

CASE REPORT

Open Access



Extensive surgical resections for rare pleural neoplasms: a single-center experience with a yolk sac tumor and synovial sarcoma

Tom Vandaele^{1,2*}, Jan Van Slambrouck^{1,2}, Patrick Schöffski^{3,4}, Herlinde Dumez^{3,4}, Birgit Weynand^{5,6}, Raf Sciot^{5,6}, Annalisa Barbarossa^{1,2}, An-Lies Provoost^{1,2}, Kristof Van de Voorde⁷, Yves Debaveye^{8,9}, Sofian Bouneb^{10,11}, Philippe Naftoux^{1,2} and Laurens J. Ceulemans^{1,2}

Abstract

Background Pleural neoplasms are rare and can be subdivided into pleural metastasis and primary pleural neoplasms. Non-mesothelioma primary pleural neoplasms are a diverse group of extremely rare pathologies.

Case presentation In this case series, we describe the presentation and management of two rare primary pleural neoplasms. A first case describes a primary pleural yolk sac tumor treated with neoadjuvant chemotherapy, extended pleurectomy decortication, and hyperthermic intrathoracic chemotherapy. In a second case we describe the management of a primary pleural synovial sarcoma by neoadjuvant chemotherapy and extrapleural pneumonectomy. A complete resection was obtained in both cases and the post-operative course was uncomplicated. No signs of tumor recurrence were noted during follow-up in the first patient. In the second patient a local recurrence was diagnosed 6 months after surgery.

Conclusion Neo-adjuvant chemotherapy followed by extensive thoracic surgery, including hyperthermic intrathoracic chemotherapy, is a feasible treatment strategy for non-mesothelioma primary pleural neoplasms, but careful follow-up is required.

Keywords Pleural yolk sac tumor, Pleural synovial sarcoma, Hyperthermic intrathoracic chemotherapy, Pleural tumor

*Correspondence:

Tom Vandaele
vandaeletom@live.be

¹Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium

²Department of Chronic Diseases and Metabolism, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium

³Department of Oncology, University Hospitals Leuven, Leuven, Belgium

⁴Department of Oncology, Laboratory of experimental Oncology, KU Leuven, Leuven, Belgium

⁵Department of Pathology, University Hospitals Leuven, Leuven, Belgium

⁶Department of Imaging and Pathology, Laboratory of translational cell and tissue research, KU Leuven, Leuven, Belgium

⁷Department of Perfusion, University Hospitals Leuven, Leuven, Belgium

⁸Department of Intensive care, University Hospitals Leuven, Leuven, Belgium

⁹Department of cellular and molecular medicine, Laboratory of Intensive care, KU Leuven, Leuven, Belgium

¹⁰Department of Anesthesiology, University Hospitals Leuven, Leuven, Belgium

¹¹Department of cardiovascular science, Laboratory of anesthesiology and algology, KU Leuven, Leuven, Belgium



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Malignant pleural neoplasms are rare oncological diseases with the vast majority being pleural metastasis [1]. Among primary pleural tumors, malignant mesothelioma (MM), although rare, is most frequently encountered [1, 2]. Other primary pleural malignancies comprise a rare and diverse group of diseases, e.g. pleural desmoid tumor, malignant solitary fibrous tumor, desmoplastic small round cell tumor, Askin tumor, pleuropulmonary blastoma, or primary pleural lymphoma. These are due to their rarity mainly described in case reports or case series [1–3]. Differential diagnosis of pleural neoplasms is further complicated by a variety of benign pleural neoplasms including solitary fibrous tumors, lipomatous tumors, adenomatoid tumors, calcifying fibrous tumors, simple mesothelial cysts, multicystic mesothelioma, and schwannoma [1]. Because MM is by far the most frequent primary pleural neoplasm representing 90% of all primary pleural tumors, clear guidelines for its treatment are available [2, 4]. However, for non-mesothelioma primary pleural tumors there is a lack of robust evidence to guide therapeutic decision-making.

