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Pegylated liposomal doxorubicin with magnetothermy modification treatment, if available microcalcifications group for advanced chemoresistant breast cancer

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Abstract

Mammary microcalcifications group (MCG) are 5 and more deposits <0.5 mm in diameter within the breast tissue on the site 1-2 cm^2. MCG may play a prognostic role in breast carcinomas, and have worse outcomes compared with those without MCG. When compared to the monoeffects of the nanocomplex and officinal doxorubicin, the combination action of the manufactured nanocomplex anti-cancer medicine and local radio-frequency hyperthermia has been found to commence the propensity for an increase in the growth inhibition of breast cancer cells. to disclose details on the mammary microcalcifications group and their association with the development of advanced resistant breast cancer and treatment answer, including particular treatment possibilities with magnetothermy and pegylated liposomal doxorubicin. We checked out and treated 50 advanced resistant breast cancer patients (after 4 cycles of TC), with RECIST determining stability or progression: we drew attention to the fact that there were areas in breast tumor with groups of residual microcalcifications in primary tumor mammographically in the first group of 25 patients with residual edema; in the second group of 25 patients with residual edema without microcalcification groups (MCG). All patients were treated with pegylated liposomal doxorubicin (PLD) 50 mg/m2 every 4 weeks - a total of 4 cycles - and Magnetothermy (Regional inductive moderate hyperthermia) by MagTherm (Radmir, Kharkiv, Ukraine) - device generated electromagnetic fields with an operating frequency of 26.16±0.16 MHz and output power of 70 W during 30 minutes with monitoring of the skin temperature in the area of the electromagnetic field. The final proportion of viable tumor tissue (FPVCT), including the percentage of edema reduction. The first group was 22.9 ± 4.2%, whereas in the second group it was 24.8 ± 5.1% ($p>0.05$). In the fifth year of observation, there was a significant difference in the recurrence-free indicator between the first and second groups, with 46.8% vs 59.1%.There was a trend in the first group to have poorer overall survival than the second group. In the fifth year of observation, there was a substantial difference in the indicator between the first and second patient groups, with 52.4% versus 69.2%. MCG detection might increase their prediction usefulness by determining their malignancy and immune-histo-chemical origin. In order to overcome chemoresistance in advanced Lum B1 breast cancer, various modifiers of antitumor therapy can be used, as well as their combinations, such as magnetothermy (MT), as well as the use of liposomal pegylated forms of chemotherapy drugs, in particular liposomal Doxorubicin. Microcalcifications groups absence leads to perform more organ-preserving and oncoplastic surgical interventions for advanced resistant breast cancer patients after proposed line of PLD modified Magnetothermy.

Keywords: advanced resistant breast cancer, microcalcifications group, pegylated liposomal doxorubicin, magnetothermy

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1. Introduction

Mammary microcalcifications group (MCG) are 5 and more deposits <0.5 mm in diameter within the breast tissue on the site 1-2 cm^2 [1]. MCG may play a prognostic role in breast carcinomas, and have worse outcomes compared with those without MCG, ideas may provide light on the vital importance of detecting MCG inside an advanced breast tumors on pathology reports, the presence, composition, and

type of MCG in breast lesions might affect the outcome. The existence and morphological features of MCG in breast lesions be correctly recorded to guide appropriate therapeutic decision-making [2].

When implementing new methods and combinations of treatment for this aggressive form of breast cancer, to take into account all unfavorable factors, that may worsen the final results of treatment. Cancer cells are abnormally behaving normal cells that exist outside of the reality of life and death. Some scientists believe that their self-sufficiency and self-management are an evolutionary process in cell division. Cancer cells, like organisms that evolve via natural selection and mutation, advance to malignancy by selective transformation [3]. The truly essential mammographic aspects, such as the morphologies of individual microcalcifications and the morphology of clusters, were abstracted from their histological context and were sometimes not explored at all or minimally [4]. MCG are widely detected on mammograms, and as a result, there are well-described radiographic patterns that aid in distinguishing calcifications, particularly against the backdrop of edema [5].

Calcifications associated with cancer are often tiny and require magnification to be seen clearly. The distinction between types is essential since research indicates that type II is frequently connected with malignant lesions [6]. In clinical reality, and according to a recent literature analysis, when breast cancer patients are resistant to conventional regimens, even reserve medications do not provide the predicted tumor response to therapy [7].

