ORIGINAL ARTICLE

Hyperthermic intrathoracic chemotherapy (HITHOC) - a tertiary oncological center experience

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Summary

Introduction: This study aimed to present our experience with HITHOC in the field of multimodality treatment of heterogeneous, potentially resectable, chemotherapy-sensitive pleural malignancies—primary and metastatic—limited to the unilateral thoracic inlet.

Methods: The research included all patients who underwent a HITHOC procedure with CRS at the Institute for Oncology and Radiology of Serbia from January 2018 to December 2024. The indications for procedure were: resectable chemo-sensitive primary or residual/recurrent thoracic malignancies confined to one side of the thorax, and various metastatic diseases restricted to the unilateral thoracic inlet with achieved local disease control. HITHOC was performed with cisplatin (100 mg/m2 in 1000 ml of 5 % glucose, gradually heated to 42 °C) perfusion lasting 90 minutes.

Results: Eleven patients were included in the study, with a mean age of 48.27 ± 18.37 years. The most common tumor pathology was thymoma, followed by malignant pleural tumors. Other tumor pathologies included ovarian cancer, Ewing's sarcoma, alveolar rhabdomyosarcoma, and lung cancer. Average follow-up was 41,73 (median: 35; range: 2-72) months. The overall survival rate was 64%.

Conclusion: HITHOC procedure can be regarded as a safe, feasible, and effective approach for well-selected patients. It could be beneficial not only for its current indications, but also for chemosensitive pleural malignancies, both primary and metastatic, limited to the unilateral thoracic inlet.

Keywords: HITHOC, hyperthermic intrathoracic chemotherapy, pleural malignancies, indications, survival

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INTRODUCTION

Hyperthermic intrathoracic chemotherapy (HITHOC) involves the application of elevated temperature and a high dose of a cytotoxic drug to tumor cells. HITHOC is a synergistic interaction that improves local disease control, prolongs survival, and advances the quality of life. Introducing a cytotoxic drug into the thoracic cavity provides direct exposure of tumor cells to the drug, has better pharmacokinetic characteristics, and avoids the side effects of a systemically administered drug. In hyperthermia, the penetration of cytostatic medicines is increased, thereby increasing cytotoxic effects on tumor cells (1).

Hyperthermic perfusion of cytotoxic drugs directly into the cavity-peritoneum was first used in 1980 in a canine model for the treatment of metastatic effusion from cancer in the abdomen (2). The first report on HITHOC for treating malignant pleural seeding or pleural effusion was published in 1995 by Matsuzaki et al (3). HITHOC is only used if there is no tumor outside the thoracic cavity, and it may be used alone or as adjuvant therapy to cytoreductive surgery (CRS). Surgical removal of all visible tumor lesions in the thorax (CRS) is an important factor in the effectiveness of the HITHOC, because cytotoxic drug penetration is limited to 3-4 mm into residual microscopic deposits (4).

The primary tumors responsible for malignant pleural effusion that have shown improvement with HITHOC include malignant mesothelioma (MPM), thymic malignancies, and lung cancer (5), despite techniques and approaches for the treatment of pleural malignancies still being unclear and having not been standardized to date. Also, in the literature, some studies suggest additional indications for HITHOC.

This study aimed to present our 6 years' experience with HITHOC as a multimodal treatment for resectable, chemosensitive, unilateral, primary, or metastatic pleural malignancies.

MATERIAL AND METHODS

In this case series, we included all patients (n = 11) diagnosed with primary or secondary pleural malignancies who underwent HITHOC procedure combined with CRS at the Institute for Oncology and Radiology of Serbia, during the period from January 2018 to December 2024. The following data were collected and analyzed: demographics; pathohistological findings; initial oncological treatments; HITHOC procedure—indications and technique; postoperative period; and lethal outcomes.

