Review

Update in the Treatment of Pleural Tumours: Feasibility and Safety of Robotic Surgery Combined with Hyperthermic Intrathoracic Chemotherapy

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Update in the Treatment of Pleural Tumours: Feasibility and Safety of Robotic Surgery Combined with Hyperthermic Intrathoracic Chemotherapy

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Simple Summary: The role of surgery in the combined treatment with hyperthermic intrathoracic chemotherapy of thymoma recurrences and pleural mesothelioma has assumed a controversial role in the context of the multimodal treatment of these diseases, especially when minimally invasive techniques are considered. The aim of the authors is to propose future directions in the approach to these pathologies by placing robotic surgery at the center of reflection, starting, however, from a review of the literature available to date.

Abstract: (1) Background. Intracavitary hyperthermic chemotherapy (HITHOC) remains a part of the complex mosaic which is the multimodal approach in advanced stage thymomas and pleural malignancies, and its role is still widely debated. In recent years, several studies have demonstrated the feasibility and the efficacy of HITHOC combined with cytoreductive surgery in the treatment of thymoma relapses and malignant pleural mesothelioma (MPM). However, there are currently no studies available on pleurectomy/removal of pleural lesions using the robotic technique, in association with intrathoracic chemotherapy. The aim of this narrative review is to evaluate the feasibility and safety of robotic pleurectomy/removal of relapses and HITHOC in patients with pleural recurrence of thymoma or MPM, after having analyzed the literature concerning this controversial topic, and to report our experience with robotic surgery. (2) Methods: A review of papers published on this topic, from 1980, was conducted. Later, the data of consecutive patients affected by thymoma relapses or MPM who underwent robotic surgery in combination with HITHOC will be collected and analyzed. The surgery performed, prior to intrathoracic infusion of the high-temperature chemotherapy, consisted of the removal of the recurrences or pleurectomy, depending on the pathology. All surgeries were performed with a 4-port-fully robotic technique. (3) Results: Between 2017 and 2022, nine patients underwent robotic cytoreductive surgery in combination with HITHOC. No intraoperative complications occurred. One patient had a grade II Clavien-Dindo postoperative complication. Oncological follow-up showed results in line with the literature. (4) Conclusion: With the limitation of the small number of patients, considering the results, robotic surgery may represent the surgical approach of choice, in combination with HITHOC, in patients with pleural relapses of thymoma and early-stage MPM.

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1. Introduction

1.1. Pleural Mesothelioma

Malignant Pleural Mesothelioma (MPM) is an uncommon malignant neoplasm that arises from the cells of the pleural serosa. Due to its aggressiveness, the therapeutic strategies of mesothelioma have always been very limited, and the prognosis is still considered to be poor [1]. According to the World Health Organization, occupational or para-occupational asbestos exposure is recognized as the leading cause related to mesothelioma [2]. In fact, WHO data from 2020 confirms that 107,000 workers worldwide have died from asbestos exposure and that 125 million people have been exposed to asbestos fibers at least once. Asbestos was banned by the European Union in 2005, but, due to the long latency period, it is now mandatory to trace subjects who have been exposed in the past years, to obtain an early diagnosis of asbestos-related diseases [2].Due to the long latency period in pathology expression after exposure, the incidence of malignant mesothelioma has been recorded in a continuous increase in the last decade with a peak in 2020 [3].The countries with the highest incidence rate are the United States of America, the United Kingdom, Italy, and Australia. However, the lack of monitoring of the construction industry in countries such as India, Russia and Brazil means that asbestos-related diseases are likely to remain widespread in these regions in the future as well [4]. Moreover, several studies have demonstrated the role of genetic mutation induced by carcinogens in pleural mesothelioma. The tumor suppressor genes most involved in these mutations or copy-number alterations are *NF2*, *BAP1,* and *CDKN2A* [5]. It has also been demonstrated that the oncogenes *EWSR1* [6] and *ALK* [7] are involved in peritoneal mesothelioma and in the genesis of juvenile forms of serosa tumors, independently of asbestos exposure. The prognosis of MPM is dramatically poor and ranges from 8 to 14 months after diagnosis, with a more favorable outcome in women than in men [8]. However, due to its work-related nature, mesothelioma affects predominantly men, with a ratio of 3:1 [8]. The histological classification of MPM includes three subtypes: epithelioid, sarcomatous, and biphasic. Several studies have demonstrated the correlation between histological subtype and prognosis: the epithelioid form is associated with better survival (14.4 months) when compared to sarcomatous or biphasic mesothelioma (5.4 months) [9].

