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ORIGINAL RESEARCH ARTICLE

Thermochemotherapy with epirubicin for recurrent non-muscle invasive bladder cancers: A pilot study using the UniThermia system

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Abstract

Introduction: Bladder cancer (BC) ranks as the 10th most common cancer globally, predominantly affecting older adults. Non-muscle invasive BC (NMIBC) are known for high recurrence and progression rates despite standard treatments.
Objective: This study assesses the efficacy of chemohyperthermia with epirubicin in Bacillus Calmette–Guérin (BCG)-naïve patients with either primary or recurrent NMIBC.
Methods: We conducted a prospective pilot study on this cohort using the bladder wall thermochemotherapy – UniThermia platform, with a follow-up period of 24 months. Nine NMIBC patients (88.89% male; mean age: 70.22 ± 11.82 years) were prospectively enrolled. Inclusion criteria were NMIBC stage Ta–T1 with BCG-naïve status; patients with carcinoma *in situ* (CIS) were excluded.
Results: Tumor staging revealed pTa in six patients and pT1 in three patients; tumor grading included G1 (11.11%) and G2 (88.89%). No CIS was detected. All patients received six weekly chemohyperthermia instillations. At the 24-month follow-up, four patients (44.4%) achieved a complete response with no recurrences; all remained alive with no disease progression. All recurrences were low-grade pTa.
Conclusion: These findings suggest that chemohyperthermia with epirubicin may offer therapeutic advantages over intravesical BCG or conventional chemotherapy, especially for BCG-intolerant or refractory patients. Study limitations include the small sample size and limited follow-up duration. Further multicenter studies are warranted to validate these preliminary results. Overall, chemohyperthermia with epirubicin appears to be a promising alternative for the management of recurrent NMIBC when standard BCG treatment is ineffective or unavailable.

Keywords: Chemohyperthermia; Epirubicin; Intermediate-risk bladder cancer; Non-muscle invasive bladder cancer

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1. Introduction

Bladder cancer (BC) is one of the most common malignancies of the urinary tract, ranking 10th in global cancer incidence,[1] with approximately 573,000 new cases diagnosed annually, and second after prostate cancer.[2] This condition is often identified at advanced ages, with the average patient being approximately 73 years old at the time of detection.

Non-muscle invasive BC (NMIBC) represents the majority of BC cases and has a significant impact on public health.[3] This type of cancer is characterized by an increased risk of recurrence and progression, which requires careful and individualized management. Transurethral resection of bladder tumor (TURBT) is considered the gold standard for both diagnosis and initial treatment of NMIBC. The procedure allows the excision of visible tumors and the collection of tissue samples for histopathological examination, which is essential for the correct staging of the disease.[3]

However, TURBT alone is not sufficient to prevent disease recurrence and progression. Data show that up to 70% of patients may experience recurrence and approximately 10 – 30% progress to more invasive stages of the disease. Thus, to reduce these risks, adjuvant treatments are required post-TURBT.[4-6] Adjuvant intravesical treatments, such as Bacillus Calmette–Guérin (BCG) instillations and chemotherapy with mitomycin C (MMC) or epirubicin (EPI), have shown efficacy in reducing recurrence and delaying progression.[7,8] However, in many countries, including Romania, BCG has been either unavailable or not approved for extended periods.

Given these limitations and challenges in the management of recurrent NMIBC, we conducted a prospective pilot study to investigate the oncological outcomes of an alternative therapeutic approach. This study focused on BCG-naïve patients, that is, those who had not received BCG treatment and were undergoing EPI chemohyperthermia treatment for recurrent tumors.

Chemohyperthermia is an innovative method that combines intravesical administration of EPI with the local application of heat. This combination has the potential to increase treatment efficacy by improving drug penetration into tumor tissues and by inducing a more pronounced cytotoxic effect on cancer cells. In a recent narrative review, Gurram and Rathi[9] observed a lack of data regarding the use of the Unithermia system in BC treatment and noted that none of the existing studies used EPI as a chemotherapeutic agent. As we have recently demonstrated, EPI is an underutilized agent that may serve as an effective alternative in selected cases.[10]

Through this pilot study, we aimed to generate preliminary data to further understand the therapeutic potential of EPI-based chemohyperthermia in both recurrent and primary NMIBC. Our objective was to evaluate the feasibility of this therapy in reducing recurrence and bladder tumor lesion progression. The results of this study could offer new insights into post-TURBT adjuvant treatment and help guide future clinical practices aimed at improving the prognosis and quality of life for patients with NMIBC.

