting tumor growth and by developing chemoresistance.

It is believed that future management options will focus more not only on surgical treatment of the disease but also on ascitic fluid and secondary malignant deposits treatment and chemoresistance as well, since the disease will already have spread beyond the ovaries in 75% of cases at the time of diagnosis [26].

6. Malignant ascites—immunological factors, cytokines, and acellular components

Common features of all malignant processes include hereditary and environmental factors and immunological factors as well. A balanced immune response, from immunopresentation to immune reaction or immune response, is an important factor of carcinogenesis. An immune response has to be timely, specific, and balanced. If early recognition of carcinogenic factors and genetic mutations fails and if Th1-, Th2-, and REG-mediated cellular immune response is hyporeactive or hyperreactive, then the progression of malignant processes occurs.

A study from 2017 based on a great number of papers from the Medline database showed that elevated neutrophil-to-lymphocyte ratio (NLR) could be an important diagnostic parameter predicative of poor prognosis for ovarian cancer. Elevation of NLR correlated with advanced FIGO stage (OR, 2.32; 95% CI, 1.79–3.00), higher serum level of CA-125 (OR, 3.33; 95% CI, 2.43–4.58), more extensive ascites (OR, 3.54; 95% CI, 2.31–5.42) as well as less chemotherapeutic response (OR, 0.53; 95% CI, 0.40–0.70) [27].

Inflammatory responses may be evaluated by the changes in leukocyte reaction, as well as by C-reactive protein (CRP) measurement. An elevated CPR level is also identified in cancer patients, and along with CA 125 tumor marker specific to ovarian cancer, it can be an excellent clinical and prognostic marker of a malignant disease [28].

An increase of inflammatory factors can be detected not only in the blood but also in tumor tissue and ascitic fluid. The concentration of cancer-associated soluble factors in ascites is much higher than in the serum. For all of these reasons, ascites is a specific and useful marker for investigating diagnostic, therapeutic, and prognostic factors regarding ovarian cancer.

Natural killer cells (NK) and T lymphocytes have significantly higher concentration in the ascites than in the blood in patients with ovarian cancer [29].

Cancer is a heterogeneous disease with cellular and molecular heterogeneity. Single nucleotide polymorphism (SNP) is also present. Apart from cellular heterogeneity, heterogeneity of ascitic fluid content, as well as measurements of inflammatory protein agent quantity, may be predictive of an aggressive tumor and serve as a useful prognostic marker. Besides inflammatory parameters, it is important to evaluate the presence or absence of oncogenic and tumor suppressive factors that have an impact on final outcome of the disease. Thus, ascites in high-grade serous ovarian cancer patients has been shown to serve as a protective tumor microenvironment against drug-induced apoptosis through induction of survival signaling pathways such as PI3K/Akt in tumor cells [30, 31].

Measurements of some enzyme activities that take part in inflammatory processes may be useful in differential diagnosis between benign and malignant ascites. Expressions of cyclooxygenase-2 mRNA in benign and malignant ascites of different etiologies (liver, stomach, bladder, ovary) showed higher values in malignant than in benign ascites in the ratio of 42.9%:6.7%. In ovarian cancer, the proportion of this marker in the malignant ascites was the highest (57.1%), whereas in malignant ascites of other localizations, it was 33–40% [32].

Apart from measuring immunological and inflammatory reactions in blood, ascites, and tumor surroundings and assessing lymphocyte, macrophages, specific enzymes, NK cells, and other elements of the immune response, it is also very important to demonstrate cytokines, chemokines, and specific protein factors between the immune system communication and tumor cells. Concentration of proinflammatory cytokines in ascites is 40–500 folds higher than in serum [33].

Malignant ascites can be described as a dynamic reservoir of survival factors, including cytokines, chemokines, and growth factors, that individually or in combination suppress immune response and tumor cell growth and progression. An analysis of the ascites from a few epithelial cancers showed increased expression of several factors, including angiogenin, angiopoietin, IL-6, IL-6R, IL-8, IL-10, leptin, MCP-1, MIF, NAP-2, osteoprotegerin (OPG), and urokinase plasminogen activator receptor (uPAR) [34].