In some circumstances, the use of pegylated liposomal versions of drugs, particularly doxorubicin, which offers targeted drug delivery to tumor cells, appears highly promising [8]. When compared to the monoeffects of the nanocomplex and officinal doxorubicin, the combination action of the manufactured nanocomplex anti-cancer medicine and local radio-frequency hyperthermia has been found to commence the propensity for an increase in the growth inhibition of breast cancer cells [9]. The magnetic component of the electromagnetic field is regarded an essential influence in induction heating and non-thermal effects on tumors utilizing a frame applicator, which is one of the characteristics of magnetothermy. [10]. Magnetothermy using a frame applicator heats tissues with a high density of blood and lymphatic vessels more than fat tissue. At the same time, there is an electrical component in the applicator's electromagnetic field that contributes to the therapeutic benefits [11].

The aim - to disclose details on the mammary microcalcifications group and their association with the development of advanced resistant breast cancer and treatment answer, including particular treatment possibilities with magnetothermy and pegylated liposomal doxorubicin.

2. Materials and methods

We checked out and treated 50 advanced resistant breast cancer patients (after 4 cycles of TC), with RECIST determining stability or progression: we drew attention to the fact that there were areas in breast tumor with groups of residual microcalcifications in primary tumor mammographically *in the first group* of 25 patients with residual edema; *in the second group* of 25 patients with residual edema without microcalcification groups (MCG).

All patients were treated with pegylated liposomal doxorubicin (PLD) 50 mg/m2 every 4 weeks - a total of 4 cycles - and Magnetothermy (Regional inductive moderate hyperthermia) by MagTherm (Radmir, Kharkiv, Ukraine) - device generated electromagnetic fields with an operating frequency of 26.16±0.16 MHz and output power of 70 W during 30 minutes with monitoring of the skin temperature in the area of the electromagnetic field – Figure 1. Patients of both groups received major surgery after completing a full course of PLD treatment modified by magnetothermy.

3. Results and discussion

MCG (microcalcifications group) has a distinct form known as magnesium-substituted hydroxyapatite (Mg-HA). This kind was shown to be strongly related with malignancy, with MCG being connected with 100% of malignant lesions displaying complicated forms of MCG.

Immune-histo-chemical results of biopsies from microcalcifications groups, there are the most patients with Lum B1 - 48.00±5.24% and 52.00±6.81% in both groups (first and second respectively). Triple negative approximately the same number of patients in both groups - Table 1. Most patients were performed mastectomy with wound edges mobilization and "negative margins" determination. When it was impossible to mobilize wound edges with subsequent adequate closure of defects, Handelheim or Beck flaps mobilization technique was used: 6 - in the first group, and 3 - in the second group. Mastectomy with single-stage reconstruction with a TRAM flap deserves special attention: 2 (8.00±1.23 %) and 5 (20.00±2.12%), respectively. As a result, we can observe that in the absence of microcalcification groups, more organ-preserving and oncoplastic surgical treatments are conceivable for advanced resistant breast cancer patients after proposed afterline of PLD modificated Magnetothermy – Table 2. The following averaged statistical data of the indicators, characterizing patho-morphosis in both groups, who received neo-adjuvant chemotherapy according to generally accepted traditional schemes, depending on the subtype - were used to calculate the final proportion of viable tumor tissue (FPVCT), including the percentage of edema reduction. The first group was 22.9 ± 4.2%, whereas in the second group it was 24.8 ± 5.1% ($p>0.05$) – Figure 2. Previous study found that the pattern of MCG on mammography and MRI after neoadjuvant therapy exaggerated the true extent of the troublesome lesion [12], so like in our investigation. There were no significant differences in recurrence-free survival between the first and second groups across the two-year study period. Beginning in the third year, there was a trend in the first group to reduce the recurrence-free survival indicator when compared to the second group of patients. In the fifth year of observation, there was a significant difference in the indicator between the first and second groups, with 46.8% vs 59.1%. - Figure 3. When compared to the first group, the second group had a higher recurrence-free survival rate.