In this case series, we report the management, surgical procedure, and short-term outcome of two exceptionally rare cases of primary pleural tumors. The first patient suffered from a primary pleural yolk sac tumor which has, to our knowledge, never been described in a living patient. The second patient had a primary pleural synovial sarcoma. Both patients were treated with neo-adjuvant chemotherapy and extensive surgical resection.

Case presentation

Primary pleural yolk sac tumor treated with induction chemotherapy, extended pleurectomy decortication, and hyperthermic intrathoracic chemotherapy

A 37-year-old white female was referred to our center with worsening dyspnea (NYHA II-III), chest pain during breathing, epigastric pain, a weight loss of 5 kg over 6 months, and nocturnal hyperhidrosis. She also had a history of smoking (5 pack years), but no other relevant medical history. An initial work-up for epigastric pain, with abdominal ultrasound and gastroscopy was negative. Because of the worsening dyspnea a chest CT-scan was performed, which revealed a large left-sided pleural effusion and multiple small pleural nodules highly indicative for a malignancy originating from the pleura. (Fig. 1a&b) Initially a thoracentesis was performed, but histopathological analysis of the pleural fluid was inconclusive. Because of the highly suspicious pleural thickening a uniportal thoracoscopic biopsy was performed to rule out malignancy. Thoracoscopy revealed multiple tumoral nodules on the left parietal and visceral pleura, and left hemidiaphragm. (Fig. 2a-d) Histopathology confirmed the diagnosis of a hepatoid-type pleural yolk sac tumor.

Because yolk sac tumors often arise from a gonadal origin, a transvaginal ultrasound was performed to rule out a disseminated ovarian yolk sac tumor [5]. Furthermore, laboratory tests revealed elevated alpha-fetoprotein levels (α -FP) of 68.300 μ g/l, further confirming the diagnosis of a yolk sac tumor. To identify any distant metastasis, a PET-CT scan was performed, which only revealed localized hypermetabolic activity in multiple pleural nodules in the left hemithorax. (Fig. 3a)

Etoposide and cisplatin chemotherapy was initiated, resulting in decreased serum alpha-fetoprotein levels (3159 μ g/l) and a tumor mass reduction on CT-scan. Due to reduced response after three cycles of etoposide and cisplatin, with a further α -FP decrease to only 2453 μ g/l after the last cycle, treatment was switched to paclitaxel, cisplatin, and ifosfamide (TIP-chemotherapy). The TIP-regimen was not tolerated well and associated with hearing loss, bilateral tinnitus, peripheral sensory neuropathy, and eventually neutropenic fever, thrombocytopenia, and anemia (6.8 g/dL). Furthermore, after an initial decrease to 1943 μ g/l, α -FP levels started rising again. Therefore, after two TIP cycles, rescue with extensive surgical resection was considered.

A preoperative functional workup was performed, revealing normal pulmonary function tests with a slightly decreased diffusion capacity (FEV1 84% - FVC 89% - TLCO 54%), a normal myocardial perfusion scan and cardiac ultrasound, and a V/Q scan revealing a slight superiority of the right lung (ventilation 60% - perfusion 62%) in comparison to the left lung (ventilation 40% - perfusion 38%). Oncological workup with chest CT and whole-body PET-CT scan showed a reduction of tumoral load and confirmed the absence of extra-thoracic disease (Fig. 3b). Chest MRI visualized the persistence of multiple pleural nodules with involvement of the inferior pulmonary ligament and hemidiaphragm, but without mediastinal or chest wall invasion (Fig. 1c&d).