OPG has been known as a product of mesothelial and endothelial cell secretion, promoting tumor growth and angiogenesis and inhibiting TRAIL-induced apoptosis of ovarian cancer cells induced by TNF [35]. This is what differentiates benign from malignant ascites, since mesothelial cells in malignant ascites can produce factors that disable the impact of apoptotic TNF factor on malignant cells of ovarian cancer. Such a production is genetic in origin. Further analyses of gene expression in stimulating mesothelial cells of malignant ascites showed that 484 genes were upregulated and 165 genes were downregulated. Genes associated with the regulation of cell growth and proliferation, cell death, and organization have higher gene expression. Top networks upregulated by malignant ascites included Akt and NF-κB survival pathways.

Leptin is an adipokine predominately produced by adipocytes and promotes ovarian cancer cell growth *in vitro* [36].

Ascites of malignant potential constitutes a microenvironment that stimulates production of integrins in epithelial-mesenchymal ovarian cancer cells. These integrins assist the formation of two invasive phenotypes for migration and formation of malignant cells in spheroid structure.

Out of other already mentioned factors elevated in malignant ascites, IL-10 is worth mentioning. This interleukin may help tumor cells to evade host immunological surveillance. Its immunological suppressive activity is known to inhibit T helper cell proliferation, impede dendritic cell maturation, and inhibit T cells co-stimulatory molecules [37–39].

Consistent with that, ascites-derived ovarian tumor cells have been shown to constitutively release CD95 ligand (also known as Fas ligand), which can induce apoptosis in immune cells expressing CD95 [40].

The factors presented in the malignant ascites may also have a negative impact on natural killer T (NKT) cell activity, since GD3 ganglioside contained in ascites inhibits killer T (NKT) cell activity and the interaction of ovarian cancer cells with natural killer cells, thus protecting ovarian cancer cells from host immunity [41].

There is also a correlation between regulatory T cells (Treg) (which inhibit tumor-specific T-cell immunity) in the ascites and reduced survival in patients with ovarian cancer [42].

Besides aforementioned IL-10, the concentration of other inflammatory cytokines, such as IL-1β, IL-6, and IL-8, is significantly higher in the ascites than in the serum. Increased concentration of these interleukins due to immunosuppressive and tumorigenic effect correlates with poor prognosis and response to therapy or chemoresistance [43, 44].

Special attention should be paid to IL-6 whose increased presence in the malignant ascites promotes tumor growth, migration, and invasion, but facilitates chemoresistance [39, 40] and angiogenesis. So, high level of IL-6 is an independent predictor of patient's response to therapy [45–48].

Furthermore, ascites from ovarian cancer patients containing elevated levels of IL-1 was correlated with increased overall survival [49].

Hepatocyte growth factor in malignant ascites stimulates the migration of ovarian cancer cells [50].

Lysophosphatidic acid (LPA), a bioactive phospholipid present in high levels in the ascites of ovarian cancer patients and produced by ovarian cancer cells, with increased transcriptional regulation of vascular endothelial growth factor (VEGF), uPA, IL-6, and IL-8 affects membrane permeability and encourages ascites accumulation [51, 52].

The VEGF concentration is significantly higher in the ascites than in the serum, confirming increased angiogenic activity of the peritoneal cavity. The role of VEGF in the production of ascites is based on the increased permeability of peritoneal membranes and downregulation of tight junction protein claudin 5 and on the induction of tyrosine phosphorylation of cadherin-catenin complex, resulting in decreased endothelial junctional strength and increased permeability of the blood vessels. Neoangiogenesis and increased permeability of the peritoneal and endothelial membrane synergistically form the ascites [53, 54]. VEGF increases the permeability of venules and small veins for plasma proteins with a potency 10,000 times higher than histamine [55]. Besides a role in the pathogenesis of ascites, VEGF results in reduced effects of antiapoptotic bcl-2 protein and decreases sensitivity to chemotherapy and radiation therapy. Similar effects and chemoresistance are obtained by other vascular endogenous factors, such as endothelin-1.

Of other prognostic factors to be determined in the ascites, concentration of E-cadherin is distinguished. Its expression is most commonly lost in metastasis, but it is enhanced in the cells from chemoresistant recurrent ovarian tumors, resulting in tumor cells aggregation with limited drug penetration and in decreased susceptibility to chemotherapy [56–58].

