

## EFFICIENCY OF NEOADJUVANT THERAPY OF MALIGNANT TUMORS OF THE MEDIASTINAL AND CHEST WALL

### SKUTECZNOŚĆ TERAPII NEOADJUVANTOWEJ ZŁOŚLIWYCH GUZÓW ŚRÓDPIERSIA I ŚCIANY KLATKI PIERSIOWEJ

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wyszukiwanie i analiza literatury  
G. Funds collection  
zebranie funduszy

Tables: 2  
Figures: 5  
References: 10  
Submitted: 2023 March 30  
Accepted: 2023 May 30

#### Summary

**Background.** Primary tumors of the mediastinum and chest wall are heterogeneous in morphological structure, united only by anatomical localization. Considering their proximity to the vital structures of the mediastinum, their treatment is a complex task that requires a personalized approach in the selection of neoadjuvant therapy.

**Material and methods.** The results of surgical, combined and complex treatment of 1,375 patients with primary malignant tumors of the mediastinum, and 98 patients with malignant tumors of the chest wall were analyzed. Various treatment methods were used in the neoadjuvant regime: radiotherapy, thermoradiotherapy, chemoradiotherapy and intra-arterial regional chemotherapy.

**Results.** The results proved that the use of intra-arterial neoadjuvant chemotherapy (IACT) has a better degree of tumor regression ( $p < 0.05$ ) and the lowest frequency of metastases compared with the use of radiotherapy and thermoradiotherapy ( $p < 0.001$ ). When compared with the use of chemoradiation therapy, there were no statistically significant differences ( $p > 0.05$ ). The results of 3-year and 5-year survival rate did not have a statistically significant difference ( $p > 0.05$ ) between the variants of neoadjuvant therapy.

**Conclusions.** In the treatment of patients with malignant tumors of the mediastinum and chest wall, the use of neoadjuvant therapy is mandatory. When a malignant tumor is localized in the anterior mediastinum, anterior and side wall of the chest, in the blood circulation zone of a. thoracica interna, a promising variant of neoadjuvant therapy is intra-arterial regional chemotherapy.

**Keywords:** neoadjuvant chemotherapy, primary tumors, chest wall, mediastinum

#### Streszczenie

**Wprowadzenie.** Nowotwory pierwotne śródpiersia i ściany klatki piersiowej są niejednorodne pod względem budowy morfologicznej, łączy je jedynie ich lokalizacja anatomiczna. Ze względu na bliskość kluczowych dla życia struktur śródpiersia ich leczenie jest zadaniem złożonym, wymagającym indywidualnego podejścia w doborze terapii neoadjuwantowej.

**Materiał i metody.** Przeprowadzono analizę wyników leczenia chirurgicznego, skojarzonego i kompleksowego 1375 pacjentów cierpiących na pierwotne nowotwory złośliwe śródpiersia oraz 98 pacjentów z nowotworami złośliwymi ściany klatki piersiowej. W schemacie neoadjuwantowym stosowano różne metody leczenia: radioterapię, termoradioterapię, chemioradioterapię oraz chemioterapię regionalną dotętniczą.

**Wyniki.** Wykazano, że zastosowanie dotętnicznej chemioterapii neoadjuwantowej (IACT) charakteryzuje się lepszym stopniem regresji guza ( $p < 0,05$ ) i najniższą częstością występowania przerzutów w porównaniu ze stosowaniem radioterapii i termoradioterapii ( $p < 0,001$ ), a w porównaniu z zastosowaniem chemioradioterapii nie stwierdzono istotnych statystycznie różnic ( $p > 0,05$ ). Wyniki wskaźnika przeżyć 3-letnich i 5-letnich nie wykazały istotnej statystycznie różnicy ( $p > 0,05$ ) pomiędzy wariantami terapii neoadjuwantowej.

**Wnioski.** W leczeniu chorych cierpiących na nowotwory złośliwe śródpiersia i ściany klatki piersiowej stosowanie terapii neoadjuwantowej jest obowiązkowe. Gdy guz złośliwy zlokalizowany jest w przedziale przednim śródpiersia, przedniej i bocznej ścianie klatki piersiowej, w strefie krążenia krwi wyznaczonej przez tętnicę piersiową wewnętrzną, obiecującym wariantem terapii neoadjuwantowej jest regionalna chemioterapia dotętnicza.