This study extends our previously published work by Stojiljković et al. (6); additional patients have been treated at our oncology center using the same therapeutic approach under identical clinical indications. The extended follow-up period provides more powerful insights into the patterns of intrathoracic and distant disease recurrence and mortality, as well as into practice guidelines for optimal standardization of HITHOC in pleural malignancies.

This scientific research study was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia with the number 01-1/2025/2028 (date, July 4, 2025).

In brief, the indications for HITHOC with CRS were: resectable chemo-sensitive primary or metastatic (with achieved local disease control) thoracic malignancies confined to one side of the thorax. Patients with contralateral thoracic tumor implants or extra-thoracic metastases, as well as patients with compromised cardiopulmonary function or suffering from renal insufficiency, were excluded. Before surgery, all patients signed an informed consent. CRS was performed as an open chest surgery under general anesthesia. Intraoperative monitoring of central body temperature was performed with an esophageal probe and regulated using cooling solutions injected through the central venous catheter or warming/cooling blankets. Postoperatively, all patients were monitored at the Intensive Care Unit.

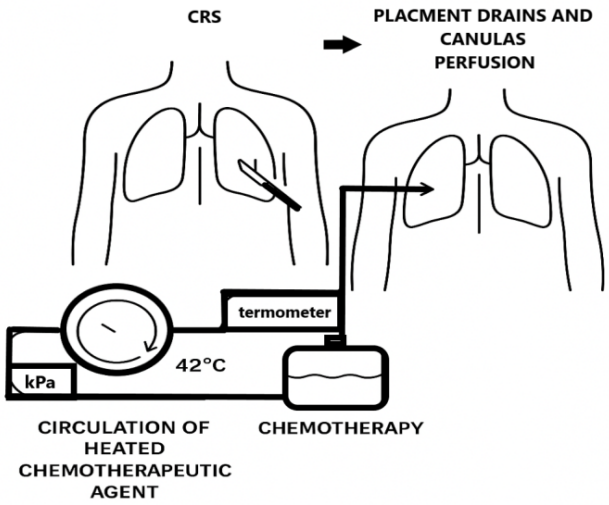

Figure 1. CRS+HITHOC procedure

CRS+HITHOC procedure is presented in **Figure 1**.

RanD® Performer perfusion system is used with cisplatin as a cytotoxic agent. The standard administered dose of cisplatin is 100 mg/m2, adjusted for creatinine clearance. A single medical oncologist calculates the drug concentration needed for each patient, taking into account the patient's comorbidities, previous systemic treatments (with particular attention to cumulative dosage), and body weight and height. Primarily, patients with pleural carcinoma localized to one hemithorax undergo cytoreductive surgical therapy. The goal of the cytoreductive surgical approach is to remove all macroscopically visible tumor lesions localized on one side of the pleural cavity.

After achieving adequate resection, the patient is connected to the RanD® Performer perfusion system by plac-

ing four drains (28 F chest tubes), two inflow and two outflow, with additional fifth superficial chest tube for fluid level control. Each tube is connected to the RanD Performer device. The next step consists of priming solution (1000 ml of 5 % glucose, 38°C), which is once inserted into the pleural space, and gradually heated until the target temperature of 42°C is achieved. In those conditions, cisplatin is added, and the intracavitary circulation of the cytostatic is extended to 90 minutes. The final step is to wash out the dissolved cisplatin using a catheter with reversed inflow and outflow. Suctioning of the remaining substance is achieved using two chest drains in anterior and posterior positions, with suction set at 15-25 cm H2O, before closing the chest in a standard manner.

For the description of relevant parameters, depending on their nature, descriptive statistical measures were used: Frequencies, percentages, mean value (average), median, standard deviation (SD), and range (span). Overall survival was presented using the Kaplan-Meier product-limit method, and the description included a median survival analysis.