As for immunological prognostic factors, a CD4/CD8 T cell ratio in ascites and the presence of Treg are of considerable importance. High T cell/Treg ratio independently predicts increased survival [59].

On the other hand, reduced accumulation of CD3+CD56+ cells (natural killer or natural killer-like T cells) in the ascites is always correlated with poor prognosis, because it is present in patients with increased platinum resistance [60].

Proinflammatory cytokines in ascites are directly associated with tumor cells phenotype and promotion of human mesothelial cells. Hepatocyte growth factor (HGF) and epidermal growth factor (EGF) are migration mediators of cancer-associated peritoneal mesothelial cells by activating cMet and possibly downstream ERK1/2 and Akt pathways. Thus, ascites not only stimulates tumor growth but also its migration and metastatic growth [61].

Ascitic fluid has been proven to contain other chemokines and chemokine receptors as well, such as CXCR3, that support migration and metastatic progression of malignant cells by triggering the migration of cancer cells along the peritoneal cavity. Increased expression of this chemokine is associated with a higher stage of the disease and positive lymph nodes. In future, this chemokine could be considered a factor of targeted therapy [62].

Besides aforementioned migration factors found in ascites, there is also vascular cell adhesion molecule-1 (VCAM-1). Its elevation in the ascites and the serum is associated with increased risk of malignant cell metastasis [63].

Ascites may also increase migration and metastatic progression by weakening the factors that cause a potential metastatic blockade by affecting TGF-β. Environmental and local factors in the ascites promote migration of malignant cells by repressing miRNA-125b. Repression of miRNA-125b under the influence of local factors stimulates metastatic progression in the ascites by the influence of TGF-β [64].

Some adipokines found in the ascitic fluid can also affect migration and metastatic progression. Visfatin is a novel adipokine exhibiting high levels in many types of carcinomas. Elevated levels of visfatin in ascites are associated with ovarian cancer intraperitoneal dissemination. Some recent studies have shown that ascites-derived visfatin promoted migration of ovarian cancer cells through Rho/ROCK signaling-mediated actin polymerization, which was required for ovarian cancer intraperitoneal dissemination. These studies are important in terms of potential future recommendations regarding ovarian cancer targeted therapy [65].

Immunosuppressive microenvironment in ascites influences not only the number of specific lymphocytes and immune response factors but also their functionality as well. A study that analyzed functional characteristics of specific lymphocytes, Treg lymphocytes, NK cells, TNF cells, and specific cytokines in ascites associated with malignant cells and in ascites without malignant cells showed that functional ability of NK cells is reduced in malignant ascites.

Functional ability of NK cells was determined indirectly by measuring the concentration of CD 107 marker, which shows the degree of degranulation and efficacy of NK cells. In ascites with malignant cells compared to ascites without malignant cells, CD 107 concentration is lower both with and without direct stimulation by IL 2, due to pronounced immunosuppressive effect of tumor microenvironment. On the other hand, the concentration of local inflammatory factors of TNF and TREG cells is greater in malignant ascites [66].

Ascites inhibits T lymphocyte function as well. Inhibition of T-cell receptor-induced nuclear factor-kappa B (NF-κB) and nuclear factor of activated T-cell (NFAT) signaling in tumor-associated T cells has been proved. This function of T cells is restored in the absence of ascites and when there is no contact with T-lymphocytes [67].

Tumor-associated macrophages (TAMs) are essential for cancer progression. The analyses of TAM in different ovarian cancers suggest that different activities are associated with specific cytokines activation. Activation of IL-6 and IL-10 is associated with increased aggressiveness of ovarian cancer, whereas the activation of IFN-γ is able to neutralize the suppressive effect of ascites on IL-12 expression, a key determinant of a cytotoxic immune response. Cytokines in malignant ascites are generally said to present a mixture of protumorigenic and antitumorigenic factors that form a unique microenvironment. Protumorigenic cytokines, including IL-6, IL-8, IL-10, IL-15, IP-10, MCP-1, MIP-1β, and vascular endothelial growth factor (VEGF), and significantly reduced levels of IL-2, IL-5, IL-7, and IL-17 result in the formation of proinflammatory and immunosuppressive tumor microenvironment [33].