To achieve a complete resection, we performed a left-sided extrapleural thoracotomy with 6th rib resection (Fig. 4a&b), followed by an extended pleurectomy decortication (ePD), including the resection of the left hemidiaphragm and a large part of the pericardium. (Fig. 4c&d) Our ePD procedure adheres to a standardized protocol used in all operable mesothelioma cases. This includes a parietal pleurectomy and visceral decortication, followed by meticulous hemostasis and aërostatics, and finally the construction of a neopleura. During the visceral decortication we create a plane between the visceral pleura and the lung parenchyma, then gently peel or strip the visceral pleura outwards while ensuring the integrity of the underlying lung parenchyma. Careful aërostatics is achieved afterwards by suturing major air leaks and constructing a neopleura using an absorbable polyglycolic acid sheet (Neoveil) and polymeric hydrogel

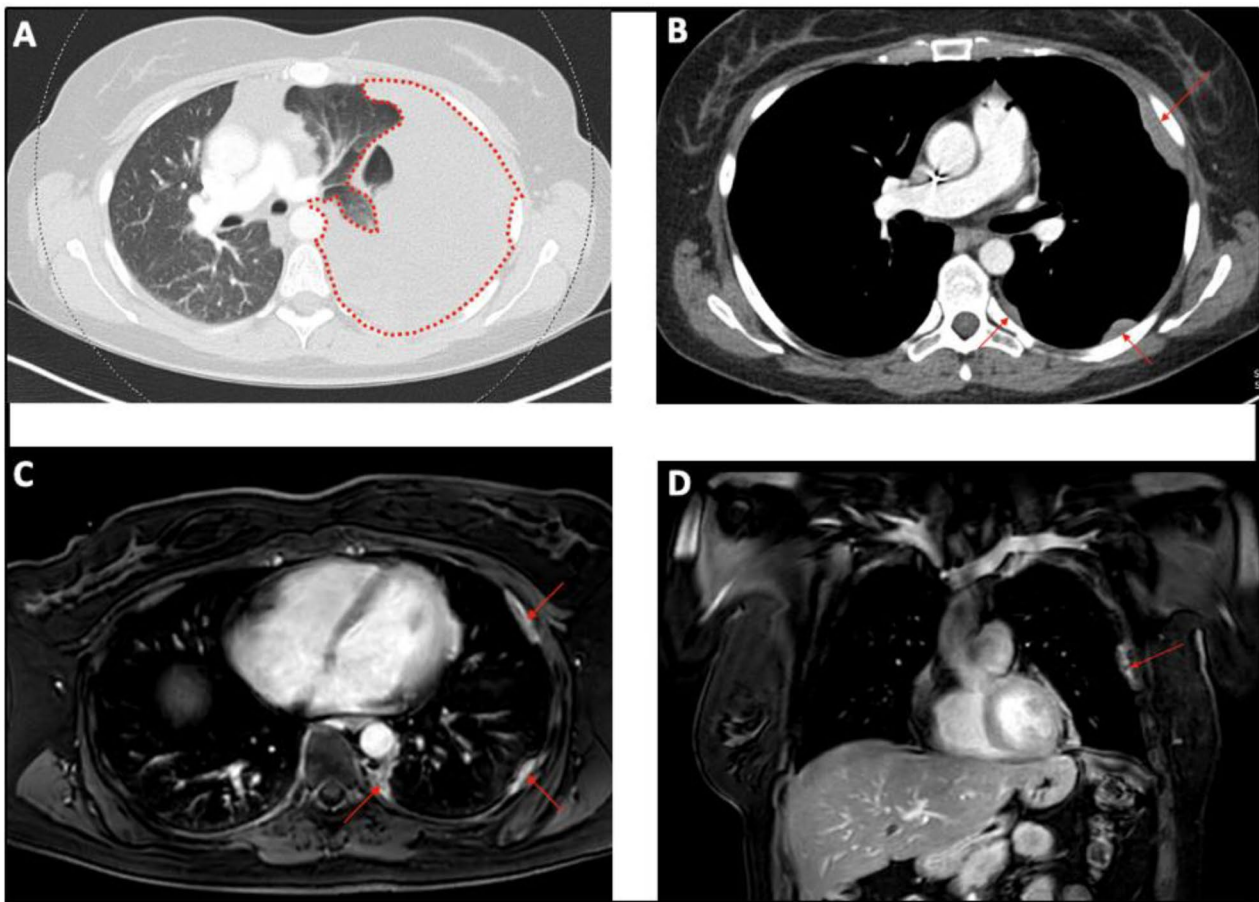


Fig. 1 (A) Chest CT showing a large left sided pleural effusion; (B) Chest CT after thoracocentesis revealing multiple pleural nodules; (C) Preoperative chest MRI showing residual pleural disease post-chemotherapy; (D) Preoperative chest MRI showing residual pleural disease post chemotherapy