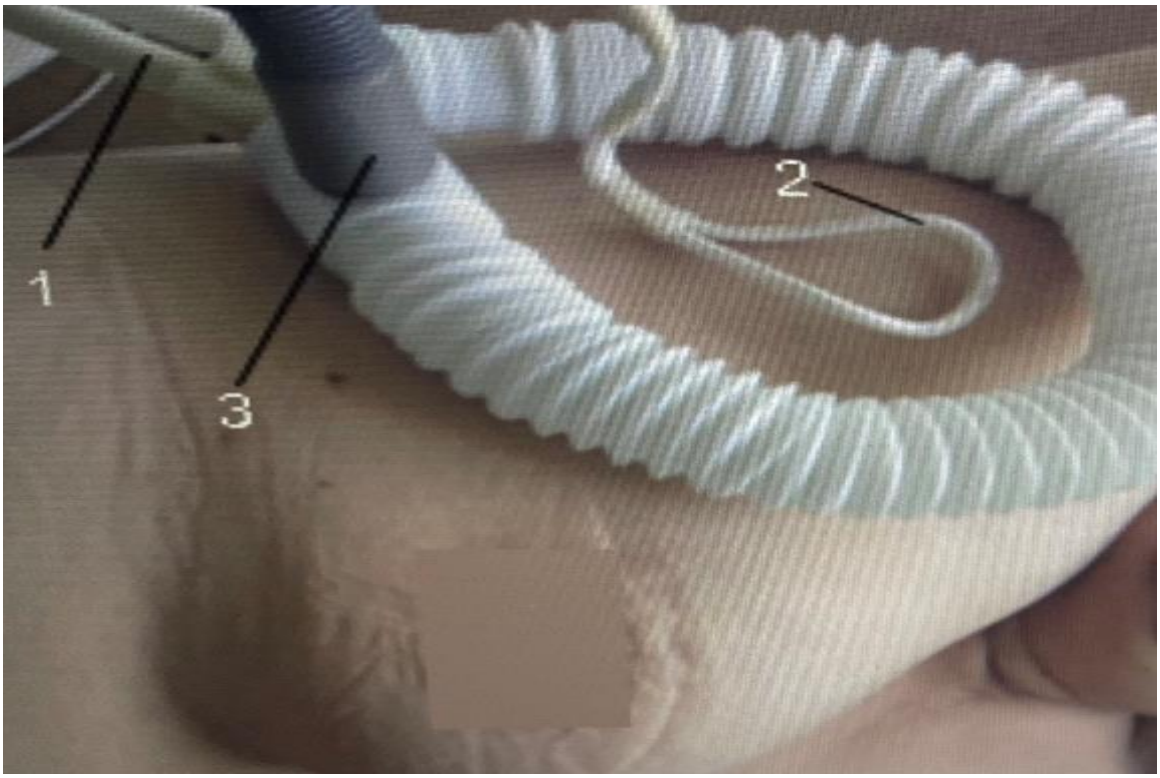

Figure 1. Typical arrangement of a patient with advanced breast cancer during an Magnetothermy session: Applicator of the "Magneterm" device:
1-main circuit; 2-additional circuit; 3-cooling supply

Table 1. Immune-histo-chemical subtypes, p<0,05

Subtypes	Group 1		Group 2	
	n	%	n	%
Lum A	5	20.00±2.12	1	4.00±0.72
Lum B1	12	48.00±5.24	13	52.00±6.81
Triple negative	8	32.00±3.93	11	44.00±5.16
All	25	100.00	25	100.00

Table 2. Surgical treatment types

	Group 1 (MCG)	Group 2 (non-MCG)
Mastectomy with wound edges mobilization	12 (48.00±2.12 %)	10 (40.00±4,65 %)
Mastectomy with Handelheim or Beck flap mobilization	6 (24.00±3.74 %)	3 (12.0±2.26 %)
Mastectomy with single-stage reconstruction	2 (8.00±1.23 %)	5 (20.00±2.12%)
Mastectomy with combined plastic surgery	5 (20.00±2.12%)	7 (28.00±4.24 %)
All	25 (100.00 %)	25 (100.00 %)