**Słowa kluczowe:** neoadjuwantowa chemioterapia, guzy pierwotne, ściana klatki piersiowej, śródpiersie

Zakharychev V, Gordiichuk P, Gordiichuk M. Efficiency of neoadjuvant therapy of malignant tumors of the mediastinal and chest wall. Health Prob Civil. 2023; 17(2): 114-121. <https://doi.org/10.5114/hpc.2023.127866>

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## Introduction

Intrathoracic neoplasms, in addition to lung cancer, include numerous tumors of the mediastinum, chest wall, and pleura, which have a benign or malignant variant of growth based on their morphological structure. Benign tumors of intrathoracic localization are subject to surgical treatment in the initial stages of their development, since certain morphological forms have a substantial risk of malignancy [1,2]. At the present time, the problem needed to be revised, since traditionally, the only surgical method of treatment of malignant tumors of the mediastinum is accepted as not being adequate. Attempts to surgically remove advanced mediastinal or infiltrative chest wall malignancies often result in palliative or trial operations, and postoperative radiotherapy or chemotherapy do not provide a radical cure for patients. Thus, such an approach cannot be regarded as adequate. This statement is supported by the low survival rates of patients, high frequency of relapses and metastasis of tumors [2,3]. A comparative analysis of the recurrence-free survival rate of patients who received different treatment methods confirms that the best results are obtained after combined and complex treatment with preoperative intensive radiation therapy or intra-arterial regional chemotherapy followed by the surgical removal of the remaining tumor mass [1,2,4].

Morphological polymorphism, according to the embryogenesis of tissues of this anatomical area, with the similarity of clinical manifestations and X-ray semiotics of neoplasms of the mediastinum and chest wall, requires the development of algorithms for differential diagnosis and optimization of treatment.

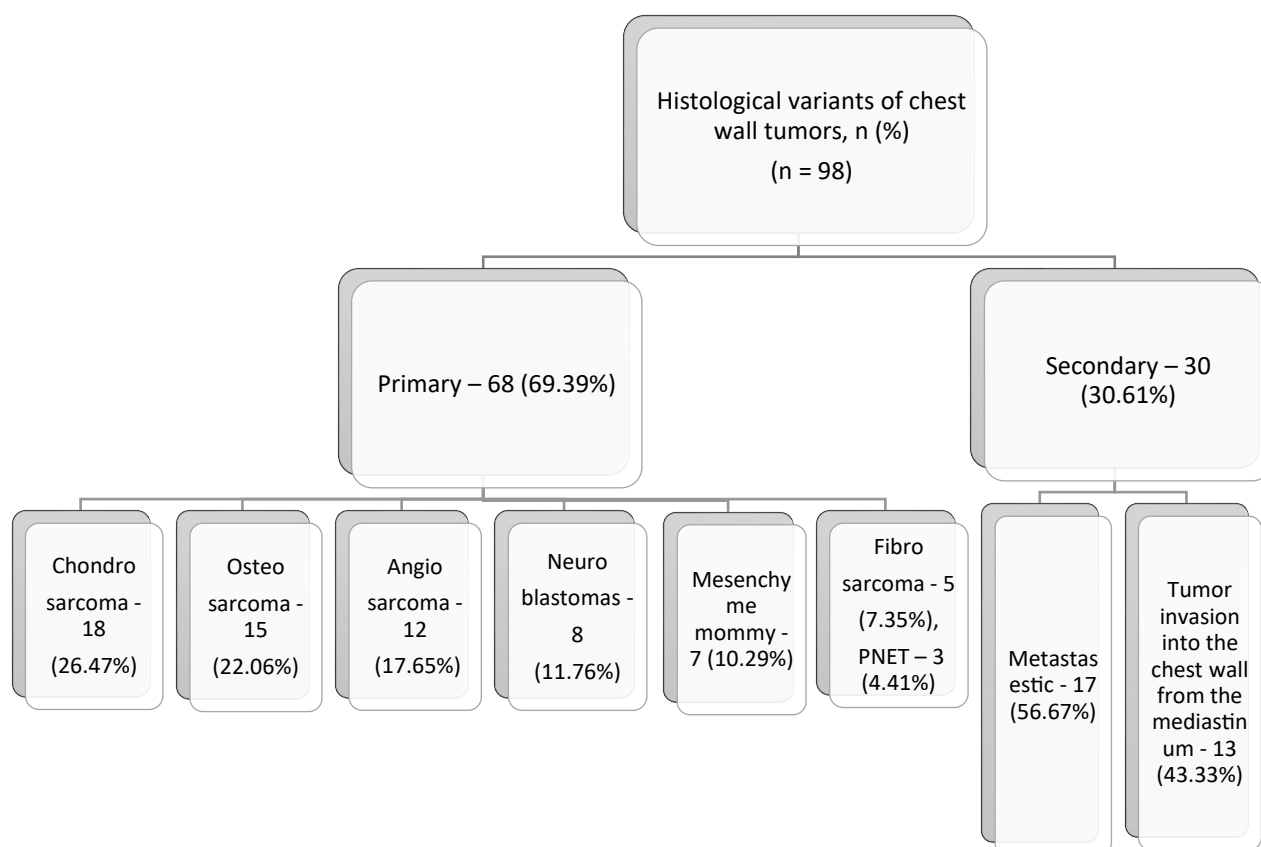
The purpose of the research was to evaluate the effectiveness of the results of complex treatment with diverse options of neoadjuvant therapy for malignant tumors of the mediastinum and chest wall.