Of all aforementioned cytokines, IL-6 and IL-10 concentration deserves special attention, since increased concentration of these cytokines is a bad prognostic parameter associated with poor response to therapy. The concentration of these proinflammatoy cytokines in ascites is 40–500 folds greater than in serum. IL-6 may be secreted in ovarian cancer cells, tumor-associated macrophages, and peritoneal mesothelial cells, which have the highest potential for secretion of this interleukin [68, 69].

An algorithm, including the concentration of aforementioned IL-6 and IL-10, as well as the concentration of leptin and CA 125 markers, is a good prognostic parameter of tumor progression and resistance to first-line therapy [28].

A lot of studies have confirmed that the association between the processes of coagulation and inflammation can be proved in oncologic patients. In this regard, it has been proved that thrombin as a central factor of coagulation may have an important role in the regulation of inflammatory response. A lot of studies have confirmed that thrombin-like activity in ovarian cancer-associated ascites may result in modulation of multiple cytokines network. On the other hand, the anticoagulant antithrombin reverses and prevents IL-12 inhibition induced by ascites. The use of specific thrombin receptors (PAR) agonist peptides has proved that IL-12 inhibition is thrombin-specific and dependent. These data suggest that there is a relationship between IL-12 concentration and coagulation, where thrombin is the key enzyme in IL-12 inhibition. This inhibition is the most important in forming the tumor microenvironment that enables the escape of immune system effects on tumorogenesis [70].

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The acellular fraction of ascitic fluid in ovarian cancer is an environment that promotes *de novo* resistance of tumor cells by producing protective microenvironment that contributes to tumor cell growth and disease recurrence. Environmental factors of ascites inhibit drug- and death receptor-induced apoptosis. The use of enzyme-linked immunosorbent assay (ELISA) for measuring IL-6 and IL-8 levels in the ascites determined that the level of these cytokines correlates with clinical and pathological parameters and progression-free survival, suggesting that elevated IL-6 is an independent predictor of shorter progression-free survival [71].

7. Malignant ascites—cellular factors

The origin and phenotype of the cells in the ascites is poorly understood. Ascites contains a complex heterogeneous mixture of resident and nonresident cell populations, each population of cells has a specific role and both populations interact with each other through soluble mediators. The resident components of the ascites include tumor cells, stromal cells, and cancer-associated fibroblasts (CAF), whereas cells recruited from the outside of the tumor environment, including infiltrating macrophages/monocytes, bone marrow-derived mesenchymal stem cells (MSC), and cytotoxic or Treg, belong to nonresident populations.

Cancer-associated fibroblasts (CAFs) are important in the autocrine-paracrine promotion, proliferation, and migration of cancer cells [72].

Similar effect on tumor progression is also attributed to human peritoneal mesothelial cells (HPMC) [73, 74]. Lysophosphatidic acid (LPA) produced by HPMC increases adhesion, migration, and invasion of ovarian cancer cells [74]. On the other hand, cancer-associated mesothelial cells have been proven to produce factors that stimulate chemoresistance in ovarian cancer cells [75]. In a response to exposure to malignant ascites, HPMC also produce dipeptidyl peptidase IV and VEGF [76, 77].

Ascitic tumor cells may be presented as individual adherent cells and as aggregates of nonadherent cells known as spheroids [78]. Spheroids have low levels of E-cadherin, express epithelial cell adhesion molecule (EpCAM) and cytokeratin, and have a pronounced ability of invasion and recurrence and a more rapid occurrence of ascites. This type of malignant cells with the aggregates is chemoresistant due to limited drug penetration through these multicellular cell aggregates [79, 80]. These spheroid cells mimic traits of cancer stem cells (CSC). CSCs are cell population resistant to chemotherapy and are a source of proliferating tumor cells with progressive differentiation potential.