The treatment of MPM has always been widely debated. Due to its histological features, its aggressiveness, and the average age at diagnosis, no single therapeutic pathway is available to date. Nevertheless, MPM can be the subject of multimodal therapies, aimed at local control of the disease and symptoms, which significantly affect the patient's quality of life. Furthermore, a non-negligible number of novel therapies are entering clinical practice, opening the scenario for more effective therapeutic options in the future. Over the years, chemotherapy has played a fundamental role in the treatment of mesothelioma. The first randomized study on the chemotherapy treatment of MPM was reported by Vogelzang in 2003. The study of the Chicago group demonstrated the efficacy of the combined pemetrexed-cisplatin therapy in improving the survival of patients affected by mesothelioma, compared to cisplatin alone. Median survival in the pemetrexed arm was 12.1 months, while it resulted in 9.3 months with cisplatin alone with a statistically significant value (0.02) [10]. Currently, chemotherapy could be also administered in resectable diseases with neoadjuvant intent. The most used protocol implies the association of cisplatin and pemetrexed, while the co-administration of bevacizumab is not currently recommended, due to the increased risk of intraoperative bleeding [1]. In 2021, Tsao and colleagues presented the SWOG1619 (S1619) trial, which aims to demonstrate the feasibility of the association of neoadjuvant chemo-immunotherapy with cisplatin-pemetrexed and atezolizumab in resectable patients diagnosed with epithelioid or biphasic mesothelioma. The results are encouraging at present, but for a confirmation of the reproducibility, more prolonged follow-up periods, for the evaluation of the oncologic outcomes and the toxicity, will be necessary [11]. In the case of unresectable disease, the association of platinum-pemetrexed with or without bevacizumab for 4-6 cycles followed by bevacizumab maintenance therapy is recommended by several studies [12]. Despite the difficulties in identifying genomic mutations, recent studies aimed at investigating the targeted therapies for pleural mesothelioma have been conducted. Except for ALK-mutated tumors, which are responsive to ALK inhibitors [13], other

