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MALIGNANT PLEURAL EFFUSION IN PATIENTS WITH OVARIAN CANCER

MALIGNA PLEURALNA EFUZIJA KOD PACIJENTKINJA SA OVARIJALNIM KARCINOMOM

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Summary

Introduction. Ovarian cancer is the most lethal gynecological cancer. The most common manifestation of thoracic metastasis is pleural effusion. Pleural effusion with positive cytology is regarded as stage IVa of the International Federation of Gynecology and Obstetrics classification, and the overall five-year survival in these patients is less than 20%. We analyzed the data of patients with ovarian cancer who were treated at the Oncology Institue of Vojvodina, in order to establish the incidence of malignant pleural effusions, laterality of pleural effusions, and clinical manifestations. **Material and Methods.** The study included 731 patients with ovarian cancer who were treated at the Oncology Institue of Vojvodina from January 2012 to May 2020. The obtained data were compared with data found in the literature in the same period. **Results.** The incidence of malignant pleural effusion in our study was 5.75%; right-sided pleural effusion was found in 57.15% of patients, 33.33% of patients had effusion on the left side, and 9.52% had bilateral effusions. Thus, unilateral effusion was found in 90.48% of cases, and bilateral in only 9.52%. The most common symptom was dyspnea, reported in 33 patients (78.6%). **Conclusion.** The incidence of malignant pleural effusion in our study was most similar to data found by Zamboni et al. published in 2015; the right side was the dominant side of pleural effusions. The most common symptoms were dyspnea, shortnes of breath and chest pain.

Key words: Pleural Effusion, Malignant; Ovarian Neoplasms; Neoplasm Metastasis; Thoracic Neoplasms; Signs and Symptoms; Neoplasm Staging; Incidence

Sažetak

Uvod. Karcinom jajnika je najletalniji ginekološki karcinom. Najčešća prezentacija torakalnih metastaza je pleuralni izliv. Pleuralni izliv sa pozitivnom citologijom se označava kao stadijum IVa klasifikacije Internacionalne federacije za ginekologiju i opstetriciju i ukupno petogodišnje preživljavanje za ove pacijentkinje je manje od 20%. Analizirali smo podatke pacijentkinja sa ovarijalnim karcinomom, koje su lečene u Institutu za onkologiju Vojvodine, da bismo utvrdili incidenciju malignog pleuralnog izliva, stranu lokalizacije izliva i kliničke manifestacije. **Materijal i metode.** Analizirali smo podatke 731 pacijentkinje sa dijagnostikovanim ovarijalnim karcinomom, lečene u Institutu za onkologiju Vojvodine od januara 2012. do maja 2020. godine. Dobijeni podaci su upoređeni sa podacima koje smo pronašli u literaturi iz istog perioda. **Rezultati.** Incidencija malignog pleuralnog izliva u našoj studiji iznosila je 5,75%, dominantna strana izliva je bila desna, kod 57,15% pacijentkinja, dok je 33,33% imalo izliv sa leve strane, a 9,52% na obe strane. Pleuralni izliv je bio unilateralan u 90,48% slučajeva i bilateralan u samo 9,52%. Najčešći simptom bio je dispnea, prijavljen kod 33 pacijentkinje (78,6%). **Zaključak.** Incidencija u našem istraživanju je najsličnija podacima koje smo našli u studiji Zamboni i saradnika iz 2015. godine, dominantna strana izliva je bila desna. Najčešći simptomi su dispnea, kratak dah i bol u grudima.

Ključne reči: maligni pleuralni izliv; tumori jajnika; metastaze; tumori grudnog koša; znaci i simptomi; stadijumi tumora; incidenca

Introduction

Ovarian cancer is the most lethal gynecological cancer. After endometrial cancer, it is the most common, and it has the same distribution worldwide. In Serbia, 820 cases of ovarian cancer are newly diagnosed every year, and it is the leading cause of death among all malignant gynecological tumors [1]. The most common histological type is epithelial (95%) (high-grade serous carcinoma in 70 – 80% of cases) adenocarcinoma. In 80% of cases it is discovered in advanced stages, International Federation of Gynecology and Obstetrics (FIGO) stage III or IV, due to the lack of symptoms in earlier stages [2].