Further evidence of spheroid aggregates showed that there are two subtypes of adherent cells—those with mesenchymal-like and epithelial-like morphology. Both types are similar to stem/progenitor cells that have a potential for self-renewal and the expression of cancer stem cells, including $CD44^{high}$, $CD24^{low}$, and $AC133^{+}$ [81]. These cells also express genes responsible for tumorigenesis and metastasis: BMP-2, BMP4, TGF-β, EGFR, and integrin $\alpha_2 \beta_1$ [23]. Future studies should be directed to these nonadherent spheroidal cell aggregates due to their role in carcinogenesis and metastatic progression.

The stromal cellular components of ascites include fibroblasts, endothelial or mesothelial cells, adipocytes, adipose tissue-derived stromal cells, bone marrow-derived stem cells, and immune cells [82, 83]. Stromal cells activate angiogenesis and growth factor and play an important role in malignant progression.

8. Metabolic and biochemical parameters of communication between cellular and acellular factors

The analysis of metabolites, chemical compounds, and metabolic profile in malignant ascites in comparison to benign ascites (cirrhosis) showed the difference in fatty acids, cholesterol, ceramide, glycerol-3-phosphate, glucose, and glucose-3-phosphate. 2-Hydroxyisovalerate is the least present metabolite, but glucose-1-phosphate (G1P) is the dominant metabolite in the malignant ascites. 2-Hydroxyisovalerate is a product of amino acids breakdown and is elevated in patients with ketoacidosis. G1P is a product of glycogenolysis suggesting an increase of glucose breakdown and increased metabolism.

Furthermore, glucose transporter (GLUT) 1 or GLUT3 and glycolytic enzymes, hexokinase (HK) II, are overexpressed in several tumor cells and suggested to be an indicator of poor prognosis in different malignancies, including ovarian cancer [84]. Overexpression of hexokinase (HK) II is associated with the disease progression and chemoresistance [85]. Additionally, glycolate, glucose, furanose, and fructose are significantly decreased, whereas glycerol-3-phosphate, cholesterol, ceramide, and monoacylglycerol (MAG; 18:0/0:0/0:0) are significantly increased in EOC patient-derived ascites [86]. Moreover, ceramide, derivatives of fatty acids, and LPA are identified only in malignant ascites [86].

Biochemical analyses of proteins in ascites of benign etiology identified about 1855 types of protein and in malignant ascites 2096 proteins. About 424 proteins were identified as specific to malignant ascites [87]. The concentration of pyruvate kinase isozymes M1/M2 (PKM1/2), glyceraldehyde phosphate dehydrogenase (GAPDH), and mesothelin (MSLN) was elevated in comparison to benign ascites. The most specific differences between these two types of ascites regarding protein occurrence were up to sevenfolds in RNA components.

Malignant ascites also exhibits higher concentration of complex glycans, unlike benign ascites that contains simple glycans. A complex N-Glycan analysis of ascitic fluids showed highly fucosylated and sialylated complex and hybrid glycans. Other protein components specific to malignant ascites include annexin, mucin, and peroxiredoxin families [88].

In malignant ascites also are an abundance of other biochemical components, including N, haptoglobin, fibronectin, lumican, fibulin, hemopexin, ceruloplasmin, alpha-1-antitrypsin, alpha-1-antichymotrypsin, and clusterin, hemopexin, and fibulin glycopeptides [89].

Exosomes in ascites—Exosomes size in malignant ascites is in the range between 30 and 100 nm in diameter. Inward budding of the late endosomal membrane to segregate the cargos, including lipids, proteins, and nucleic acids, within the membrane-covered vesicles is

responsible for their formation [90]. Molecular signatures of donor cells having the ability to circulate throughout the body and potentially transferring information between cells to alter gene expression in recipient cells have been identified in exosomes [91]. Furthermore, it has been determined that exosome-derived molecular cargos contain distinct subsets of disease-specific biomarkers, including miR-200c, miR-214, CA125, Muc-1, and CD24 [92].

The level of 9 of 10 tested agents (CCL2, CXCL1, CXCL5, CXCL8, CXCL12, HGF, PAI-1, TGF-β1, and VEGF) was found to be the greatest in the fluids from undifferentiated and advanced cancers, but the concentration of remaining 2 agents (IL-6 and uPA) was the highest in ascites from serous carcinoma [93].

9. Therapeutic approach for the patients with ascites

Primary treatment option in the management of ovarian cancer is cytoreductive surgery and platinum-based therapy with an expected response rate of 70%. However, many women experience recurrence of the disease within 12–18 months, refractory to standard platinum treatment.

