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TALC PLEURODESIS IN MANAGING BREAST CANCER-CAUSED MALIGNANT PLEURAL EFFUSIONS

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Abstract: **Introduction**: Breast cancer (BC) is the most common malignant tumor and the leading cause of cancer-related deaths among women in Serbia. Malignant pleural effusion (MPE) is a common manifestation of metastatic BC. Among solid tumors, BC accounts for the second-highest prevalence of MPE, occurring in 25% of cases. Current guidelines identify talc pleurodesis (TP) as one of the most effective treatments for MPE in most patients. This study aims to evaluate the effectiveness of TP in managing breast cancer-caused MPE.

Patients and Methods: This retrospective study included 21 patients with metastatic BC and MPE who were hospitalized at the Clinic for Thoracic Surgery, University Clinical Center Niš, during 2023. The success of TP was assessed using predefined clinical and radiographic criteria.

Results: TP was successful in 15 patients (71.4%). Luminal B BC was the most common subtype (42.9%). In the majority of cases, MPE was serous (71.4%) and ipsilateral (61.9%) to the primary breast tumor. Pleural cytology was positive in 28.6% of cases.

Conclusion: TP is an effective treatment for breast cancer-caused MPE. MPE is predominantly associated with Luminal B BC, and patients typically present with ipsilateral, serous MPE.

Keywords*:* malignant pleural effusion, breast cancer, thoracic drainage, talc pleurodesis.

INTRODUCTION

MPE is the pathological accumulation of free fluid in the pleural space, caused either by a malignant tumor originating in the pleura or by a metastatic tumor affecting the pleura (1). It occurs in approximately 15% of oncology patients and is often a manifestation of terminal disease (2, 3).

In developed countries, MPE is the third most common cause of pleural effusion, following congestive heart failure and parapneumonic effusion (1). Among malignant tumors, breast cancer (BC) is the second leading cause of MPE, accounting for 25% of cases, while lung cancer ranks first, with a prevalence exceeding 40% (1).

The primary goal of MPE treatment is to improve quality of life and prolong survival (4, 5). Treatment options include thoracocentesis, tube thoracostomy, drainage and pleurodesis, indwelling pleural catheter, pleuroperitoneal shunt, pleurectomy, and, in rare cases, extrapleural pneumonectomy (1, 6). Chemical pleurodesis, categorized as a secondary treatment option for MPE according to the 2023 BTS guidelines, is the focus of our research. Our study specifically evaluates BC patients undergoing this treatment (4).

The term "pleurodesis" originates from "pleura" (the lining of the lung) and "desis" (binding), reflecting its purpose: to obliterate the pleural space and prevent fluid accumulation (7). This effect is achieved by introducing an appropriate chemical agent (e.g., talc slurry, doxycycline, bleomycin, povidone iodine) into a previously well-drained pleural space, inducing iatrogenic pleurisy that results in pleural membrane adhesion and fibrosis (8).

This research aims to evaluate the success of TP in patients with breast cancer-caused MPE. Additionally, it examines the characteristics of the study subjects, including gender, age, immunohistological subtype of BC, macroscopic appearance and cytological features of pleural effusion, and the side of the effusion relative to the primary BC.

PATIENTS AND METHODS

This study was designed as a retrospective, monocentric study. It included 21 patients with metastatic

Table 1. *Inclusion and exclusion criteria for study*

Inclusion criteria	Exclusion criteria
1) patients with histologically verified BC and radiograph-confirmed pleural effusion	1) MPE patients with histologically verified malignancy elsewhere
2) data on the performed TP with a minimum of 4g of medical talc	2) patients treated using thoracentesis or thoracic drainage without TP
	3) record of previous chemical pleurodesis with less than 4g of medical talc or using another chemical agent
	4) other medical conditions associated with pleural effusion (pneumonia, heart / kidney / liver failure, etc.)

BC and MPE, comprising 20 females and one male, with an average age of 53.6 ± 10.9 years. All patients were hospitalized at the Clinic for Thoracic Surgery, University Clinical Center Niš, between January 1, 2023, and December 31, 2023. The youngest subject was 29 years old, and the oldest was 78. Disease-related data were obtained from the medical database.

Subjects were selected for the study based on predefined clinical and radiographic criteria (Table 1).

Therapeutic Procedure

For thoracic drainage, polyvinyl chloride chest tubes (size 24 Fr.) were used. Effusion was evacuated through an underwater or active drainage system (-20 cm H_2O) until complete lung re-expansion or for up to 48 hours. After achieving lung re-expansion, a previously prepared talc slurry was administered through the chest tube into the pleural space, which was then clamped for 4–6 hours. At the end of this period, the chest tube was returned to active drainage mode until secretion dropped to < 150 mL/24 h or for the next 48 hours.

The talc slurry was prepared by mixing 4 g of medical talc, 20 mL of 2% lidocaine-chloride solution (40 mg/2 mL), and 100 mL of 0.9% sodium chloride solution (NaCl).