Omentum and peritoneum are the most common metastatic sites of ovarian cancer, while lymphatic and hematogenous metastases occur in only 2 – 3% of patients. The most common extra-abdominal metastases are malignant pleural effusion and pleural nodules [3]; metastatic ovarian carcinoma is the fourth

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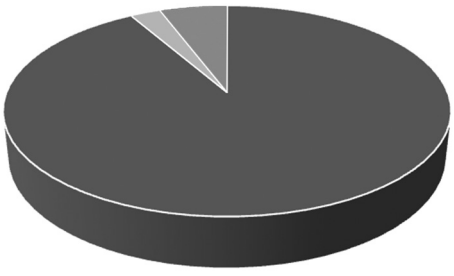
Abbreviations

MPE – malignat pleural effusion
FIGO – International Federation of Gynecology and Obstetrics
VEGF – vascular endothelial growth factor
CT – computed tomography
MRI – magnetic resonance imaging
VATS – video-assisted thoracoscopic surgery

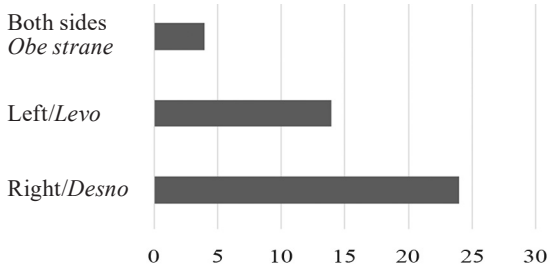
leading cause of malignat plerual effusions (MPE) [4]. Pleural effusion with positive cytology is regarded as FIGO IVa, which means that the overall five-year survival in these patients is less than 20% [2].

The most common presentation of thoracic metastases in these patients is pleural effusion, while pulmonary parenchymal metastases, lymphangitis, and nodal involvement are less common [5]. The MPE is defined as the accumulation of a significant amount of exudate in the pleural space, accompanied by the presence of malignant cells or tumor tissue [6]. There are several theories about the pathophysiology of MPE; currently it is believed that a combination of increased fluid production due to fluid extravasation from hyper-permeable parietal or visceral pleural and/or tumor vessels and impaired lymphatic outflow underlie the development of MPE [7]. Direct cause of pleural effusion is the impaired lymphatic drainage of the pleural space due to obstruction of the lymphatic system at any point from the stroma of the parietal pleura to the mediastinal and internal mammary lymph nodes, or by direct tumor involvement of the pleura. Indirect cause of pleural effusion includes inflammatory response inducing increased microvascular permeability as a result of pleural tumor invasion into the structures of the lymphatic system, resulting in increased entry rate of liquid into the pleural space [4]. The cytokine vascular endothelial growth factor (VEGF) plays a vital role in the induction of further vascular leakage, which has been shown not only in pleural effusions but also in ascites [8]. Also, important mechanism is transdiaphragmatic lymphatic drainage of peritoneal fluid (ascites) into pleura. Positive pleural cytology is an indicator in the diagnosis of MPE; unfortunately, about 30% of cytological pleural fluid results are false-negative [8].



91.65% (patients without pleural effusion)
91,65% (pacijentkinje bez pleuralne efuzije)
2.6% (patients with pleural effusion, less than 2 cm, seen on chest x-ray or thorax CT/MRI)/*2,6% (pacijentkinje sa pleuralnom efuzijom, manjom od 2 cm, viđenom na rendgenskom snimku grudnog koša ili kompjuterizovane tomografije/magnetne rezonantne tomografije)*
5.75% (patients with cytology confirmed MPE)
5,75% (pacijentkinje sa citološki potvrđenom malignom pleuralnom efuzijom)

Graph 1. Ovarian cancer and prevalence of pleural effusion
Grafikon 1. *Ovarijalni karcinom i prevalencija pleuralne efuzije*



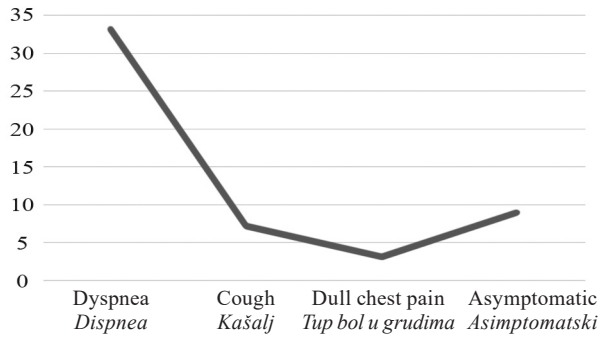
Graph 2. Distribution of MPE and laterality of pleural effusion
Grafikon 2. *Distribucija maligne pleuralne efuzije po stranama pleurane šupljine*

Material and Methods

We analyzed the data of 731 patients with ovarian cancer who were treated at the Oncology Institue of Vojvodina from January 2012 to May 2020, in order to establish the incidence of MPE, laterality of pleural effusion, and clinical manifestations. These data were compared with the data found in the literature in the same period.