Successful treatment of ascites is limited by the fact that the complete pathogenic mechanism is still poorly understood, and on the other hand, the advanced stage of the disease limits the successful management of the disease and quality of life.

Standard therapy of ascites mainly includes repeated paracentesis in more than 96% of cases. This method is effective in rapid control of distressing symptoms, such as dyspnea, orthopnea, pain, and peritoneal content.

Paracentesis is the most commonly used treatment modality in more than 98% of cases. This method is minimally invasive and may be used under ultrasound control, and the relief of symptoms is reported in 78% of cases. First, patients show relief of abdominal bloating and anorexia, then dyspnea, insomnia, and fatigue. Paracentesis is performed by inserting a 14-gauge needle with a 16-gauge catheter. The drainage of more than 9 L increases the risk of intravascular pressure, hypotension, hypovolemia, hypoproteinemia, and electrolytic imbalance [94].

However, this method has its limitations, since more than 5 L of ascitic fluid removal may affect plasma volume and renal function. For these reasons, 5% dextrose infused simultaneously with paracentesis has been advocated. Possible complications of this method also include hypoproteinemia, hypotension, secondary peritonitis, perforation, and pulmonary embolism [95, 96]. In order to prevent possible complications and homeostatic imbalance, it is necessary to perform blood tests control, focusing on protein and electrolyte levels, and the catheter needle should not stay in one site longer than 24 hours. In order to reduce the risk of infection, antibiotic therapy is sometimes used during the first week of treatment after puncture. Courtney et al. [97] reported their results regarding the use of pleurx

catheter that could be kept in a patient for 70 days, reducing the incidence and the risk of septic complications.

Serial paracentesis not only provide relief of symptoms but also promote loss of proteins, hypovolemia, and potential spread of cancer cells to site of drainage.

Complications may include pain, perforation, peritonitis, frequent hospitalizations, and corrections of hypoproteinemia and hypoalbuminemia.

Diuretic therapy in the management of the ascites is rarely performed (61% of all ascites) and is less effective than paracentesis (45%) [98]. Unlike benign ascites (liver cirrhosis and congestive heart failure), malignant ascites respond poorly to the therapy including fluid and salt restrictions and diuretics that may cause complications such as a decrease in volume, electrolytic imbalance, and renal dysfunction.

Pockros et al. proved in his paper that renin levels were elevated in patients with hepatic metastases, whereas normal renin levels were confirmed in carcinomatosis without hepatic metastases [99]. Patients without hepatic metastases and with diuretic use had 1 kg/d in weight loss without hypotension, and those without metastases and in carcinomatosis group had 0.5 kg/d in weight loss with hypotension and renal dysfunction.

The most common medical therapeutic approach includes diuretics therapy. Diuretic drugs used in the management of the disease are aldosterone antagonist such as spironolactone at a dose of 100–200 mg daily and furosemide at an initial dosage of 40–80 mg per day [100]. The use of these drugs increases the risk of hypovolemia, hypotension, and renal failure [101], so their usage is allowed, but with a time limit. Contraindications are hyponatremia <125 mmol/l, hepatorenal-related decrease of sodium excretion to <30 mmol/day, renal insufficiency with serum creatinine >1.5 mg/dl, acute encephalopathy, and acute bacterial infection [102]. The use of diuretics also increases the risk of thromboembolic complications due to chemotherapy drug concentrations, and possible additional symptoms include gynecomastia, renal tubular acidosis, and hyperkalemia.

Another palliative attempt to moderate the symptoms of ascites is the application of chemotherapeutics into the peritoneal cavity. This treatment aims at delivering higher concentrations of drugs to the target site and minimizing resorption toxic effects. The intraperitoneal application of cisplatin and paclitaxel cytostatic drugs is most commonly used in the treatment. Complications of this method include infections, pain, blockage or leaks, and abdominal pain. Limiting factors are short-term effects and a maximum of 5 mm penetration into a tumor deposit with limiting effects to existing adhesions. Other side effects include abdominal pain, ileus, peritonitis, abscess, and necrosis.