## Material and methods

An analysis of surgical, combined and complex treatment was carried out in 1,375 patients with primary malignant neoplasms of the mediastinum and in 98 patients with malignant tumors of the chest wall, who were treated in the Department of Chest Cavity Tumors of the National Cancer Institute of the Ministry of Health of Ukraine. Characteristics of primary malignant neoplasms of the mediastinum by origin and morphological structure are presented in Table 1, and malignant neoplasms of the chest wall according to the morphological structure are presented in Figure 1.

**Table 1.** Primary malignant neoplasms of the mediastinum by origin and morphological structure

| Tumor type                    | Number of patients,<br>n (%)<br>(n = 1375) | Gender, n (%) |             |
|-------------------------------|--|---------------|-------------|
|                               |  | male          | female      |
| Thymomas                      | 913 (66.4)                                 | 390 (42.71)   | 523 (57.29) |
| Germinogenic tumors           | 91 (6.6)                                   | 69 (75.82)    | 22 (24.18)  |
| Neurogenic tumors             | 147 (10.8)                                 | 70 (47.62)    | 77 (52.38)  |
| Lymphomas (LGM of the thymus) | 134 (9.7)                                  | 59 (44.03)    | 75 (55.97)  |
| Mesenchymal malignant tumors  | 55 (4.0)                                   | 35 (63.64)    | 20 (36.36)  |
| Unclassified malignant tumors | 35 (2.5)                                   | 21(60.0)      | 14 (40.0)   |