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molecular targets are still the object of clinical trials. Olaparib, a PARP (poly ADP ribose - polymerase) inhibitor has given good results in BAP1 wild-type patients [14], Abemaciclib (CDK4/6 inhibitor) could lead to promising outcomes in patients with a lack of p16, as reported by a recent preliminary experience conducted by Fennel and colleagues from the University of Leicester [15]. Cell therapy with dendritic cells and chimeric antigen receptors is currently under investigation, based on the recognition of specific antigens expressed by tumour cells [16].The use of surgery is still debated in the complex mosaic of multimodal treatment of mesothelioma. The objective of a surgical approach to the patient affected by MPM is the macroscopic excision of the disease, therefore considering that complete microscopic eradication is not an achievable goal. Surgery in MPM assumes a transversal role ranging from the histological diagnosis to the curative intent, up to palliation. The NCCN guidelines indeed recognize the role of surgery in pleural biopsy for the diagnosis of MPM, as well as macroscopic removal of the tumor by pleurectomy/decortication (PD) or extra pleural pneumonectomy (EPP) [17]. Surgery also acquires importance in the advanced stages of the disease, for the palliative treatment of recurrent pleural effusion, when pleural drainage placement alone is not sufficient to control symptoms. Furthermore, before surgery, patient evaluation within a multidisciplinary team remains mandatory, for the purpose of defining the most effective and appropriate therapeutic strategy in relation to the patient's condition. The EPP is defined as the resection of the parietal pleura *en bloc* with the ipsilateral lung, diaphragm, and pericardium [18]. The diaphragm and the pericardium can still be spared from surgical resection if there is no gross evidence of involvement by the tumor. Pleurectomy\decortication is instead a less demolition surgery which implies the removal of the parietal and visceral pleura with the pericardium and the ipsilateral diaphragm [18].Over the years, several studies have been conducted to demonstrate the superiority of one surgical options over the others, without being able to obtain univocal results [19].Therefore, the orientation of clinicians has increasingly been directed towards less invasive and debilitating therapies, to reduce the deterioration of the clinical condition and the quality of life of the patients, without impacting oncological outcomes. For all these reasons, the use of high-temperature chemotherapy in conjunction with cytoreductive surgery, first in the abdomen, and then in the thorax, has found widespread use since the 1980s. In fact, it has been amply demonstrated that during the intraoperative chemo-hyperthermia (HITHOC), the high temperature (40-43° Celsius) is able to improve the permeability of cell membranes, favoring the locally cytotoxic action of the chemotherapy as proven by Schaff and colleagues in an in vitro study [20]. Furthermore, the possibility of local chemotherapy avoids the potentially harmful effects of systemic therapies. The first experience of the use of intracavitary cytotoxic agents in association with elevated temperature dates to the 1980s, for the treatment of a pseudomyxoma of the peritoneum [21]. While, in the treatment of thoracic neoplasms, the first experience of the use of intracavitary chemotherapy for MPM is reported in the study by Rusch in 1992 [22]. Subsequently, in 1999, Ratto and colleagues demonstrated largely positive pharmacokinetics and few systemic effects on the organism in 10 cases of stage I-II MPM treated with hyperthermic intrathoracic perfusion using cisplatin [23]. Based on the positive results of the previously cited studies, Jarvinen and colleagues published a systematic review on this topic in 2021, analyzing a total of 11 observational studies which focused on the comparison between MPM patients who underwent surgery followed by HITHOC and control patients who were not subjected to HITHOC. The review revealed a statistical significance in terms of survival, favoring the HITHOC group, particularly in patients affected by epithelioid mesothelioma [24]. Therefore, taking into account the literature data, cytoreductive surgery with HITHOC is routinely considered in the clinical practice of several centers.

1.2. Thymoma and thymic carcinoma.

Thymoma is a rare malignant neoplasm that represents a large part of anterior mediastinal tumors (47%) [25]. Thymoma originates from thymic epithelial cells and it is often associated with several immunologic disorders such as myasthenia gravis, red cell aplasia and connective tissue diseases. Particularly, about 30% of patients with thymoma are affected by myasthenia gravis and this correlation allows an early diagnosis of thymic diseases. The incidence of thymoma is between

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0.13 and 0.32/100.000/year and the most affected age group is the middle age, 45–55 years. [26,27]. In 1981, Masaoka and colleagues proposed the classification of thymoma, which is still the most used, based on the extent of either macroscopic or microscopic invasion into mediastinal structures. [28]. Both the International Collaboration on Cancer Reporting (ICCR) and the new guidelines of the NCCN (National Comprehensive Cancer Network) contemplate the use of TNM staging systems [29,30]. Thymoma is often described as an indolent tumor; only 10% of cases are metastatic at the time of diagnosis. A local invasion is more common than to lymph nodes or distant organ metastases, which are seen in less than 5% of cases [31].