2. Materials and methods

The study was conducted at the County Clinical Hospital from Targu Mures, Clinical Urology Department, between June 2021 and January 2022. The study included a follow-up period of 24 months to evaluate the medium-term oncological results of the patients undergoing the treatment studied. We aimed to include a maximum of 10 patients, with each patient receiving treatment using six single-used Unithermia catheters.

2.1. Inclusion criteria

The following criteria were used to select patients eligible for the study:

(i) BCG-naïve patients, that is, those who had not previously received BCG treatment and were undergoing EPI chemohyperthermia treatment for recurrent tumors.
(ii) Histopathological diagnosis of NMIBC at stage Ta–T1.
(iii) Consecutive patients who provided informed consent to enroll.

2.2. Exclusion criteria

Patients were excluded based on the following criterion:

(i) Patients with carcinoma *in situ* (CIS), due to its distinct biological behavior and the need for specific treatment.

2.3. Treatment protocol

Eligible patients underwent six weekly chemohyperthermia instillations using the bladder wall thermochemotherapy (BWT) – UniThermia platform (Figure 1). All treatments were performed by a single surgeon trained in the use of the platform.

In this study, a simple method was used to heat and recirculate the instilled substance at constant pressure and a temperature of 44.5°C for 50 min, using the UniThermiaVR system (Elmedical, Israel[11]).

The device combines chemotherapy treatments with controlled heat therapy to enhance treatment efficacy and

Figure 1. The UniThermia platform for bladder wall thermochemotherapy

reduce cancer drug resistance. It features advanced systems for monitoring the patient's body temperature during hyperthermia sessions, ensuring both safety and comfort. The system is equipped with multiple sensors and safety mechanisms that continuously monitor the patient's vital parameters and respond promptly if needed. The device has an intuitive interface for operators, allowing quick setup of treatment parameters and real-time progress monitoring. Designed for maximum patient comfort, it incorporates ergonomic materials and a layout suitable for extended treatment sessions. The system is applicable to a range of oncological treatments and can be tailored to the specific needs of each patient and treatment protocol. It complies with international standards for safety and efficacy in oncological care and is currently available in Switzerland, Germany, Spain, Turkey, Italy, the Czech Republic, Croatia, France, Netherlands, Austria, Romania, and Israel.

The BWT system is unique in that the heat content of the circulating drug solution exceeds that required for transfer to the thermally conductive bladder wall. High heat, maintained at a constant non-ablative temperature, ensures optimal efficacy without causing tissue damage. No burns occur, as the bladder lumen temperature remains below 45°C. These simple principles enable precise and uniform hyperthermia throughout the bladder lumen, despite individual variations in blood perfusion and tissue characteristics. In addition, the system's simple control mechanism effectively compensates for dynamic changes that occur over time (such as vasodilation), without the need for manual or software adjustments.

As part of the adjuvant therapy, patients received 50 mg of EPI. The temperature was monitored using a thermometer located at the tip of the catheter. Operating on the principle of conductive heating, the system is designed to achieve an even distribution of temperature throughout the bladder, eliminating hot or cold spots.

2.4. Patient assessment and monitoring

During the 24-month follow-up period, patients were periodically monitored to assess their response to treatment and detect possible tumor recurrences. The assessment protocol included control cystoscopy at regular intervals (3, 6, 12, and 24 months). Additional cross-sectional imaging (e.g., bladder ultrasound and computed tomography) was performed in cases where recurrence was suspected.

2.5. Statistical analysis

The collected data were statistically analyzed to determine the rates of tumor recurrence and progression, as well as to assess the safety and tolerability of the treatment. Relevant clinical and oncological parameters, including disease-free survival and overall survival, were also evaluated. Statistical analysis was performed using STATA 11.0 (StataCorp, United States of America).