RESULTS

Demographic characteristics, pathohistological diagnosis, and initial oncological treatments in patients

The study included 11 patients who underwent a HITHOC procedure with CRS. The mean age of patients was 48.27 ± 18.37 (median: 55, range: 16 – 68) years, and the female-to-male ratio was 5:6. The most common tumor pathology was thymoma, histopathological subtype B (4 patients), followed by malignant pleural tumors (mesothelioma and malignant solitary fibrous tumor of the pleura-3 patients). Other tumor pathologies included one patient each for ovarian cancer, Ewing's sarcoma, alveolar rhabdomyosarcoma, and lung cancer. Oncological treatments before HITHOC with CRS for cystadenocarcinoma serosum ovarii (G2, NG2, with peritoneal carcinomatosis) included CRT with hyperthermic intraperitoneal chemotherapy followed by adjuvant chemotherapy (paclitaxel+carboplatin) (1 patient, female, 48 years old) or bilateral adnexectomy (1 patient, female, 62 years old); for malignant pleural tumor included tumor excision (2 patients, males, 55 and 63 years old) + systemic chemotherapy (1 patient, male, 68 years old), for thymoma (B2, type, Ki67 70-90%) included thymomectomy with atypical lung resection (1 patient, male, 62 years old), thymomectomy with systemic chemotherapy (paclitaxel, adriamycin and cisplatin), adjuvant irradiation and second-line chemotherapy (ifosfamide, oncovin, adriamycin) due to intrathoracic relaps 165 months after last treatment (1 patient, male, 45 years old) or thymomectomy and adjuvant irradiation (1 patient, female, 59 years old); for Ewing Sarcoma of the sacral bone, conventional subtype (1 patient, female, 19 years old) radiotherapy and chemotherapy (first-line to fourth line) and lung surgery (1 patient, female, 19 years old); specific oncological treatments for Li-Fraumeni syndrome (unilateral breast high-grade phyllodes tumor, rosette-forming glioneuronal tumor of the 4th ventricle, adrenocortical carcinoma and pheochromocytoma) (1 patient, female, 32 years old), and for alveolar rhabdomyosarcoma (chest wall tumor mass, localized in the 7-8th intercostal space, with suspicious pleural nodules) initial chemotherapy (1 patient, male, 16 years old).

HITHOC with CRS

The extent of CRS depended on the size, number, and localization of tumor masses within one side of the chest. In 11 patients, all macroscopically visible tumor tissue was removed from the thoracic cavity, and upon receiving the definitive pathohistological results, R0 resection was confirmed. The duration of the heated cytotoxic agent (cisplatin) circulation within the thoracic cavity was 90 minutes. All HITHOC procedures with CRS were uncomplicated, both intraoperatively and postoperatively.

Postoperative follow-up and oncological results, survival time following HITHOC with CRS

Following hospital discharge, all patients underwent evaluation by multidisciplinary teams, and 6 of 11 subsequently received further oncological therapy (chemotherapy, irradiation) according to disease-specific protocols. Out of a total of 11 patients, a lethal outcome was noted in four, among whom were patients with metastatic disease (ovarian cancer and Ewing sarcoma), as well as patients with primary intrathoracic tumors (malignant mesothelioma and solitary malignant pleural tumor), initially graded as stage IV. The overall survival rate was 64%.

Table 1 presents the median overall survival time (MOS) for patients who underwent the HITHOC procedure as part of multimodal treatment, depending on pathology and disease stage. The mean follow-up time after the HITHOC procedure was 41.73 months (median: 35; range: 2-72). The median survival after HITHOC was 72 months **(Figure 2)**.

All patients in our study with thymoma are still alive, with a mean follow-up of 43.6 months (median 33, range 23–71) in stage IVa. Given that the majority of our patients remain alive, ongoing monitoring is maintained. Based on the data from deceased patients, it can be concluded that patients treated with the HITHOC procedure, as part of multimodal therapy, showed a longer survival time than expected.