Due to its slow progression and low rate of distant metastases, the prognosis of thymoma is good and it depends mainly on resection status, tumor stage (Masaoka-Koga staging system) and histology. Thymic carcinomas (TC) represent a distinct group and they are typically not associated with myasthenia gravis. TC accounts for less than 10% of thymic neoplasms. Characteristically, it is more aggressive than thymoma and, at the time of diagnosis, it is often associated with a local invasion[32].The strategy of treatment of thymoma is based on the possibility of radical resection and surgery represents the gold standard in early stages[33].On the other hand, the treatment of advanced stages and the treatment of TC is still strongly debated, making the role of surgery integrated in a multimodal approach. Modh and colleagues investigated patients affected by stage III–IVa Masaoka-Koga thymoma and patients affected by thymic carcinoma in a retrospective study published in 2016. The authors made a comparison between patients treated with a three-modality treatment (surgery, chemotherapy and radiotherapy) and patients treated with no-three modality protocol. The chemotherapy was performed in both ways, pre- and post-operatively and the most common regimen was cyclophosphamide, doxorubicin, and cisplatin. This study shows greatest benefit from three-modality therapy, including improved OS in patients with stage III disease, although no statistically significant differences were found according to the aggressiveness of treatment received [34]. Multimodal treatment protocols, including systemic medical therapy in combination with surgery, have improved the therapeutic options not only in advanced thymic tumors but also in recurrences. Pleural dissemination is the most common localization of relapses (75%) after first surgical treatment [34] and the resection of the pleural recurrence is a major predictor of favorable outcomes in this setting, with the possible integration of systemic therapy. Despite the absence of many randomized trials, HITHOC is indicated for patients with stage IVa thymoma, characterized by pleural or pericardial dissemination [35], in which the chemo-hyperthermia (42°C) is performed after the excision of the relapses. In 2001, Rafaely and colleagues conducted the first study focused on the role of surgical resection and intrathoracic perfusion of chemotherapy for stage IVa thymic malignancies, describing positive results in terms of locoregional disease control and postoperative morbidity rate. Similar outcomes were reported by De Bree et al., one year later. In both of these studies no mortality rate was reported; concerning the surgical complications all the authors described a low rate of events and particularly they reported bleeding, fever and air leak without hemodynamic or respiratory events during the procedure [36,37]. In 2015 Ambrogi published a prospective study of a single-center experience of patients with pleural recurrence of thymoma who underwent surgery followed by HITHOC. This study demonstrated that HITHOC was feasible in all cases, with a postoperative morbidity rate of 38%. Furthermore, 85% of patients were alive after a mean follow-up period of 64.6 months; this result is in line with the literature, reporting 5-year survival rate after surgery, between 30 and 75% in different series, with or without neoadjuvant chemotherapy [38]. More recently, in 2023, a systematic review was published by Vandaele et al. focused on the role of cytoreductive surgery combined with HITHOC for pleural disseminated thymoma (TPR)or de novo Masaoka stage IV thymoma (DNT). According to this review the Disease-Free Interval (DFI) ranged from 6 to at least 88 months in the whole study population cohort, and 5-year survival rate ranged from 70% to 92%. Despite multicentric randomized trials are still lacking, the previously published studies seem to support the role of surgery combined with HITHOC in this stage of thymic disease. Therefore, this combined approach could be considered a promising treatment with the potential to improve disease control without compromising the postoperative outcomes [39]. To date, the studies concerning the role of surgery and HITHOC for pleural

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dissemination of thymoma or mesothelioma was exclusively conducted on patients treated with open technique. Minimally invasive surgery could have a positive impact on the outcomes of patients eligible for pleurectomy/removal of pleural lesions plus HITHOC, minimizing the surgical trauma, with lower complication rate and faster recovery, reducing the risk of delays in starting adjuvant therapy. Robotic surgery is currently the most advanced form of minimally invasive surgery, allowing complex procedures to be performed with high precision. Thanks to its features, robotic surgery also allows access to the remote areas, with a complete and accurate exploration of the pleura. The focus of this study is to analyze a single center experience in the robotic treatment of mesothelioma and pleural thymoma relapses combined with HITHOC.

2. Robotic surgery combined with HITHOC, our experience.

2.1. Materials and Methods

The data of patients who underwent robotic surgery in combination with HITHOC, from 2017 to 2022, were analyzed. Patients affected by clinical stage I MPM and with pleural recurrence of thymoma (clinical stage IVa) were selected. Clinical characteristics of the patients, surgical, short-term postoperative and oncological results were collected. The surgical parameters analyzed were time of surgery, rate of conversion, post-operative complications (according to Clavien-Dindo classification), chest tube duration and the length of hospital stay.