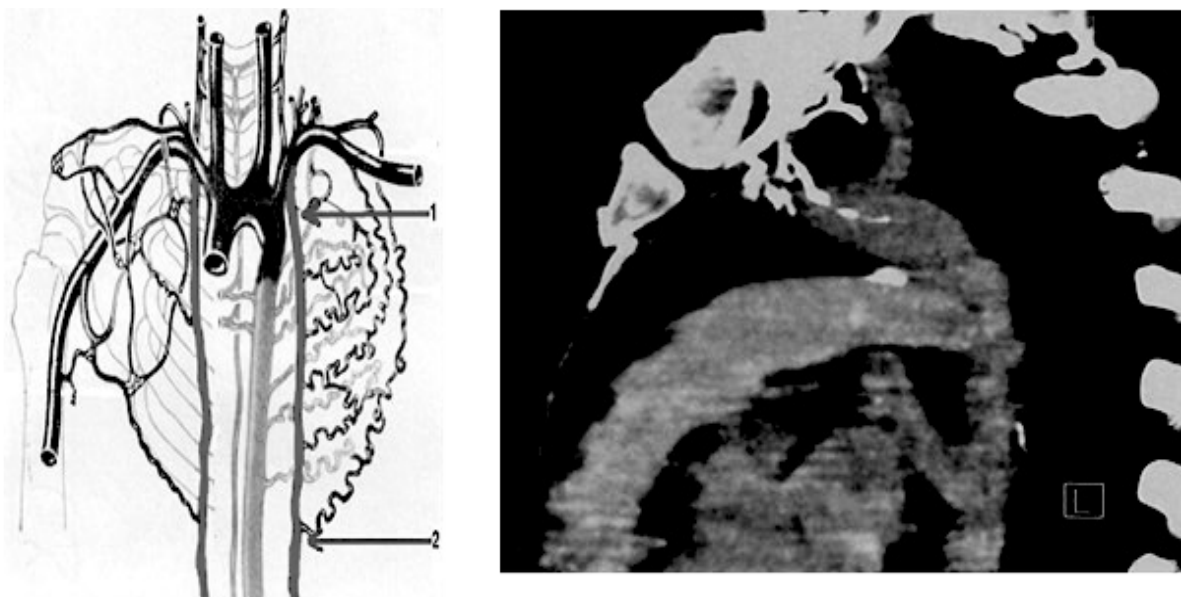


**Figure 1.** Malignant neoplasms of the chest wall according to their morphological structure

The choice of treatment option has been dependent on the spread of malignant neoplasms of the mediastinum and chest wall. Surgical treatment as an independent method was effectively used only in the initial stages of the development of malignant neoplasms. In all other cases, complex or combined treatment was used, in which preference was given to the use of neoadjuvant chemotherapy or chemoradiotherapy, which made it possible to achieve tumor regression, limit invasion into surrounding structures, and convert an unresectable process into a resectable one.

Regional intra-arterial neoadjuvant chemotherapy (IACT) was used to increase the antitumor effect of cytostatics, obtain maximum regression of the tumor and its devitalization with a decrease in total doses, and a decrease in toxicity. The rationale was that, through the internal thoracic artery, there is blood supply to the adipose tissue of the anterior mediastinum with lymph nodes, the thymus, the anterior surface of the pericardium, the trachea and main bronchi, as well as the anterior and lateral chest wall. Catheterization of the internal thoracic artery was performed under general anesthesia. On the side of the lesion, the costo-diaphragmatic branch, which runs along the lower edge of the costal arch, was isolated and mobilized. A 0.2 mm catheter for epidural anesthesia was inserted along the main trunk of the internal thoracic artery to the level of the cartilage of the first rib. The length of the intravascular part of the catheter for each patient was calculated individually when planning the surgical intervention, measuring the distance from the lower edge of the costal arch to the level of the lower edge of the clavicle, parallel to the sternum (Figure 2).

The clinical study was approved by the Ethics Commission of the National University of Health Care of Ukraine (protocol No. 14 dated 07.12.2020).

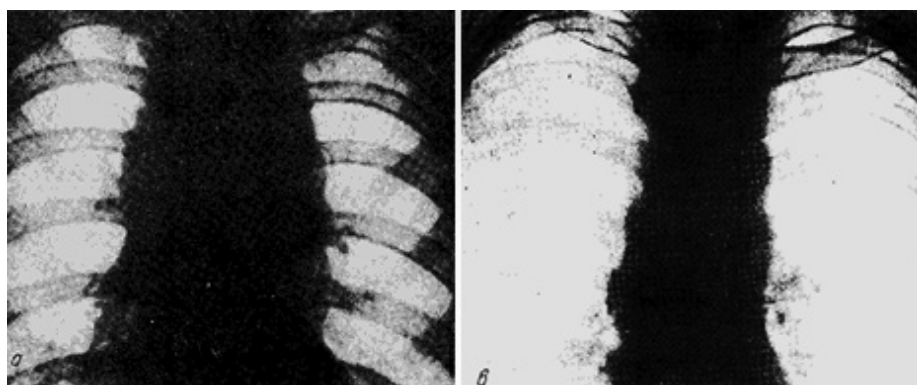


**Figure 2.** Diagram of catheter location and angiogram of the internal thoracic artery

Notes: 1 – placement level; 2 – catheterization site.