Table 1. The expected survival time based on disease stage and follow-up

Tumor type	Disease stage	MOS witout HITHOC (months)	Follow-up MAX (months)
MSFTP	no TNM	94.4	51+
Thymoma	I	166	48+
Lung adenocarcinoma	IIIa	27-34	2+
Alveolar rhabdomyosarcoma	IV	NA	54+
Malignant mesothelioma	IV	16	35
Ewing Sarcoma	IVa	16.8	32
Thymoma	IVa	98	71+
Ovarian carcinoma	IVb	31	72

Legend: MOS-median overall survival of patients treated with other forms of treatment without the HITHOC procedure, data taken from other publications; MSFTP-malignant solitary fibrous tumor of pleura; TNM-tumor, node, metastasis stage; NA-not applicable; Folow up MAX- the maximum follow-up duration of our patients treated with HITHOC; + - the patients remain alive and are maintained on a schedule of regular follow-up evaluations

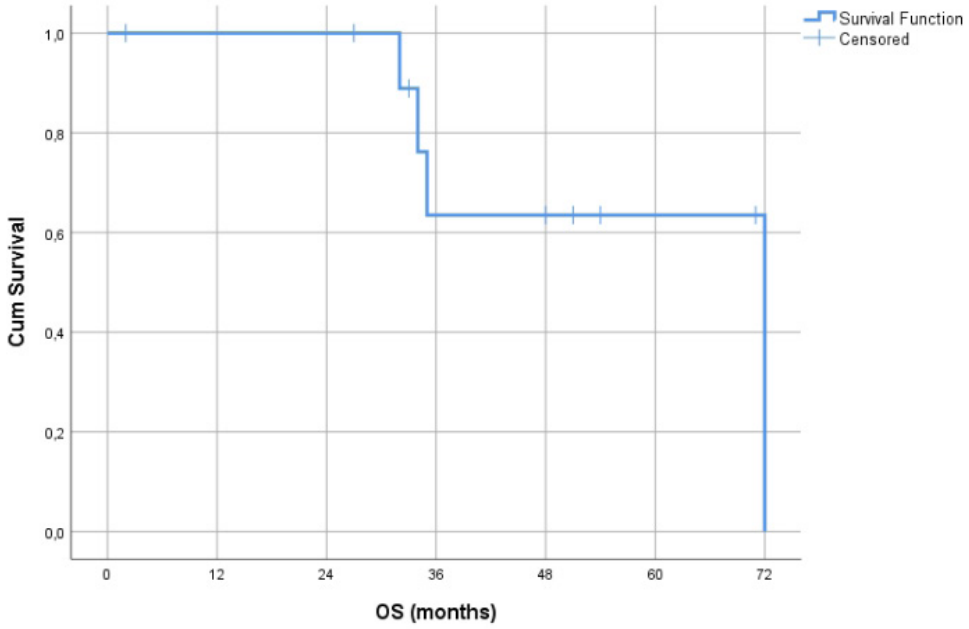

Figure 2. Overall survival (OS) after HITHOC

DISCUSSION

The HITHOC procedure has been utilized in thoracic surgery for over two decades. Nevertheless, its clinical implementation remains non-standardized with respect to crucial variables, such as cytotoxic drug dosage, perfusate volume, temperature, and perfusion duration. Despite this lack of uniformity, efforts to harmonize these parameters continue (7). In a review encompassing 27 studies, 8 identified cisplatin as the most frequently administered chemotherapeutic agent, followed by doxorubicin and mitomycin C. Reported perfusion temperatures ranged from 38 to 43 °C (8). Also, in some literature data, combinations of two cytotoxic agents are used for HITHOC. (9). Although a universal recommendation on the ideal cisplatin dose is lacking, most authors report using 80 - 250 mg/m^2 (10). In this study, we used a cisplatin dose of 100 mg/m2. At our institution, since the adoption of HITHOC, cisplatin has been the agent of choice in accordance with the national Health Insurance Fund guidelines. For priming, we use 1,000 mL of a 5% glucose solution. After introduction into the pleural cavity, the solution is progressively heated to a target temperature of 42 °C. Once the desired temperature is reached, cisplatin is added, and the perfusion is maintained for 90 minutes, although shorter durations are mentioned in some publications (11). This protocol has demonstrated no HITHOC-associated adverse effects while maintaining effective local disease control. The evidence, including data from this study, confirms that CRS combined with HITHOC is a safe, feasible, and effective treatment option for carefully selected patients (12-15). The majority of reports emphasize HITHOC therapeutic benefits in managing malignant pleural mesothelioma and pleural spread of thymoma, whether in stage IV, in "de novo" cases, or in recurrences (16). These conditions represent nearly half of the patients treated at our center. Furthermore, the literature suggests a growing interest in