The oncological results are expressed in terms of adjuvant treatments with the number of therapy cycles, the rate and the date of eventual relapses, the treatment of the relapse and the overall survival.

The surgery was performed with a four-access robotic technique under general anesthesia and selective orotracheal intubation. The dedicated circuit for the continuous infusion of chemotherapy, diluted in crystalloids, is connected directly to the two pleural drains positioned at the end of surgery, through two of the surgical accesses. A 0.4 cm diameter thermometric probe is introduced into the pleural cavity to constantly monitor the temperature. The perfusion of the chemotherapy drugs, cisplatin (80 mg/m^2) and epirubicin (25 mg/m^2), was performed at the end of the cytoreductive phase for 60 minutes at a constant temperature of 42°C. The therapeutic peri-operative protocol presented in this experience consists of 2000 cc of hydration with different electrolytic solutions, pantoprazole, loop diuretic and 8 mg of corticosteroid the day before surgery. Subsequently, the day of surgery 3000 cc of hydration, pantoprazole, loop diuretic and corticosteroid were administered. At last, from the first to the 5th postoperative day, 2000 cc of hydration with gastric protection, loop diuretic and 4 mg of corticosteroid were infused. In addition, the patients are treated with enoxaparin during the postoperative stay.

2.2. Results

The data of 9 patients affected by thymoma relapses or MPM who underwent robotic surgery in combination with HITHOC, from 2017 to 2022, were collected and analyzed. Epithelioid mesothelioma was diagnosed in 4 (44%) patients;3 were females (75%) and 1 male (25%), with mean age of 64, 5 (SD 9, range 55-78). One conversion (25%) to posterior-lateral thoracotomy was reported, due to tenacious pleural adhesions. The mean time of surgery, including the docking time and HITHOC has resulted in 287 minutes (SD 70). In all cases the drugs used for infusion were Cisplatin and Epirubicin. Post-operative complication was observed in 2 (50%) cases, represented by 1 (25%) case of Atrial Fibrillation, Grade II according to Clavien- Dindo classification, treated with cardioversion and 1 (25%) case of prolonged air leak (Grade I). The main duration of the chest tube was 6 days (SD 1.4) (range 5-8); the length of stay was 9 (SD 1.7) (range 7-11). The adjuvant therapy was administered in 3 (75%) patients affected by MPM; in all cases consisted of 6 cycles of Pemetrexed and Cisplatin. During the follow-up, 2 (50%) patients showed a relapse, respectively 36 and 20 months after the procedure. Both recurrences involved the ipsilateral pleura and one of them also the ipsilateral lung. The treatment of the relapse was in both a combination of radiotherapy and Pemetrexed. After a mean follow-up of 52 months (SD 25.2) (range 15-72), all the patients were alive.

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The patients with diagnosis of cIVa thymoma treated with HITHOC were 5 (56%); 3 were men (60%) and 2 women (40%), with a mean age of 50 (SD 13.2, range 34-62). Previously, 3 patients (60%) underwent thymectomy by sternotomy, while in 2 cases (40%) the procedure was performed by robotic approach. The thymoma histology was represented by B1 in 1 (20%) case, B2 in 2 (40%) patients, B3 in 1 (20%) case and thymic carcinoma 1 (20%) case. 4 patients (80%) were treated with an adjuvant protocol after the thymectomy. The surgical procedure combined with HITHOC was pleurectomy in 1 (20%) case and removal of pleural recurrences in the other 4 (80%) cases. There was no conversion to open surgery in this group of patients. The mean operative time resulted in 313 (SD 98.8) minutes, including the docking time and HITHOC. No intraoperative complications were registered. Concerning postoperative complications 1 patient (20%) presented prolonged air leak (Grade I). The time of chest tube duration resulted in 6 days (SD 2.2, range 4-10); the mean length of stay was 6 (SD 0.8, range 6-8). After surgical procedure, 1 (20 %) patient was treated with chemotherapy plus radiotherapy because of a mediastinal residual disease ,1 (20%) with adjuvant chemotherapy. During the follow-up, 3 (60 %) patients showed an ipsilateral pleural recurrence, and 1 (20%) a pleural and lung contralateral relapse. The median time of relapse was 23 months (DS 17.3). 1 (20%) of them were treated with chemotherapy while 3 (60%) patients underwent a second surgical procedure with HITHOC, in 2 cases on the same side and in 1 case on the opposite side. After a mean follow up of 58 months (SD 6.8, range 48-69) all the patients are alive.