The attempts to increase the cytotoxicity of cisplatin and paclitaxel in intraperitoneal application resulted in utilization of hyperthermic medium (40.5–43°C). This procedure is called hyperthermic intraperitoneal chemotherapy (HIPEC). The method was approved by Japanese National Insurance in 1981. The results of HIPEC treatment regarding overall survival rate are better in comparison to reduction of ascitic fluid, but without statistically significant difference [101].

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Chemotherapy in the management of ascites can be systemic and intraperitoneal. Intraperitoneal chemotherapy has local cytotoxicity 2–3 times higher than systemic one without systemic absorption or cytotoxicity. Hyperthermia (over 39°) increases local cytotoxic effects by inhibiting replication and repair. The best results are achieved directly after the surgery (complete cytoreduction) since fibrin depositions and adhesion formations are thin at that time. Combined modality treatment of surgical procedure and intraperitoneal chemotherapy using cisplatin, bleomycin, and mitomycin C prevents recurrence of ascites in 75% of patients. The fact that patients without positive peritoneal cytology do not develop ascites suggests that cytostatic therapy administration can prevent formation of ascites [103].

Besides intraperitoneal application of cytostatics, other drugs can be used intraperitoneally, such as intraperitoneal tumor necrosis factor (TNF), interferon, vascular endothelial growth factor, and other immunomodulators.

TNF at 0.08–0.014 mg/m^2 diluted in 5% human albumin is applied into the abdomen for 24–48 hours, and the procedure is repeated on the 8th day.

Improvements regarding reduction of ascitic fluid can be seen after three doses, but improvements in mucinous ovarian cancer have not been reported [104].

Intraperitoneal interferon-α (IFN-α) 2b application was described in studies by Sartori et al. [105]. Complete response was achieved in 29.3%, a partial response in 36.6%, and no response in 34.1%. Ovarian cancer patients had the highest global response (65%).

Clinical importance of immunomodulator OK-432 application has been studied. It is a lyophilized powder of *Streptococcus pyogenes*, showing effects only in patients with malignant ascites associated with gastrointestinal-related cancer. Studies of ascites and ovarian cancer are not available [101].

One of the surgical methods used in palliative treatment of ascites is peritoneovenous shunting. Surgical options in treating ascites include peritoneovenous shunts and radical peritonectomy. The first data on peritoneovenous shunts date back to 1974 when LeVeen first introduced it. A modified Denver shunt was developed later. The benefits of this method in comparison to paracentesis include reduced need for repeated paracentesis and maintenance of normal serum albumin concentrations. In malignant ascites, reduction and control of ascites are achieved in 75% of shunts [106]. Patients selected for shunt placement should undergo cardiac and respiratory evaluations.

Faught et al. [107] evaluated some possible complications of this method, such as fever, coagulopathy, infection, and tumor embolization [101]. Contraindications are loculated ascites, portal hypertension, coagulation disorders, elevated bilirubin levels, advanced cardiac or renal failure, hemorrhagic ascites, or fluid protein >4.5 g/l. The study has not proven increased probability of disseminating malignant cells by this treatment modality. What is important is that the application of this shunt showed better clinical results for ascites in ovarian cancer patients than in gastrointestinal cancer patients, in relation 50:15%, respectively. However, the application of shunts is indicated only for patients who cannot benefit from any other treatment and who can profit from it if their life expectancy is long enough. The median survival ranged in

the different studies from 52 to 266 days, reflecting the high heterogeneity of patients, and possible fatal complications are pulmonary edema or emboli [96, 108].

Finally, other surgical therapeutic procedures include radical peritonectomy. It is an extensive surgical intervention involving complete removal of the peritoneum combined with intraperitoneal chemotherapy. This is an extensive operation with significant morbidity, although initial results appear to demonstrate that it decreases the production of ascites.

A modern, innovative approach in treating malignant ascites is monoclonal antibody therapy, directed at one of the basic etiological factors of ascites—neoangiogenesis. In that respect, the drugs used, such as anti-vascular endothelial vascular factor (VEGF), may have potential tumor-suppressive effects.

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a recombinant humanized monoclonal antibody to VEGF composed of human IgG_1 framework regions and antigen-binding complementarity-determining regions from a murine antibody that blocks the binding of human VEGF to its receptors [109].