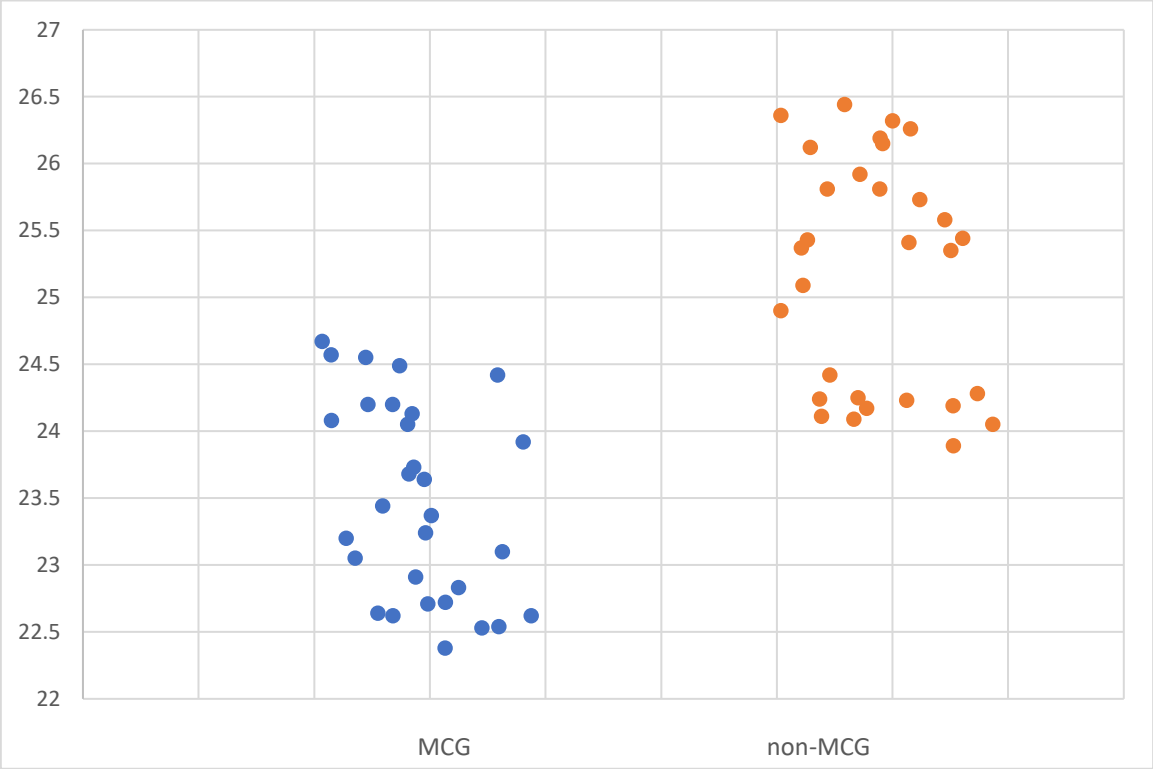

Figure 2. Dynamics of pathomorphosis - final proportion of viable tumor tissue (FPVCT)