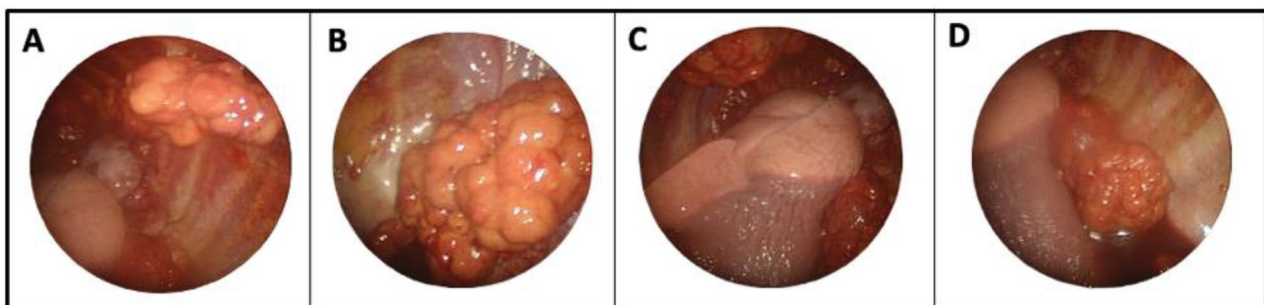


Fig. 2 (A, B, C, D) Pleural yolk sac tumor on thoracoscopy

sealant (Progel). After complete macroscopic resection, further control of tumor load was pursued with Hyperthermic IntraTHORacic Chemotherapy (HITHOC). The left pleural space was rinsed with 806 mg Oxaliplatin for 45 min. The intrathoracic temperature was kept between 41.6 °C and 42.5 °C. Our HITHOC setup consisted of a RAND Performer HT and a disposable RAND Hang&Go HT basic set containing three 28 Fr outflow drains and two 24 Fr inflow tubes. The total intrathoracic fluid volume was 3500 cc and flow rates of 940 cc/minute were

achieved. Eventually the thoracic cavity was rinsed with 3000 cc of Physioneal 40 after 45 min of perfusion. (Fig. 4e) Finally, the diaphragm and pericardium were reconstructed using a Gore-tex patch (Fig. 4f). Postoperative recovery was uneventful, and the patient was discharged from hospital on postoperative day (POD) 26. A brief readmission was needed after presentation with a fever and fatigue caused by a urinary tract infection. Ten months after surgery PET-CT scan showed no signs of recurrence (Fig. 3c&d), and serum α -FP levels decreased