## Results

Neoadjuvant intra-arterial chemotherapy for malignant thymomas was performed for 225 patients according to the scheme – adriamycin, cisplatin, vincristine, cyclophosphane – with a dosage of 75% of the accepted dose of medication. For administration, the necessary concentration of doxorubicin and cisplatin solutions was used – no more than 25 mg in 500 ml of physiological sodium chloride solution to prevent local reactions. The introduction was conducted in two courses lasting 6-8 hours for four days, with the next cycle after 2-3 weeks according to the same scheme. If, during the examination, it was found that tumor regression was achieved by more than 50%, then three weeks later, surgical removal of the tumor was performed. If tumor regression was less than 50%, a third course of polychemotherapy was prescribed, or the use of radiation therapy was followed by removal of the tumor three weeks later. After one cycle of intra-arterial chemotherapy in 111 patients with thymoma, partial regression (decrease in tumor size >30%) was registered in 62 (55.85%) cases, and in 42 (38%) of 114 patients with poorly differentiated thymoma, which was statistically significant ( $p < 0.05$ ); after the second cycle of chemotherapy, tumor regression was obtained in 81 (73.2%) and 69 (62.1%) patients, respectively, which was not statistically significant ( $p > 0.05$ ). The volume of viable tumor tissue was from 0 to 6% (on average – 2.7%), with poorly differentiated thymoma – from 2 to 12% (on average – 10.2%). A radiograph of the chest cavity organs is presented, on which complete regression of the tumor was obtained after IACT (Figure 3).



**Figure 3.** X-ray of chest organs of regression of malignant thymoma after IACT

Notes: a – bilateral expansion of the mediastinal shadow. Histological conclusion of the tumor biopsy: epithelial thymoma (type B3); b – after intra-arterial chemotherapy according to the ADOC scheme.

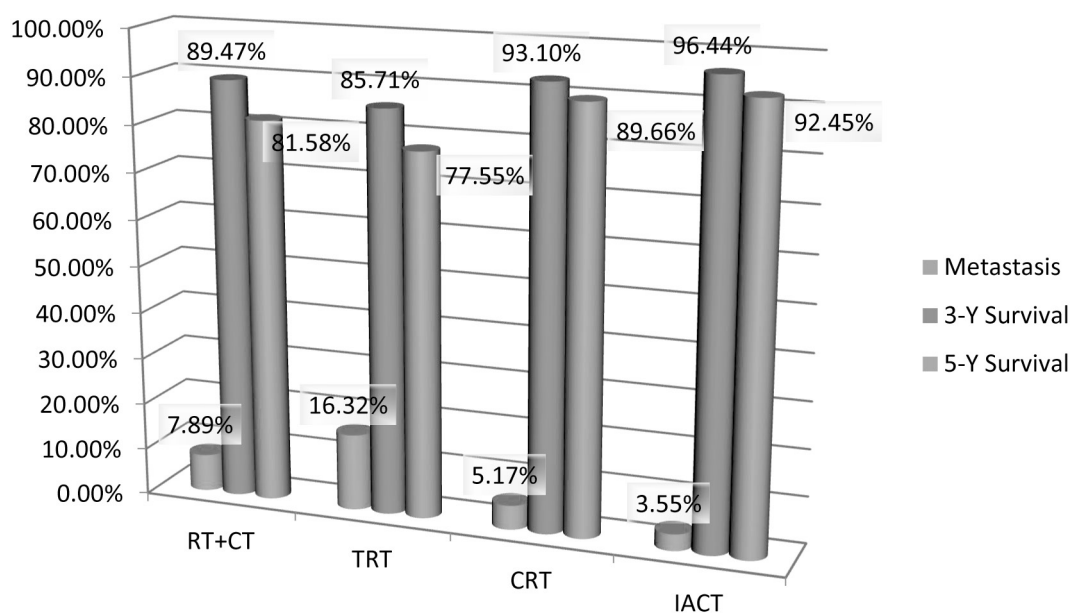
The type of surgical treatment performed in patients with invasive thymoma had a direct correlation with whether neoadjuvant therapy was performed. The effectiveness of the options for neoadjuvant therapy for invasive thymoma, based on tumor regression and the type of surgical treatment performed, is presented in Table 2.

**Table 2.** Type of surgical treatment and frequency of regression of invasive thymoma depending on the variant of neoadjuvant therapy performed

| Neoadjuvant therapy, n (%)          | Tumor regression, n (%) | Type of surgical treatment, n (%) |             |            |
|-------------------------------------|-------------------------|-----------------------------------|-------------|------------|
|                                     |                         | Radical                           | Palliative  | Diagnostic |
| It was not held (n=543)             | 0                       | 261 (48.07)                       | 211 (38.86) | 71 (13.07) |
| Radiotherapy (n=38)                 | 16 (42.11)              | 29 (76.31)                        | 7 (18.42)   | 2 (5.26)   |
| Thermoradiotherapy (n=49)           | 27 (55.1)               | 41 (83.67)                        | 5 (10.21)   | 3 (6.12)   |
| Chemoradiotherapy (n=58)            | 37 (63.79)              | 49 (84.48)                        | 7 (12.07)   | 2 (3.45)   |
| Intra-arterial chemotherapy (n=225) | 165 (73.33)             | 205 (91.11)                       | 18 (8.0)    | 2 (0.89)   |