TP success criteria

1) post-interventional secretion via chest tube < 150 ml/24h,

2) absence of respiratory problems within 7-10 days of drain removal, or

3) absence of clinically significant radiographic progression of MPE within 7-10 days of drain removal.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent from individuals was waived due to the retrospective nature of the study.

RESULTS

TP was successful in 71.4% of cases (Figure 1).

Luminal B BC was the most prevalent histological subtype of BC in the sample, accounting for 42.9%. In second place, in terms of frequency, was Luminal A BC (23.8%), followed by *triple-negative* BC (19%) and *HER2+* BC (4.8%). In 9.5% of cases (2 subjects), the histological subtype of BC was not defined (Figure 2a).

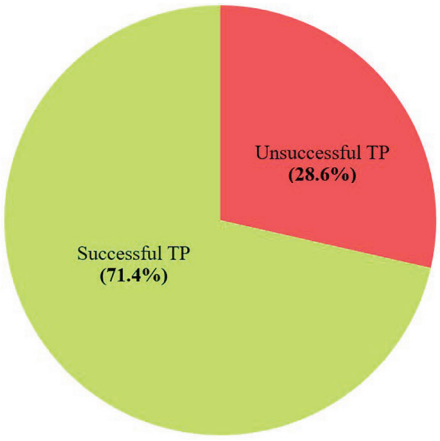

Figure 1. *Research results*

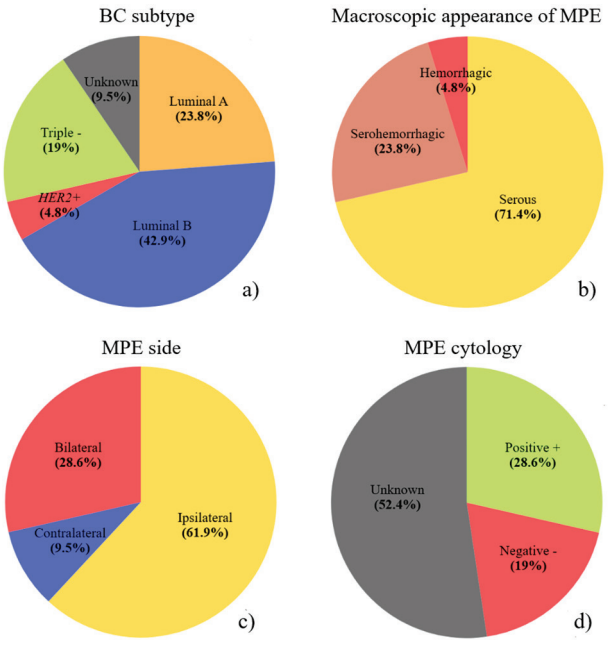

Figure 2. *Research results*

Regarding the macroscopic appearance of the pleural fluid, MPE was serous in 71.4%, serohemorrhagic in 23.8%, and hemorrhagic in 4.8% of cases (Figure 2b).

Relative to the side of the primary BC, MPE was ipsilateral in 61.9%, contralateral in 9.5%, and bilateral in 28.6% of cases (Figure 2c).

Cancer cells were identified in the pleural fluid in 28.6% of cases. In 19%, no cancer cells were present, while data on cytological examination were missing in 52.4% of cases (Figure 2d).

DISCUSSION

BC is the most common malignant tumor and the leading cause of cancer-related deaths in women in Serbia and globally (9). Thanks to organized screening programs, the disease is increasingly detected at an early stage, where treatment success is higher and prognosis more favorable. However, in some cases, BC can be insidious, presenting without obvious symptoms for extended periods, which leads to late-stage detection.

MPE can often be the first manifestation of advanced BC. It occurs in 7-11% of women at some stage of their illness, with over 15% of cases having MPE as the first sign (10). Among oncology patients with MPE, BC patients typically have a longer expected survival, ranging from 6.1 to 15.7 months, according to various studies (1, 10-16).

While BC in men is less common, with approximately one hundred times lower prevalence than in women (17), it is still notable. In men, MPE is present in about 7% of BC cases at the time of diagnosis (17).

The development of MPE is a complex, multifactorial pathological process. It is primarily caused by an imbalance between pleural fluid production and resorption. Pleural fluid hyperproduction can be driven by tumor cells and/or cytokines (e.g., interleukin-2, tumor necrosis factor, angiopoietin 1 and 2). Reduced resorption occurs due to obstruction of the parietal pleura pores and lymphatic capillaries, often as a result of direct invasion or lymphatic spread of the malignancy (6, 18). Most researchers believe that impaired pleural fluid resorption is the primary cause of MPE in BC patients (15, 19, 20).

Given these mechanisms, it is unsurprising that the majority of our patients had effusions on the ipsilateral side of the primary BC (61.9%), which aligns with findings in other studies (10, 13-15, 21-23). Only Chemow et al. reported differing results, with 64.7% of patients having bilateral MPE (16).

MPE can be serous, serohemorrhagic, or hemorrhagic in nature (2, 6), with the presence of hemorrhagic fluid often indicating metastatic invasion of the pleura (2). According to the Light criteria, an effusion containing > 100,000 erythrocytes/μL (in the absence of trauma) suggests an occult malignancy as the likely underlying cause (24). In our study, most patients had serous MPE (71.4%).