expanding the indications for this approach, as supported by multiple studies (17-20).

In our study, four patients were diagnosed with thymoma. One of them was classified as stage I, while the remaining three had stage IVa disease, all of whom exhibited histopathological subtype B and a high proliferative index (Ki-67 exceeding 70%). Complete surgical resection remains the most important prognostic factor in thymoma, and surgery should always be considered when achieving complete resection is feasible. Some data suggest that for patients with stage I thymoma, the expected median overall survival reaches up to 166 months. When tumors are resectable in stage IV disease, the median survival drops to approximately 98 months (21). According to Raffael et al., the HITHOC procedure yielded promising results in stage IVa thymoma patients, with 90% survival at 3 years and 70% at 5 years following surgery. (22)

Further supporting these findings, a 2015 study on patients with recurrent pleural thymoma treated with HITHOC reported a mean follow-up time of 64.6 months (median: 78 months; range: 13–107 months). At that point, 85% of patients (11 individuals) were still alive, and 10 of them showed no evidence of disease (23).

As outlined in our results, all patients with thymoma in our cohort remain alive to date. Among those in stage IVa, the average follow-up duration was 43.6 months.

Malignant mesothelioma is typically associated with a poor prognosis, with median overall survival ranging from 9 to 12 months following diagnosis (24). For patients in advanced stages of malignant pleural mesothelioma, chemotherapy remains the cornerstone of treatment—either administered alone or in combination with radiotherapy and/or surgical intervention when the disease is deemed resectable.

In the case of biphasic malignant mesothelioma, as confirmed pathohistologically in our patient, recent publications (2022) report a median survival of approximately 16 months. Even among those who underwent pleurectomy/decortication followed by adjuvant chemotherapy or radiotherapy, recurrence of the disease was frequent and often quickly followed by a fatal outcome.

A 2017 quantitative meta-analysis of 5 studies found a statistically significant improvement in survival among malignant mesothelioma patients who underwent surgical treatment with the HITHOC procedure compared with those who did not (25).

Our patient with malignant mesothelioma underwent surgical resection combined with HITHOC, followed by adjuvant radiation therapy. Although the patient experienced disease recurrence during follow-up, survival was prolonged, and the patient passed away 35 months after the initial treatment.

One of the patients in our study, diagnosed with malignant solitary fibrous tumor of the pleura (MSFTP), was considered for reoperation due to an R1 resection following the initial surgery. Afterward, the patient received adjuvant chemotherapy—initially one cycle consisting of Adriamycin and Ifosfamide, followed by Carboplatin and Etoposide. However, an allergic reaction occurred, prompting a switch to second-line treatment with the VP16-CBDCA protocol. Despite these interventions, the patient experienced a lethal outcome 34 months after the initial follow-up began.

Another patient in our cohort, also diagnosed with MSFTP and treated using a comprehensive multimodal oncologic strategy, remains alive and under follow-up, now at 51 months.

According to the literature, patients with MSFTP had an estimated average survival of 94.4 months (30.6-124.9 months), and survival rates were 84% at 1 year, 67% at 3 years, and 55% at 5 years (26).