The presented results prove that, without neoadjuvant therapy, it was possible to perform radical surgical intervention in only 48.07% of cases. When performing neoadjuvant therapy, regardless of its variant, radical surgical intervention was performed from between 76.31% to 91.11% of cases, which is statistically significant ( $p < 0.05$ ). After IACT, the degree of tumor regression was better compared with other variants of its implementation. Compared with radiotherapy, it was determined to be statistically significant ( $p < 0.05$ ), with the results after chemoradiotherapy being more effective, but without a statistically significant difference.

The oncological results revealed that the recurrence after conducting these options of neoadjuvant therapy was rare, apart from pure surgical treatment, in which the rate was approximately 70%; therefore, it is not correct to compare them. The obtained oncological results after neoadjuvant therapy are presented in Figure 4.

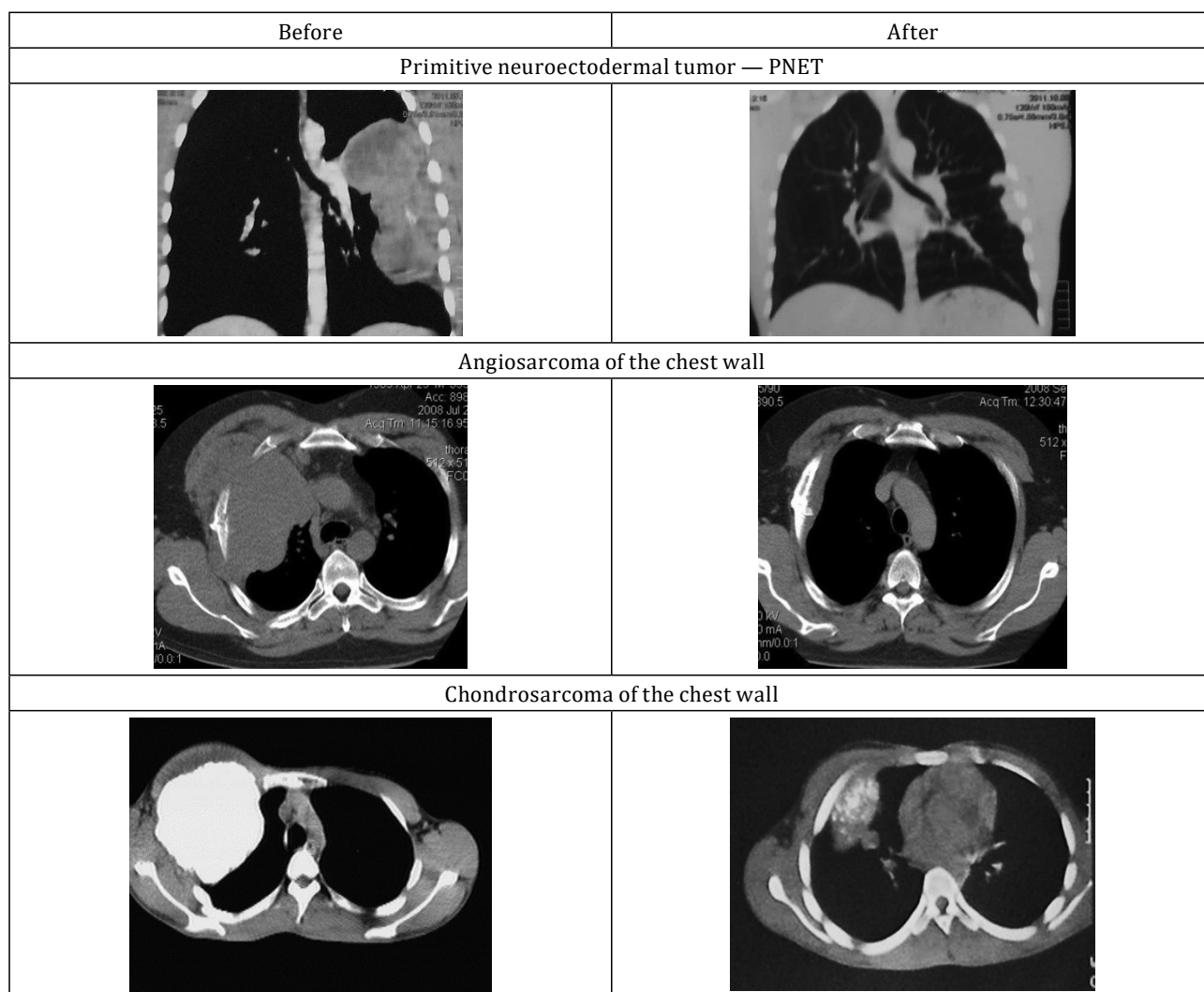


**Figure 4.** Oncological results after neoadjuvant treatment of invasive thymoma

Notes: RT+CT – radiation therapy with postoperative chemotherapy; TRT – thermoradiotherapy; CRT – chemoradiation therapy; IACT – intra-arterial chemotherapy.

The presented results indicate a statistically significant effect of the use of IACT on the frequency of metastases in comparison with the results obtained after thermoradiotherapy ( $p < 0.001$ ), and in comparison with the use of chemoradiotherapy, there was no statistically significant difference ( $p > 0.05$ ). The results of 3-year and 5-year survival rates did not have a statistically significant difference ( $p > 0.05$ ), except when comparing groups after IACT and thermoradiotherapy ( $p < 0.05$ ).

The experience of neoadjuvant intra-arterial chemotherapeutic treatment of neurogenic tumors of the mediastinum, with the use of cisplatin, vincristine, dacarbazine, and cyclophosphane, has proven the effective regression of the tumor in most of its morphological variants. IACT was used as an option of neoadjuvant therapy for highly malignant tumors (angiosarcomas, leiomyosarcomas) with 2-3 courses and using cisplatin, doxorubicin, dacarbazine, ifosfamide or taxanes. After non-adjuvant treatment, re-staging and examination were performed; in the presence of resectability, surgical treatment was performed. The results of tumor regression after regional intra-arterial neoadjuvant chemotherapy are presented in Figure 5.