Cytological examination of pleural effusion revealed cancer cells in only 28.6% of cases, which is lower than the range of 47.5% to 78% reported in other studies (11, 13-15, 25, 26). The absence of cytological data for 52.4% of patients is due to the retrospective design of our study (whereas the aforementioned studies were prospective). Despite this, the presence of cancer cells was only one inclusion criterion, so the lack of cytological data did not affect the overall study results.

The classification of BC based on membrane receptor expression (ER, PR, HER2) plays a critical role in guiding treatment and determining prognosis. The disease is divided into four subtypes: Luminal A, Luminal B, HER2+, and triple-negative BC (27). Although some studies suggest MPE is more common in patients with triple-negative BC (28, 29), the majority of our subjects had Luminal B BC (42.9%), likely due to the small sample size.

According to the British Thoracic Society (BTS) and American Thoracic Society (ATS) guidelines, TP is one of the most effective treatments for MPE in patients who have achieved complete lung re-expansion through thoracic drainage, possess good performance status, and have a longer expected survival (> 1 month) (4, 30). As mentioned in the introduction, the goal of TP is to obliterate the pleural space and prevent fluid buildup, which has a long-term positive effect on the clinical course and prognosis of the disease (7, 31). While the precise mechanism of pleurodesis remains unclear, it is known that transforming growth factor-β plays a key role. This cytokine induces epithelial-mesenchymal transition and collagen production in mesothelial cells, leading to pleural space obliteration (2).

A meta-analysis published in 2020 confirmed the superiority of talc over other chemical agents (e.g., doxycycline, silver nitrate, bleomycin, povidone iodine, tetracycline, and mustin) in terms of effectiveness (7). Furthermore, talc is more cost-effective than other options (32, 33), and in 12-month survival analyses, bedside TP was found to be the least expensive treatment for MPE (32).

Our study is the first to evaluate the efficacy of TP specifically in the BC population. A 2024 meta-analysis by Rodrigues et al. (which included at least 117 BC patients treated with TP) found the overall effectiveness ranged from 54.2% to 96.5%, depending on the study

(34). In our study, TP was effective in 71.4% of cases, which is within the range reported in these studies.

CONCLUSION

From the results of our research, it can be concluded:

1) TP is an effective MPE treatment method,

2) MPE is most commonly associated with Luminal B BC, and

3) The majority of BC patients with MPE exhibit ipsilateral, serous effusions

Study limitations and future directions

The main limitations of our study include its retrospective design, small sample size (n = 21), and incomplete medical records in some cases (particularly the absence of data on cytological examination and BC subtypes). We attribute the small sample size to the fact that, prior to 2023, pleurodesis in our clinic was predominantly performed using less than 4g of talc or alternative chemical agents.

Future research should involve a prospective study with a larger sample size, conducted under controlled conditions, to assess the response of different BC subtypes to TP treatment.

Abbreviations

ATS – American Thoracic Society
BC – Breast cancer
BTS – British Thoracic Society
ER – Estrogen ceceptor
HER2 – Human epidermal growth factor 2 receptor
MPE – Malignant pleural effusion
PR – Progesterone receptor
TP – Talc pleurodesis

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

TALK PLEURODEZA U TERAPIJI MALIGNIH PLEURALNIH IZLIVA IZAZVANIH KARCINOMOM DOJKE

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Uvod: Karcinom dojke (*engl.* BC) je najčešći maligni tumor i vodeći uzrok smrti od malignih bolesti kod žena u Srbiji. Česta manifestacija metastatskog BC je MPE. Među solidnim tumorima, BC je drugi najčešći uzročnik MPE, sa prevalencom od 25%. Prema aktuelnim smernicama, TP je terapija izbora za većinu pacijenata sa MPE. Cilj našeg istraživanja je procena uspešnosti TP kod pacijenata sa MPE zbog BC.

Ispitanici i metode: Istraživanje je dizajnirano kao retrospektivna studija. Studijom je obuhvaćen ukupno 21 ispitanik sa metastatskim BC i MPE. Svi pacijenti uključeni u studiju bili su hospitalizovani na Klinici za grudnu hirurgiju Univerzitetskog kliničkog centra u Nišu, tokom 2023. godine. Efikasnost TP smo procenjivali na osnovu unapred definisanih kliničkih i radiografskih kriterijuma.

Rezultati: TP je bila uspešna kod 15 ispitanika (71,4%). Luminalni B BC je bio najzastupljeniji u uzorku (42,9%). U većini slučajeva MPE je bila serozna (71,4%) i ipsilateralna (61,9%) u odnosu na stranu primarnog tumora dojke. Citologija pleuralnog punktata je bila pozitivna u 28,6% slučajeva.

Zaključak: TP je uspešna metoda lečenja MPE izazvanih BC. U osnovi MPE uglavnom leži Luminalni B BC. Pacijenti najčešće imaju ipsilateralnu, seroznu MPE.

Ključne reči: maligna pleuralna efuzija, karcinom dojke, torakodrenaža, talk pleurodeza.

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