Results

The study included 731 patients. A total of 61 patients with stage IVa were diagnosed with pleural effusion, seen on chest x-ray or computed tomography (CT)/magnetic resonance imaging (MRI). Pleural effusion with positive cytology was found in 42 patients (5.75%) confirming MPE. Among them, 29 patients were treated with thoracentesis and 13 needed thoracic drainage due to reaccumulation of effusion. Diagnostic thoracentesis was not performed in 19 (2.6%) patients with CT/MRI pleural effusion diameter less than 2 cm **(Graph 1)**.



Graph 3. Symptoms in patients with MPE
Grafikon 3. *Simptomi kod pacijenata sa malignom pleuralnom efuzijom*

Right-sided pleural effusions were more common; 24 patients (57.15%) had right-sided, 14 patients had left-sided (33.33%), and 4 (9.52%) had bilateral effusions. Thus, unilateral effusion was found in 90.48% of MPE cases, and bilateral in only 9.52% **(Graph 2)**.

The symptoms that were associated with MPE were dyspnea, cough and pain, while 9 patients were asymptomatic. The most common symptom was dyspnea, reported in 33 patients, out of whom 7 also reported cough, and 3 a dull chest pain **(Graph 3)**.

The incidence of MPE in our study was 5.75%; in most cases effusions were unilateral (90.48%) and right-sided (57.15%). The leading symptom of MPE was dyspnea, reported in 33 (78.6%) patients.

Discussion

In 2012, Porcel et al. published a paper on clinical implications of pleural effusions in ovarian cancer. They showed that in a sample of 364 patients, in 14% of cases ovarian cancer was the cause of pleural effusion. According to their study, ovarian cancer was the third most common cause of MPE, after breast (34%) and lung cancer (14.5%). Pleural effusion was unilateral in 77%, mostly right-sided (60%), bilateral in 23%, and two thirds of effusions occupied half or more of the hemithorax. Shortnes of breath was the leading symptom. After chest x-ray, all of the patients underwent a diagnostic thoracocentesis [9].

A research of Zamboni et al., on prognostic factors for the survival in patients with MPE, included 165 patients with MPE, and showed that ovarian cancer was the cause of effusion only in 3.6% of cases. The patients presented with the following symptoms: dyspnea, dull chest pain and nonproductive cough, while 15% of patients were asymptomatic. In 52% of cases, the effusions were large, affecting two tirds or more of the hemithorax, and in 33% they were massive. The diagnosis was confirmed by thoracocentesis as a standard method, and in a small percentage of cases by pleural biopsy, and if needed by video-assisted thoracoscopic surgery (VATS) or thoracotomy. Patients with ovarian cancer that caused MPE had the best median survival (21 months) compared to those with other primary tumors [10].

In the research of Perez Warnisher et al., who analyzed the characteristics of patients with MPE as debut of gynecologic malignancy, 17% of all MPE were associated with gynecological cancer, mostly with ovarian cancer. The most common symptoms in these patients with MPE were dyspnea (82%), cough (32%) and chest pain (25%). In 89% of patients thoracocentesis was performed for diagnosis, while in a small percentage they underwent blind pleural biopsy and thoracoscopy. All patients had a positive citology. In 64% of cases, MPE with ovarian cancer was located in the right hemithorax and ovarian adenocarcinoma was the most frequent primary tumor [11].

In 2018, Shitai et al. studied thoracic manifestations of gynecological tumors, and in a sample of 100 patients with ovarian cancer with thoracic manifestations, 19% of patients had pleural effusion, 38% had a lung mass, and lymphangitic carcinomatosis was found in 11% of cases. Respiratory symptoms included shortness of breath in most cases, cough, chest pain, and sometimes wheezing and hemoptysis. The diagnosis of pleural effusion was made using ultrasound of the pleural space, chest radiography and pleural fluid aspiration. This study showed that pleural effusion is the second most common thoracic manifestation of ovarian malignanices, while the most common was lung mass [12].

A research of Khotimah et al. from 2018, investigated pleural and lung metastases in patients with ovarian cancer who were treated in "Dr. Soetomo Hospital" in Indonesia from 2014 – 2015. It showed that there were only 1.7% of patients with stage IVa ovarian cancer. Only 5 of 292 patients had pleural effusion, of whom 4 patients were diagnosed initially, and only 1 was diagnosed in a 6-mounth period from the initial diagnosis of ovarian cancer. All patients underwent thoracocentesis, and they had positive cytology of the pleural fluid [13].