**Figure 5.** Tumor regression after IACT

**Discussion**

The experience has shown that, among malignant diseases of the anterior mediastinum, epithelial diseases of the thymus predominated; namely, thymomas, thymic carcinomas, and less – often – endocrine tumors of the thymus, which was previously confirmed by studies [3,5-7], which established an increase in the aggressiveness of these diseases with a deterioration in the treatment prognosis. After surgical treatment alone, a statistically significant high recurrence rate with insufficiently effective adjuvant therapy was obtained. Therefore, when using a personalized approach, the need for neoadjuvant therapy has been confirmed in most patients. When a malignant tumor is localized in the anterior mediastinum, anterior and lateral chest wall, IACT was considered the most promising option for neoadjuvant therapy.

Neurogenic tumors of the anterior mediastinum and tumors of the chest wall, which were located in the blood circulation zone of a. thoracica interna, responded effectively to IACT. About 90% of primary tumors of the chest wall are tumors from the rib or sternum, or rather, from their cartilage tissue. According to Cipriano et al. [7] and Thomas et al. [8], these are almost always malignant, subject to removal within healthy tissue, resulting in large chest wall defects. They require plastic closure of chest tissue defects, and sometimes the use

of artificial implants. Reconstruction of large chest wall defects can be difficult and often requires the use of prostheses and biological mesh materials [9,10].

Having received a positive result from neoadjuvant therapy, one of the variants of which is IACT, we have tried the opportunity to perform a radical surgical intervention, which is less traumatic – without the use of artificial implants.

## Conclusions

1. The choice of treatment method for patients with malignant tumors of the mediastinum and chest wall should be based on a personalized approach, with the mandatory use of neoadjuvant therapy.
2. When a malignant tumor is localized in the anterior mediastinum, anterior and lateral chest wall, in the blood circulation zone of a. thoracica interna, intra-arterial regional chemotherapy is a promising option for neoadjuvant therapy.

## Disclosures and acknowledgements

The authors would like to thank all the staff who were involved in this project. The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. The research was funded by the authors.

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