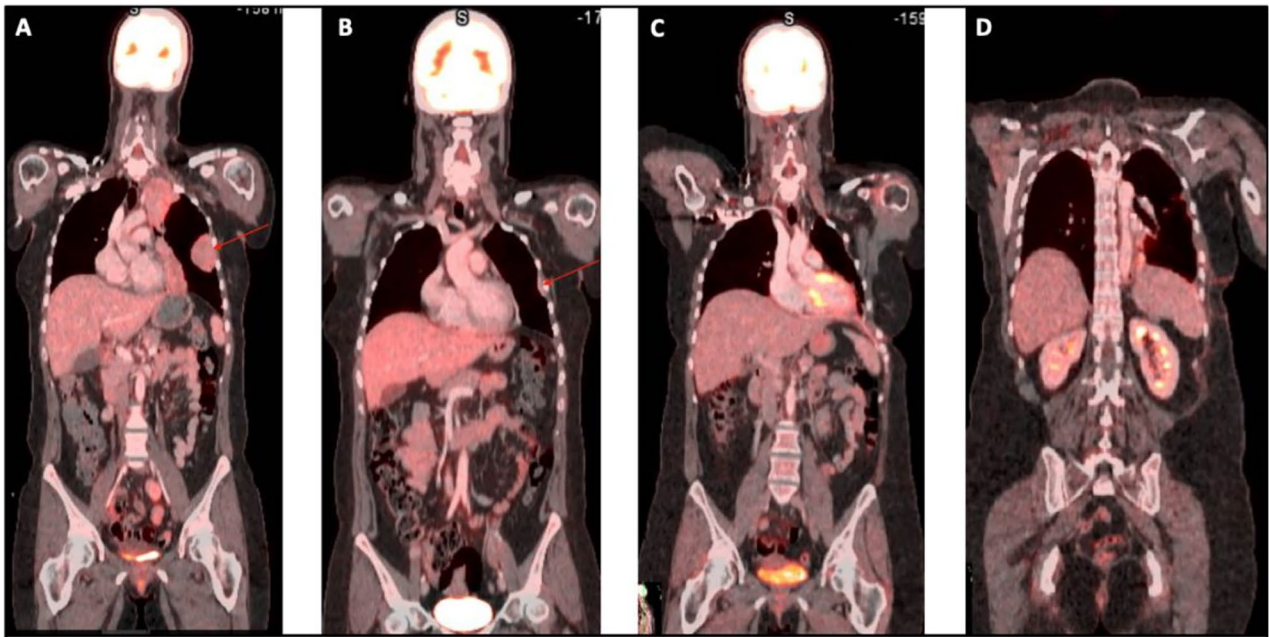


Fig. 3 (A) PET-CT prior to chemotherapy; (B) PET-CT after neoadjuvant chemotherapy; (C-D) PET-CT 6 months after surgery