3. Conclusions and future directions

The advent of robotic surgery has been a game-changing improvement compared to the minimally invasive approaches of the past. [40]

Over the years, in the thoracic field, the robotic approach have allowed to overcome all the limits of video-assisted thoracoscopic surgery, thanks to the 3D high-definition vision, the magnification of image up to 10 times, the 7 degrees of freedom of the instruments and the filtration of physiologic hand tremor.

The robotic system has become progressively widespread, and published studies have demonstrated improved intraoperative and postoperative outcomes and extension of surgical indications [41]. Furthermore, robotic surgery can play a role in patients affected by early stage of pleural mesothelioma or in case of pleural recurrence of thymoma. In fact, in scientific literature, recurrence with a pleural dissemination is reported also after radical resection of thymoma. [42]

As Ruffini et al described in their article published in 1997, the total resection of the recurrences offers the best chance of long-term survival, when compared to the medical treatment. Moreover, the authors underline how the surgical removal of the relapses could be difficult due to the second time surgery and the disseminated localization of the pleural disease, which may be undetectable at the preoperative CT scan [43]. The technical characteristics of robotic system can help to overcome these challenges, as Cavaliere reported in a case report in 2017. The robotic technique was found to be useful and effective to explore the whole chest cavity with the aim to identify also small and previously undetected pleural relapses [44].Agustin and coworkers reported the same advantage in the use of robotic technique in a paper published in 2006: the technical features of the da Vinci™ system are most advantageous in tiny and difficult-to-reach anatomical regions with a low rate of intra operative complications [45]. Concerning the MPM, the first case of robotic pleurectomy in patients with MPM were described in a case report published in 2015. The Author observed a higher freedom of motion of the instruments in the chest cavity and a low blood loss during the procedure, confirming how this approach could be considered feasible and safe even for demolitive surgeries [46]. According to Optiz and colleagues, surgery for MPM is still considered associated with too high morbidity and mortality. The best long-term results are achievable just with a multimodality treatment and surgery has its pivotal role [47]. In our experience, both for patients affected by early-stage pleural mesothelioma or stage IVa thymoma, no intraoperative complication were reported in association with a low rate of postoperative complication, comparing to the literature data [48]. Moreover, the duration of the chest tube and the length of stay in our patients affected by MPM and treated with pleurectomy and HITHOC with robotic approach seems to be shorter than the same

procedure with other approaches [49,50]. The surgical outcomes achieved by robotic technique in our case series could represent a fundamental factor for the post-operative management: a short hospital stay allows a faster recovery and an early start of adjuvant therapy. The importance of adjuvant therapy in MPM patients is known from the first publication of Butchart in the early 80s. As the author described, the barrier to the effectiveness of the adjuvant treatment was the high rate of perioperative morbidity and mortality [51]. As Cao et al. discussed in their systematic review, the improvements in surgical techniques and perioperative care have resulted in significantly superior outcomes in patients treated with multimodality therapy [52]. The limitations of our experience are the small sample of patients and the short follow-up period for patients affected by thymoma. Although more data is needed, robotic surgery combined with hyperthermic intraoperative chemotherapy seems to be effective in terms of favorable surgical outcomes of patients and faster recovery, allowing an appropriate integration in multimodal therapy.

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