Bevacizumab is a humanized monoclonal antibody directed against VEGF-A as target therapy [110]. After its initial approval by the Food and Drug Administration (FDA) in 2004 for unresectable colorectal cancer, its indication for the treatment of different cancers has been accepted [111, 112]. The trials GOG-0218 and ICON7 reported benefits of this therapy combined with platinum therapy in patients with ovarian cancer. The AURELIA trial studied bevacizumab in combination with non-platinum chemotherapy and proved its success in platinum-resistant ovarian cancer [113]. In 2014, FDA approved bevacizumab for use only in recurrent, platinum-resistant ovarian cancer [114]. In 2016, this drug also received FDA approval for platinum-sensitive recurrent ovarian cancer, based on findings of a large GOG-0213 trial.

Therapeutic application of bevacizumab has also demonstrated significant benefits in patients with recurrent disease and ascites. Most common side effects are neutropenia and thrombocytopenia. Other serious, but rare side effects include gastrointestinal bleeding, thromboembolic events, hypertension, and proteinuria.

The studies analyzing quality of life and the recurrence of the disease in patients with ascites treated with repeated paracentesis and monoclonal anti-vascular drugs have shown that palliative treatment of malignant ascites using paracentesis or combined paracentesis and intraperitoneal chemotherapy negatively impacts patients' health-related quality of life (HRQL) and shortens the disease-free interval. Monoclonal antibody treatment results in better quality of life and in a longer disease-free interval. The median puncture-free survival with catumaxomab is 46 days versus 11 days in the group with paracentesis [115].

Complications of the procedure may be local: shunt occlusion and infections and systemic: DIC (due to coagulation factor dilution, introduction of collagen into the bloodstream), pulmonary edema (9.5–12%), pulmonary embolism (5–7%), and tumor emboli by direct infusion of malignant cells into the bloodstream (3–7%) [116].

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Other new therapeutic approaches to be pointed out include immunotherapy with interferon, tumor necrosis factor, Corynebacterium parvum, and Streptococcal preparation OK-432 [117].

10. Conclusion

Due to low symptomatology, a lack of screening, and relatively complicated diagnostic procedures of ovarian carcinoma, more and more women are believed to visit their doctors in advanced stage of the disease, complicated with ascitic fluid.

Cytological findings of ascitic fluid determine the stage of the disease. On the other hand, there is an increasing evidence that peritoneal cytology is a subjective assessment with certain percentage of false-positive and false-negative results that may cause application of unnecessary chemotherapy or nonapplication of necessary chemotherapy. Utilization of available and the development of new immunohistochemical markers should help in increasing sensitivity and specificity of ascitic fluid cytology.

Ascites has unfavorable outcomes and detrimental effects on overall quality of life in affected patients.

The pathophysiology of the incidence of ascites is unclear, complex, and is a combination of increased vascular permeability and obstructed lymphatic drainage.

Because the mechanism of ascites formation is poorly understood, there are no validating guidelines for preventing the formation of ascites. Maximal cytoreductive surgery followed by intraperitoneal or systemic chemotherapy remains to be the gold standard in preventing ascites formation.

Ascites is not only a symptom of a disease but also a specific microenvironment for formation and mediation of protumorigenic signals that control ovarian cancer progression, including proliferation, invasion and anti-apoptosis, chemoresistance, and tumor heterogeneity. Acellular cytokines, protein, and immunological factors influence ovarian cancer progression and its ability to prevent immune responses of the body and tumor reaction to chemotherapy. On the other hand, ascites contributes to disease dissemination, changing its course, and final outcomes.

Management of patients with ascites and ovarian carcinoma is complex, with additional recurrences, and often the goal of the treatment is to target palliative procedures that necessitate hospital environment.

Multidisciplinary approach is necessary in the management of patients and includes not only a gynecologist but also an anesthesiologist, gastroenterologist, surgeon, oncologist, chemotherapist, palliative care doctor, and an oncology pharmacist.

In order to improve overall quality of life and survival of these patients, further investigations of new drugs, monoclonal antibodies, and immunomodulators are needed aiming at prolonged periods between relapses.

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