-In 2018, our oncology center performed its first HITHOC procedure on a 48-year-old female patient diagnosed with metastatic ovarian carcinoma (19). The initial treatment included CRS combined with hyperthermic intraperitoneal chemotherapy (HIPEC), followed by adjuvant chemotherapy. Due to peritoneal relapse, the patient underwent reoperation, which successfully controlled the local disease. However, 22 months later, pleural metastases appeared, localized to the unilateral thoracic inlet, making the patient eligible for CRS combined with HITHOC. While the typical overall survival for patients with this diagnosis is approximately 31 months, our patient survived six years following the HITHOC procedure. This was achieved despite multiple relapses and ongoing targeted oncological treatments, marking a significant advancement in therapeutic outcomes.

More recently, a case involving a 58-year-old patient with ovarian cancer accompanied by peritoneal and pleural carcinomatosis (27) has been reported. This case demonstrated the successful use of an integrated approach combining CRS and HIPEC, followed by CRS with HITHOC. During a 20-month follow-up period, the patient showed notable improvement in disease-free survival, with reduced recurrence rates and an overall survival exceeding expectations for standard treatment options. The application of HITHOC in managing this condition proved effective in controlling disease progression and alleviating symptoms related to advanced ovarian cancer.

-Sacral Ewing's sarcoma presents a considerable diagnostic challenge, largely due to its distinctive anatomical location. When considering the application of the HITHOC procedure in patients with Ewing's sarcoma, large-scale studies demonstrating its efficacy are scarce. This scarcity is understandable, given that this pathology represents less than 5% of all soft tissue sarcomas, according to NCBI data.

During our literature search, we identified a report describing the successful use of HITHOC in a 16-year-old adolescent treated at the Apollo Proton Cancer Centre in Asia (2022). Our patient, diagnosed with sacral bone

Ewing's sarcoma, began multimodal oncological therapy at age 13. By age 17, the disease had progressed to a metastatic stage and was managed according to standard protocols for this condition.

Since the metastatic disease was limited to one side of the thorax, with local control achieved but ongoing progression of intrathoracic involvement during the fourth line of chemotherapy, the decision was made at age 19 to perform CRS combined with HITHOC. Subsequent treatment included a fifth line of chemotherapy. Unfortunately, the patient experienced a lethal outcome 32 months following HITHOC treatment. However, it is important to note that the median overall survival for patients with this pathology is approximately 16.8 months. Remarkably, our patient, who received multimodal treatment including CRS and HITHOC, survived close to nine years from the initial diagnosis (28).

RMS is the most frequent soft tissue sarcoma among children and adolescents, accounting for approximately 3–4% of all pediatric cancers (29). The introduction of multi-agent chemotherapy has significantly improved the prognosis for children diagnosed with RMS. According to a multicenter study published in 2012, patients with alveolar RMS tend to have a poorer prognosis compared to those with embryonal RMS, with a 5-year overall survival rate of 21.9±6.1% (30).

A literature review reveals a lack of data on the application of the HITHOC procedure for this specific pathology. In our study, we treated one patient diagnosed with RMS. The disease was staged as IV using the modified TNM classification, due to the presence of pleural implants and the primary tumor originating from the chest wall (31).

Following initial chemotherapy, the patient achieved complete radiological regression. Given the chemo-sensitive nature of the primary tumor, which was confined to the unilateral thoracic inlet, the decision was made to perform radical parietal pleurectomy followed by HITHOC. Since that treatment, the patient has remained free of disease relapse and continues to be monitored, currently at 54 months of follow-up.

Stage III non-small cell lung cancer (NSCLC) represents a highly heterogeneous group of patients, distinguished by variations in disease extent and localization, with adenocarcinoma comprising approximately 50% of cases. Median survival tends to be higher in surgically treated patients than in those receiving other therapies, with survival rates ranging from 27 to 34 months in operable cases (32). Regarding the role of the HITHOC procedure in lung cancer management, studies indicate that HITHOC may improve survival for patients with malignant pleural effusion classified as M1a (stage IV) NSCLC (33,34).