2.6. Ethics and informed consent

The study was approved by the Ethics Committee of the G.E. Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures (approval no. 1147, dated October 15, 2020). All patients underwent TURBT according to standard protocols and provided written informed consent. The decision to administer EPI as an adjuvant treatment was made by an oncology committee consisting of a urologist and an oncologist. As the local standard of care at the time involved TURBT followed by six weekly EPI instillations, patients consented to receive this standard treatment with the addition of hyperthermia.

3. Results

3.1. Characteristics of patients

A total of nine patients with a history of NMIBC were included in this study. Of these, eight (88.89%) were men. The mean age of the patients was 70.22 ± 11.82 (median: 74.00) years, with an average range of 50 – 83 years. Five patients had primary tumors, and four had a history of tumor recurrence, with the number of previous episodes varying between one and three. These characteristics are summarized in Table 1. No treatment-related adverse events or complications were reported during follow-up.

3.2. Tumor stage and grade

At the initiation of hyperthermia treatment, most patients (n = 6) had NMIBC classified as stage pTa, while three patients were at stage pT1. The tumors demonstrated a low or moderate degree of malignancy, with histological grades of G1 (11.11%) or G2 (88.89%). No CIS was detected in any of the cases during the follow-up period.

Table 1. Characteristics of patients treated with hyperthermia

Patient	Sex	Age	Previous TURBTs	Stage	Grade	No. instillations with hyperthermia	Recurrence after TURBT
1	M	50	1	pT1	G1	6	No
2	M	66	1	pTa	G1	6	No
3	F	77	2	pTa	G1	6	Yes
4	M	83	2	pT1	G2	6	Yes
5	M	79	3	pT1	G2	6	Yes
6	M	83	2	pT1	G1	6	Yes
7	M	57	1	pTa	G1	6	No
8	M	74	2	pTa	G1	6	Yes
9	M	63	1	pTa	G1	6	No

Abbreviations: F: Female; M: Male; No.: Number; TURBT: Transurethral resection of bladder tumor.

Table 2. Association between age and clinicopathological factors

Age	Stage before other chemotherapy		Sex		Stage at hyperthermia		Grade at hyperthermia		Recurrence	
	Ta	T1	Female	Male	Ta	T1	Low grade	High grade	No	Yes
<70 years	4	0	0	4	3	1	4	0	4	0
≥70 years	2	3	1	4	3	2	3	2	0	5
Total	6	3	1	8	6	3	7	2	4	5
	p=0.058		p=0.343		p=0.635		p=0.151		p=0.003	

3.3. Response to treatment and subsequent evolution

At the 24-month follow-up, a complete response (i.e., no recurrence) was observed in four of the nine patients included in the study, representing 44.4% of the cohort. No patients with an initial G1 tumor developed recurrence during follow-up. In addition, all patients in the complete response group were alive at the end of follow-up, with no evidence of tumor progression. All recurrences were of low-grade pTa tumors. Associations between age and clinicopathological factors are presented in Table 2.

Age ≥70 years at the time of hyperthermia was not associated with sex, grade, or stage, but was significantly associated with a higher rate of recurrence (p=0.003). All recurrences occurred in elderly patients (≥70 years), while younger patients (<70 years) exhibited a 100% response to hyperthermia with EPI.

Kaplan–Meier estimates of recurrence-free survival over 24 months following hyperthermia treatment showed a significant decline in recurrence-free survival within the first 6 months. This decline continued gradually up to 12 months, after which the probability of remaining recurrence-free stabilized at approximately 50% (Figure 2). This pattern suggests that most recurrences occur within the first year post-treatment, with the risk of recurrence decreasing considerably thereafter.