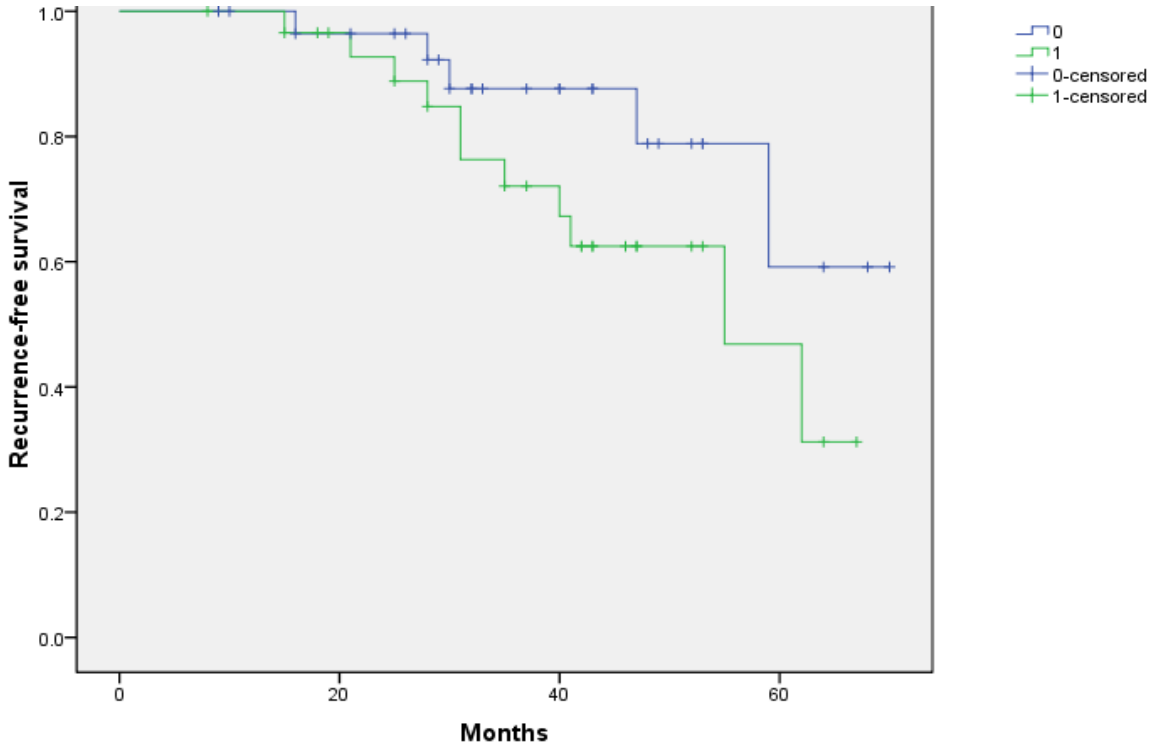

Figure 3. Recurrence-free survival: green curve (first group); blue curve (second group)

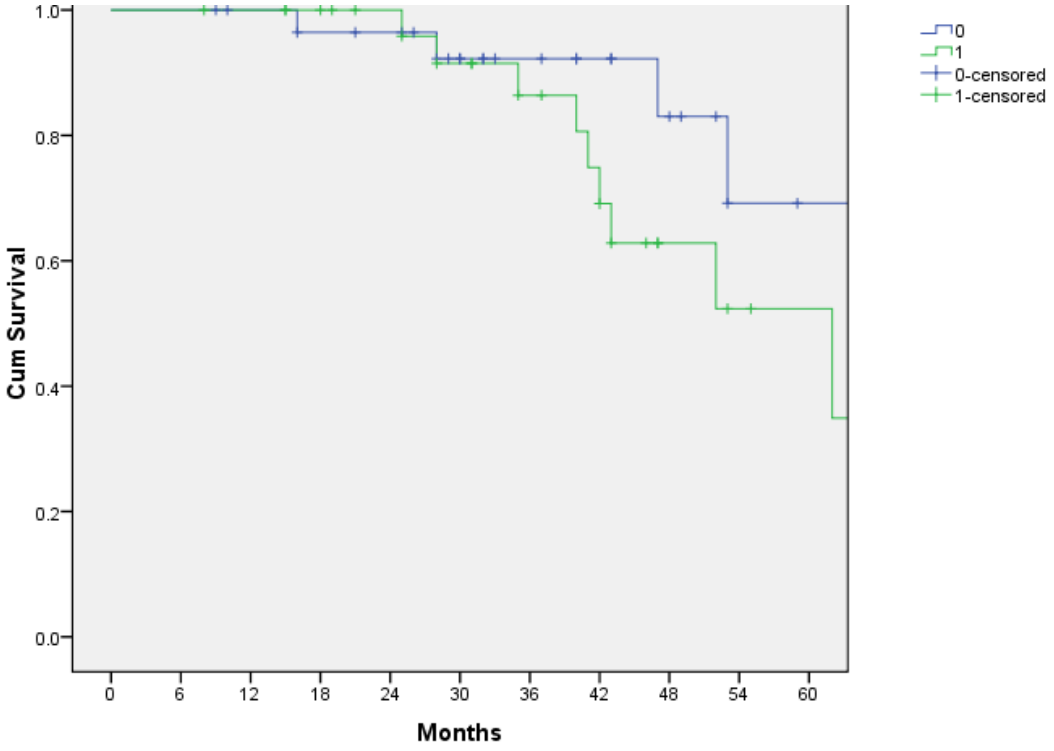

Figure 4. Overall survival: green curve (first group); blue curve (second group)

There were no significant differences in the overall survival of the first and second patient groups throughout the three-year monitoring period. Beginning in the fourth year, there was a trend in the first group to have poorer overall survival than the second group. In the fifth year of observation, there was a substantial difference in the indicator between the first and second patient groups, with 52.4% versus 69.2%. - Figure 4. When microcalcifications groups focused detection during mammography in the breast glands for the first patient group, it became able to adequately establish a diagnosis, including tumor subtype, and execute a more or less timely special combination therapy.