The final patient in our study initially underwent oncological treatment for a borderline seromucinous ovarian tumor, which included bilateral adnexectomy. Thirty-six months later, a biopsy of a lung lesion performed at an outside facility confirmed metastatic disease originating from the ovarian tumor. Subsequent treatment consisted of chemotherapy, followed by CRS combined with the HITHOC procedure at our center. Definitive histopathological analysis identified the lesion as mucinous adenocarcinoma of the lung (T4N0M0). Two months post-surgery, the patient remains under regular follow-up.

Given that our two patients with pleural metastases originating from primary tumors outside the thoracic cavity (ovarian cancer and Ewing sarcoma) had undergone extensive oncological treatments over several years, as well as a patient with alveolar rhabdomyosarcoma—a pathology not previously reported for HITHOC treatment—showed favorable local disease control following CRS plus HITHOC, we believe that HITHOC's application may extend beyond established indications. This approach holds promise for select cases involving heterogeneous, chemo-sensitive, and potentially resectable primary or metastatic pleural malignancies confined to the unilateral thoracic inlet, without compromising any future systemic therapies.

CONCLUSION

The median overall survival time for patients who received the HITHOC procedure as part of multimodal treatment is longer than for those who did not, depending on pathology and disease stage. Patients with stage IV tymoma have the highest survival rate. As the sole center in Southeastern Europe offering the HITHOC procedure, our experience with 11 patients, though limited in scale, provides meaningful insights. However, comprehensive, multicenter studies are necessary to establish definitive evidence regarding its oncological efficacy.

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Ethical approval: This scientific research study was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia with the number 01-1/2025/2028; date approved by the Ethics Committee: July 4 2025.

Informed consent: Written informed consent was obtained from the patients for the publication of this paper.

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HIPERTERMIČKA INTRATORAKALNA HEMIOTERAPIJA (HITHOC) - ISKUSTVO TERCIJARNOG ONKOLOŠKOG CENTRA

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Sažetak

Uvod: Ova studija ima za cilj da predstavi naše iskustvo sa hipertermičkom intratorakalnom hemioterapijom (HITHOC) - procedurom u oblasti multimodalnog lečenja heterogenih, potencijalno resektabilnih, hemiosenzitivnih pleuralnih maligniteta, primarnih i sekundarnih, ograničenih na jednu polovinu grudne duplje.

Metode: Istraživanjem su obuhvaćeni svi pacijenti lečeni hipertermičkom intratorakalnom hemioterapijom (HITHOC) uz citoreduktivni hirurški tretman (CRH) u Institutu za onkologiju i radiologiju Srbije, u periodu od januara 2018. do decembra 2024. godine. Indikacije su bile: resektabilni hemiosenzitivni primarni ili rezidualni/rekurentni torakalni maligniteti ograničeni na jednu polovinu grudne duplje, kao i različite metastatske bolesti sa istim ograničenjem kod kojih je postignuta lokalna kontrola bolesti. Kod svih pacijenata HITHOC je izvođen perfuzijom cisplatinom tokom 90 minuta (100 mg/m^2 cisplatin u 1000 ml 5%-glukoze, postepeno zagrevana do 42 °C).

Rezultati: Studijom je prikazano 11 pacijenata, prosečnog uzrasta 48,27 ± 18,37 godina. Najčešća patologija tumora je timom, praćena pleuralnim primarnim malignitetima. Ostalu patologiju činili su karcinom jajnika, Ewing-ov sarkom, alveolarni rabdomiosarkom i karcinom pluća. Prosečno vreme praćenja pacijenata nakon procedure je 41,73 (medijana 35; opseg: 2-72) meseci. Ukupna stopa preživljavanja je 64%.

Zaključak: HITHOC procedura se može smatrati bezbednom i efikasnom metodom lečenja kod dobro odabranih pacijenata. Pokazuje korist ne samo za trenutne indikacije, već potencijalno i za druge hemiosenzitivne, ograničene pleuralne malignitete, kako primarne tako i metastatske.

Ključne reči: HITHOC, hipertermička intratorakalna hemioterapija, maligniteti pleure, indikacije, preživljavanje

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