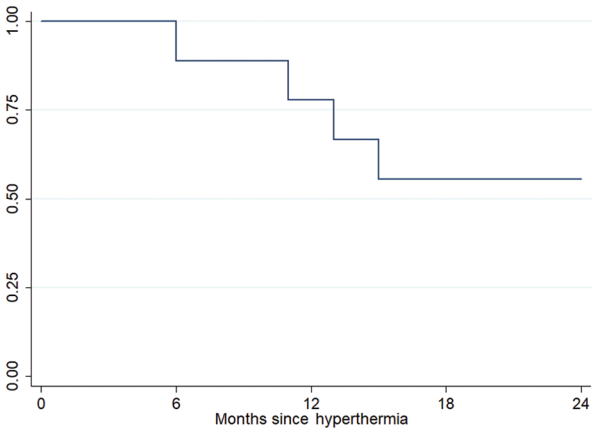

Figure 2. Kaplan–Meier estimate of recurrence-free survival after hyperthermia

Kaplan–Meier analysis stratified by age demonstrated a significant difference in recurrence-free survival. Patients younger than 70 years experienced no recurrences within the 24-month follow-up, maintaining a 100% probability of recurrence-free survival. In contrast, all patients over 70 years of age exhibited a progressive increase in recurrence rate, with recurrences occurring in all individuals within 16 months post-treatment. The risk of recurrence was significantly higher in patients aged ≥70 compared to their younger counterparts (log-rank p=0.014, Figure 3).

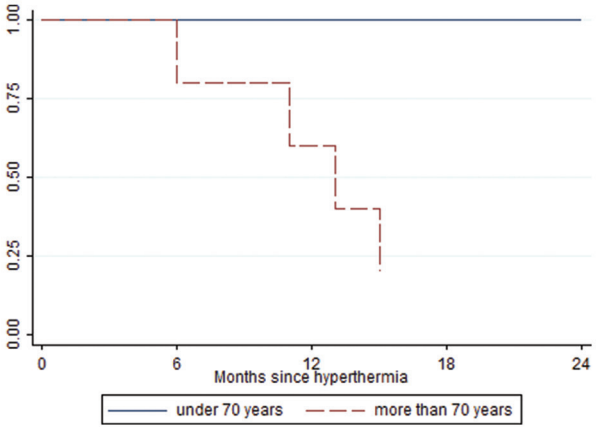

Figure 3. Kaplan–Meier estimate of recurrence-free survival by age

4. Discussion

4.1. Interpretation of results

The results obtained in this pilot study provide valuable insights into the feasibility of chemohyperthermia treatment using EPI in BCG- naïve patients with recurrent non-muscle-invasive bladder tumors.[12-18] The complete response rate (44.4%) observed indicates promising potential for this therapeutic approach in controlling tumor recurrences in this patient population. Moreover, the absence of tumor progression and mortality in the complete responder subgroup suggests that this treatment may offer significant benefits in terms of survival and quality of life. A recent study reported outcomes of UniThermia with EPI in BCG-unresponsive patients. Two Swiss centers observed that, after a median follow-up of 28 months (range: 4 – 59), 25 out of 39 patients (64%) experienced no recurrence within the bladder.[19]

However, these results are modest in comparison to the largest BCG trial, which, at a median follow-up of 7.1 years, reported that 587 patients (43.3%) experienced recurrence, of which 37.4% had Ta/T1 recurrence, 6.7% had CIS, 8.0% progressed to ≥pT2 tumors, and 67 (4.9%) developed distant metastases.[20]

4.2. UniThermia with MMC

The group from the Urology Department in Turin published initial results on the use of UniThermia with MMC in a pilot study involving nine patients who received six weekly instillations.[21] This was followed by a report from Soria *et al.*,[22] which included patients with non-grade 3 NMIBC recurring after at least a full induction course of BCG. These patients received six weekly MMC instillations with UniThermia (®) following complete TURBT. At a median follow-up of 41 months, they reported a complete response rate of 44%. Similarly, Gözen *et al.*[23] reported favorable outcomes using 80mg of MMC in a 6-week induction course followed by maintenance therapy. Among the 18 patients with high-risk NMIBC, 83% remained disease-free at one year.

On the other hand, a propensity-matched study by Ekin *et al.*[24] comparing UniThermia to BCG found no significant difference in the odds of recurrence and progression between the two treatments. Based on our pilot study, the findings align with those reported in the MMC cohorts, suggesting that EPI is a viable and effective chemotherapeutical agent when used with the UniThermia platform.