According to Skok et al., who investigated MPE and its managment, in a literature review from 2019, MPE was found in 18 – 20% of all ovarian cancer patients, that is much higer than in our study. In 33 – 35% of cases, it was also the most common peritoneal manifestation of epithelial ovarian cancer.

In 15% of newly diagnosed patients, MPE is the first clinical sign of the disease, and it presents in 77% of cases ipsilaterally and in 23% bilaterally. Patients who are suffering from ovarian cancer and have MPE have almost twice longer median survival in comparison to other cancer patients with MPE, with 21 months on average **(Table 1)** [2].

Table 1. Distribution of MPE in patients with ovarian cancer (OC)
Tabela 1. *Distribucija maligne pleuralne efuzije (MPE) kod pacijentkinja sa ovarijalnim karcinomom (OK)*

Incidence of MPE in patients with OC *Incidencija MPE kod pacijentkinja sa OK*		OC as the cause of MPE *OK kao uzročnik MPE*	
Perez Warnisher et al. 2016	17%	Porcel et al. 2012	14%
Shitai et al. 2018	19%	Zamboni et al. 2015	3.6%
Khotimah et al 2018	1.7%		
Skok et al. 2019	18 - 20%		

Table 2. Symptoms, localization and diagnosis of MPE
Tabela 2. *Simptomi, lokalizacija i dijagnostika maligne pleuralne efuzije*

Research *Istraživanje*	Symptoms *Simptomi*	Localization *Lokalizacija*	Diagnostic procedure *Dijagnostička procedura*
Porcel et al. 2012	Shortnes of breath *Kratak dah*	77% unilateral (right-sided 60%)/*77% unilateralna (desna strana 60%)*	Chest x-ray thoracocentesis *Rendgenografija i torakocenteza*
Zamboni et al. 2015	Dyspnea, dull chest pain and nonproductive cough 15% asymptomatic/*Dispnea, tup bol u grudima i neproduktivan kašalj 15% asimptomatično*	52% two thirds of hemithorax 33% massive *52% dve trećine hemitoraksa 33% masivno*	Thoracocentesis VATS thoracotomy *Torakocenteza VATS torakotomija*
Perez Warnisher et al. 2016	Dyspnea (82%), cough (32%) and chest pain (25%) *Dispnea (82%), kašalj (32%) and bol u grudima (25%)*	64% right hemithorax *64% desni hemitoraks*	89% Thoracocentesis pleural biopsy thoracoscopy *89% torakocenteza pleuralna biopsija torakoskopija*
Shitai et al. 2018	Shortness of breath, cough, chest pain, wheesing and hemoptysis/ *Kratak dah, kašalj, bol u grudima, wheesing i hemoptizije*	No data *Bez podataka*	Ultrasound, chest x-ray and pleural fluid aspiration *Ultrazvuk, rendgenografija i aspiracija pleuralne tečnosti*
Khotimah et al. 2018	No data *Bez podataka*	No data *Bez podataka*	Thoracocentesis *Torakocenteza*
Skok et al. 2019	No data *Bez podataka*	77% ipsilaterally and 23% bilaterally/*77% ipsilateralno i 23% bilateralno*	No data *Bez podataka*

Porcel et al., in their research from 2012, found a much higer rate of ovarian cancer causing MPE than Zamboni et al. in 2015. In regard to the incidence of MPE in patients with ovarian cancer, three papers published in 2016, 2018 and 2019 reported similar incidence, from 17 – 20%, while Khotimah et al. reported a much lower incidence of only 1.7%. Our research is betwen the study of Khotimah et al. and other studies published in 2016, 2018, and 2019, with an incidence of 5.75%. The localization of MPE in most studies was unilateral, and in two researches (Zamboni and Perez Warnisher) the right side was dominant, like in our study. According to Skok et al., about 25% of MPEs were bilateral.

The most common symptoms found in these studies were dyspnea, shortnes of breath and chest pain, that is in line with the results of our research **(Table 2)**.

Conclusion

The most common manifestation of thoracic metastasis in patients with ovarian cancer is pleural effusion, while pulmonary parenchymal metastases, lymphangitis, and nodal involvement are less common. The incidence of malignat pleural effusion in our study was 5.75%, and this finding is the most similar to data reported by Zamboni et al. from 2015.

In most cases pleural effusion was unilateral (90.48%), with right-sided dominance (57.15%) and these data were similar to data that we found in other analyzed studies.

The leading symptom of malignat pleural effusion was dyspnea, reported in 78.6% of patients. The most common symptoms found in the literature were dyspnea, shortness of breath and chest pain, and these data correspond to data in our study.

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