MCG is difficult to detect and interpret since, even in advanced resistant breast cancer, there is typically only one cancer lesion. Because small, grouped MCG are easy to ignore and misinterpret [13]. Tabár et al. show, that the presence of MCG in advanced breast carcinomas gives a poorer result in terms of metrics [14], and corresponds with our results, so several contributions have gathered data about presence of MCG, particularly those of the casting-type shape in invasive advanced resistant breast cancer, is linked with poor prognosis, greater risk of death, propensity for resistant and recurrence (viable tumor tissue (FPVCT), including the percentage of edema reduction. The first group was 22.9 ± 4.2%, whereas in the second group it was 24.8 ± 5.1% ($p>0.05$; In the fifth year of observation, there was a significant difference in the indicator between the first and second groups, with 46.8% vs 59.1%). The number and extent of MCG may remain steady, shrink, or even expand depending on the tumor's response to neo-adjuvant therapy and the presence of necrosis and fibrosis, that corresponds Conti M and colleagues [15]. The majority of writers discovered no significant relationship between full pathological response and MCG patterns following neo-adjuvant treatment [16]. Therefore, the conventional approach is total removal of all undetermined or suspicious calcifications. The use of PLD in conjunction with magnetothermy in the comprehensive treatment of breast cancer patients did not result in negative changes in hemogram and biochemical blood indicators, nor did it result in the development of complications that significantly impacted the patients' overall condition or length of stay in the hospital. Chemotherapy combined with magnetothermy greatly enhanced the immediate outcomes of treatment: the number of instances of process stability increased by 21.25%, and the number of cases of partial regression increased by 12.6% [17]. The analysis of clinical studies patients treatment effectiveness and toxicity when advanced breast cancer, indicates that in the near future after chemotherapy and local magnetothermy stage II-III breast cancer patients, the number of cases of partial regression of the primary tumor increased by 36.4% and by 24.7% — regression of metastatically affected regional lymph nodes, side effects of treatment decreased compared to the group of patients who only chemo Magnetothermy patients endured 20% more organ-sparing surgeries [18]. This is the first trial to look at the efficacy of combination regimens with pegylated liposomal anthracyclines and Magnetothermy in patients with advanced resistant Luminal B1 breast cancer. When paired with Magnetothermy, PLD showed to be equally efficacious and less cardiotoxic than standard anthracyclines.

4. Conclusions

i. MCG detection might increase their prediction usefulness by determining their malignancy and immune-histo-chemical origin.
ii. In order to overcome chemoresistance in advanced Lum B1 breast cancer, various modifiers of antitumor therapy can be used, as well as their combinations, such as magnetothermy (MT), as well as the use of liposomal pegylated forms of chemotherapy drugs, in particular liposomal Doxorubicin.
iii. Microcalcifications groups absence leads to perform more organ-preserving and oncoplastic surgical interventions for advanced resistant breast cancer patients after proposed line of PLD modified Magnetothermy.

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Authors' contributions
Movchan O.Vol.(MOVol), Prof. Smolanka I.I.(SII), Lyashenko A.O. (LAO), Dosenko I.V.(DIV), Loboda A.D (LAD), Ivankova O.M.(IOM), Batryn O.V. (BOV), Movchan O.Vas (MOVas)

MOVol designed the study and wrote the manuscript. MOVol and LAD, LAO, IOM, DIV contributed to manuscript writing, images and tables. MOVol, SII, LAO critically reviewed the manuscript for important intellectual content. MOVas, BOV edited the information regarding the association of the context of the legal and ethical relations. All the authors have read and approved the final version of the manuscript. MOVol and SII confirm the authenticity of all the raw data of the paper.

Ethics approval and consent to participate
This study was approved by the institutional Ethics Committee of the National Cancer Institute of Ukraine (Minutes No. 167 of May 20, 2021).

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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