4.3. Comparison with other therapeutic options

Compared with other therapeutic options available for recurrent NMIBC, such as intravesical BCG instillations or classical chemotherapy, EPI chemohyperthermia presents some potential advantages.[13-18] While BCG remains the gold standard for this condition, Chiujdea *et al.*[10] in their review, conducted a comprehensive comparison between these two agents. Nine studies evaluated the recurrence and progression rates of patients treated with EPI compared to those receiving BCG instillations. These studies encompassed a total of 1,422 patients, including 316 females. Prognostic factors considered in these studies included age, gender, tumor stage (pTa–pT1), and grade (G1–G3). The findings indicated a lower recurrence rate for patients treated with BCG instillations. However, with regard to progression, the studies observed either limited or no significant differences between the two treatments. Compared to the treatment with EPI, intravesical BCG instillations have specific disadvantages. While EPI has side effects, they are generally better tolerated and more predictable than those of BCG. For example, BCG can cause severe systemic reactions, including systemic infections and sepsis, which are rare with EPI. BCG may induce fever, chills, and flu-like symptoms, which can be debilitating. EPI, on the other hand, may cause nausea, vomiting, and hair loss, but systemic flu-like symptoms are less common. In addition, as BCG is a live attenuated bacterium, there is a risk of infection, especially in immunocompromised patients. EPI, being a chemotherapeutic agent, does not pose this risk. BCG can also lead to the development of granulomatous cystitis, a specific form of chronic inflammation, not observed with EPI treatment. Moreover, BCG, as an immunotherapeutic agent, can trigger immune reactions that, while beneficial in controlling cancer, may be unpleasant or even severe. EPI, as a chemotherapeutic, has a different adverse reaction profile, characterized more by hematological toxicity and mucositis, with fewer immune-related side effects. The BCG treatment regimen involves multiple instillations and a more intense schedule of clinic

visits, which can be less convenient for patients. In contrast, EPI can be administered in a simpler and less frequent regimen. Furthermore, patients with certain conditions, such as active urinary tract or bladder infections, cannot receive BCG until the infection is resolved. EPI also has contraindications, but these are generally different and better understood.[25-34]

Aging appears to be linked to a higher risk of recurrence and progression in cases of pure CIS of the bladder. Elderly patients may respond less effectively to BCG therapy. Given the limited data available in the literature, further research is needed to assess not only the impact of age but also the influence of other factors, such as body mass index, multifocality, and the origin of CIS (primary or secondary), on disease recurrence and progression.[35]

The United States Food and Drug Administration has approved N-803 (Anktiva), a first-in-class interleukin-15 receptor agonist immunotherapy, to be used with BCG for treating patients with BCG-unresponsive NMIBC with CIS. This approval is based on findings from the QUILT-3.032 trial, which demonstrated significant clinical benefits. In cohort B of the trial, the combination therapy resulted in a complete response rate of 62% to 73% among 77 evaluable patients, with the duration of complete response exceeding 47 months at the time of data cutoff. In addition, 58% of patients maintained a response for 12 months or longer, and 40% for 24 months or longer.

The trial included patients with BCG-unresponsive high-grade Ta/T1 papillary NMIBC. The primary endpoints were complete response incidence and disease-free survival, with secondary endpoints including durability, cystectomy avoidance, progression-free survival, disease-specific survival, and overall survival. Previous data showed a complete response rate of 71% in cohort A, with a median follow-up of 23.9 months and a median duration of complete response of 26.6 months.

N-803 demonstrated a favorable safety profile, with most treatment-emergent adverse events being mild to moderate. This approval follows a previous FDA decision to decline approval due to deficiencies in the manufacturing process, which have since been addressed by ImmunityBio.

The approval of N-803 marks a significant advancement in NMIBC treatment, potentially establishing a new standard of care and improving outcomes for patients with this challenging condition.[36]

Overall, although both treatments have their risks and benefits, BCG presents specific disadvantages related to its immunotherapeutic nature and risk of infections, whereas EPI, as a chemotherapeutic agent, has a different side effect profile. The choice of optimal treatment should be based on an individual assessment of the patient, the stage of the disease, and tolerance to treatment. Early detection of BC using risk calculators may help to identify aggressive diseases in a timely manner to ensure the most appropriate treatment is administered.[37] In addition, pathological characteristics are fundamental in decision-making.[38]

In certain cases, patients become refractory to treatment or develop intolerance or severe complications. In addition, classical chemotherapy may be associated with significant side effects and may have limited efficacy in controlling tumor recurrences. In this context, chemohyperthermia with EPI represents a promising alternative, offering a viable management option for patients who do not respond to or tolerate other therapeutic strategies.

4.4. Hyperthermia and BC treatment

Recent studies[39] have shown that hyperthermia can modulate heat shock protein expression, immune activation, and DNA repair pathways, which may affect treatment outcomes. Understanding these mechanisms could help refine patient selection and optimize treatment protocols, potentially increasing the efficacy of EPI-based chemohyperthermia in the treatment of BC. To establish chemohyperthermia with EPI as a viable alternative to BCG, future studies should increase sample sizes and conduct randomized controlled trials comparing EPI with BCG and MMC-based chemohyperthermia. Further investigation into age-related differences in treatment response, using molecular profiling, is needed to understand why older patients experience higher recurrence rates. Moreover, long-term follow-up studies are essential to determine the true durability of treatment responses. This study provides important preliminary evidence that EPI chemohyperthermia using the BWT UniThermia system may be a promising alternative for NMIBC patients who are BCG- naïve, intolerant, or unresponsive to standard therapies. The results suggest that this approach effectively reduces the risk of relapse, particularly in younger patients, and may help prevent progression to muscle-invasive disease. However, larger, well-controlled studies are needed to confirm these findings, refine patient selection criteria, and determine the long-term safety and efficacy of EPI-based chemohyperthermia. If future studies validate these findings, this method could become an important addition to NMIBC treatment strategies, particularly in settings where BCG therapy is unavailable or inappropriate.

Nevertheless, it is important to acknowledge the limitations of this study, including the relatively small sample size and limited follow-up period. The lack of a control group (e.g., BCG- or MMC-treated patients) makes it difficult to directly compare the efficacy of EPI chemohyperthermia with standard treatments. The

24-month follow-up provides mid-term data, but a longer follow-up is necessary to determine long-term recurrence and progression rates. In addition, the study did not investigate potential biomarkers that could predict treatment response, nor did it report on patient-reported outcomes (e.g., quality of life, urinary symptoms), which would be valuable for assessing treatment tolerability. Further studies with larger samples and a longer follow-up period are required to confirm and validate the current findings. In addition, an evaluation of cost-effectiveness compared to other therapeutic regimens could provide new insights into the optimal management of recurrent NMIBC. It is also important to note that none of the patients in this study had the opportunity to benefit from BCG immunotherapy, a treatment recognized for its effectiveness in NMIBC. This limitation was due to Romanian legislation, which, at the time, did not approve the use of BCG therapy. In addition, the special catheters for UniThermia were not reimbursed by health insurance. This situation highlights the impact of legal and financial constraints on the treatment options available to patients in certain regions or countries.

In the future, integration of EPI chemohyperthermia into clinical practice guidelines may be warranted if further studies confirm and extend the findings of this pilot study.

However, it is important to recognize that the results of the current study are preliminary and require further validation through multicenter studies involving larger patient cohorts. These studies could confirm the benefits of EPI-based chemohyperthermia and, more precisely, evaluate its role in the therapeutic algorithm for recurrent NMIBC. In addition, investigating the long-term effects of the treatment and assessing its associated costs are essential for determining the place of chemohyperthermia in routine clinical practice.

5. Conclusion

Chemohyperthermia with EPI emerges as a promising therapeutic option for patients with recurrent NMIBC, particularly in cases where BCG treatment is unavailable or ineffective. The outcomes of this pilot study highlight the feasibility of this approach, demonstrating a significant complete response rate with no evident tumor recurrence in BCG-naïve patients.

Our findings emphasize age as a critical risk factor for recurrence-free survival following hyperthermia, showing that older patients are significantly more likely to experience recurrence shortly after treatment. These results suggest that post-hyperthermia monitoring and treatment strategies should prioritize increased surveillance and potentially additional interventions for older patients.

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Conflict of interest

Mihai Dorin Vartolomei is an Editorial Board Member of this journal but was not involved in the editorial or peer-review process for this paper, either directly or indirectly. Separately, all other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: All authors
Formal analysis: All authors
Investigation: All authors
Methodology: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures (Approval No. 1147/15/10/2020). All patients included in the study provided informed consent to participate.

Consent for publication

Informed consent was obtained from all subjects involved in the study to publish their data.

Availability of data

The data presented in this study are available from the corresponding author on request. Any reproduction, in whole or in part, of the results and article content is prohibited without the consent of all authors.

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