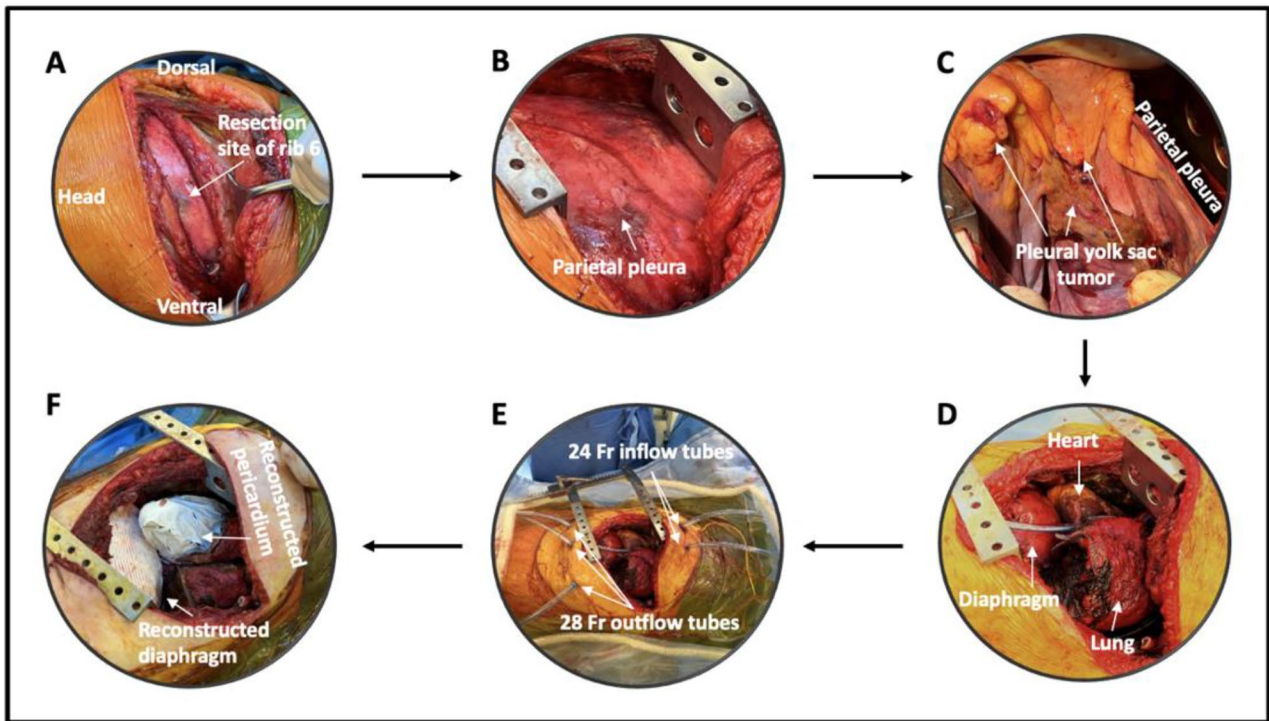


Fig. 4 Step by step extended pleurectomy decortication with resection of the left hemi-diaphragm and partial pericardial resection followed by HITHOC and reconstruction. (A) Left sided thoracotomy with resection of the 6th rib, (B) Extrapleural pleurectomy; (C) Visualization of the pleural yolk sac tumor and decortication (D) Completion of the extrapleural pneumonectomy with left hemi-diaphragmatic and partial pericardial resection, (E) HITHOC setup, (F) Final result after diaphragmatic and pericardial reconstruction

to a minimum of 18 $\mu\text{g/l}$. Currently, the patient is in good physical and mental health, and she has regained weight and functional status.

The pathology report confirmed a successful and complete (R0) resection of a hepatoid type pleural yolk sac tumor, as evidenced by positive staining for perkeratine, Alpha-Fetoprotein, and Glypican-3. (Fig. 5) However, it is worth noting that SALL4 staining was only weakly positive, and a pure hepatoid growth pattern was observed. Additionally, although a significant decrease in $\alpha\text{-FP}$ was noted during neo-adjuvant chemotherapy, the histopathological analysis revealed very little response to the neo-adjuvant chemotherapy with extensive residual disease in the resection specimen. The limited response to chemotherapy is rather unusual for a yolk sac tumor. Despite these atypical findings, thorough imaging examinations, and endoscopy with gastric and esophageal biopsies did not reveal any evidence supporting alternative diagnoses such as metastasis from a primary hepatocarcinoma or a hepatoid carcinoma originating from the gastric or esophageal regions. It is possible that different growth patterns, apart from the hepatoid pattern, might have been eliminated by the chemotherapy, challenging final pathological diagnosis.

Due to the rarity, aggressive nature, and ultimately the high risk for recurrence in this young patient, a strict follow-up program is proposed. During the first 2 years post-surgery, a 3 monthly follow-up is scheduled with

an alternating control PET-CT and CT scan. After two years, follow-up intervals are extended to 6-months.

Pleural synovial sarcoma treated with neoadjuvant chemotherapy and extrapleural pneumonectomy

A 26-year-old male patient was referred to our center with progressive dyspnea (NYHA III), chronic pain in the left hemithorax, inspiratory stridor, and absent breath sounds on the left side. Chest X-ray and CT scan revealed a large left-sided pleural effusion with complete collapse of the left lung and abnormal pleural thickening (Fig. 6a-c). Thoracocentesis drained 2.7 L of pleural fluid in which no cytological evidence for malignancy was found. To exclude tuberculosis, a PCR test and an auramine staining was performed on the pleural fluid but both came back negative. Due to the suspicious nature of the pleural thickening, an exploratory thoracoscopy was performed. Thoracoscopy confirmed diffuse pleural thickening of which multiple biopsies were taken. Microscopic analysis was highly suggestive for a synovial sarcoma. Further histopathological analysis discovered an *ss18* rearrangement in 53% of nuclei on FISH analysis, hereby confirming the diagnosis of a pleural synovial sarcoma. Further work-up with whole-body PET-CT scan did not reveal any metastasis. (Fig. 6d)

The tumor was initially deemed borderline inoperable, but the recent pleurodesis complicated the evaluation of the extent of pleural involvement on imaging. As such,

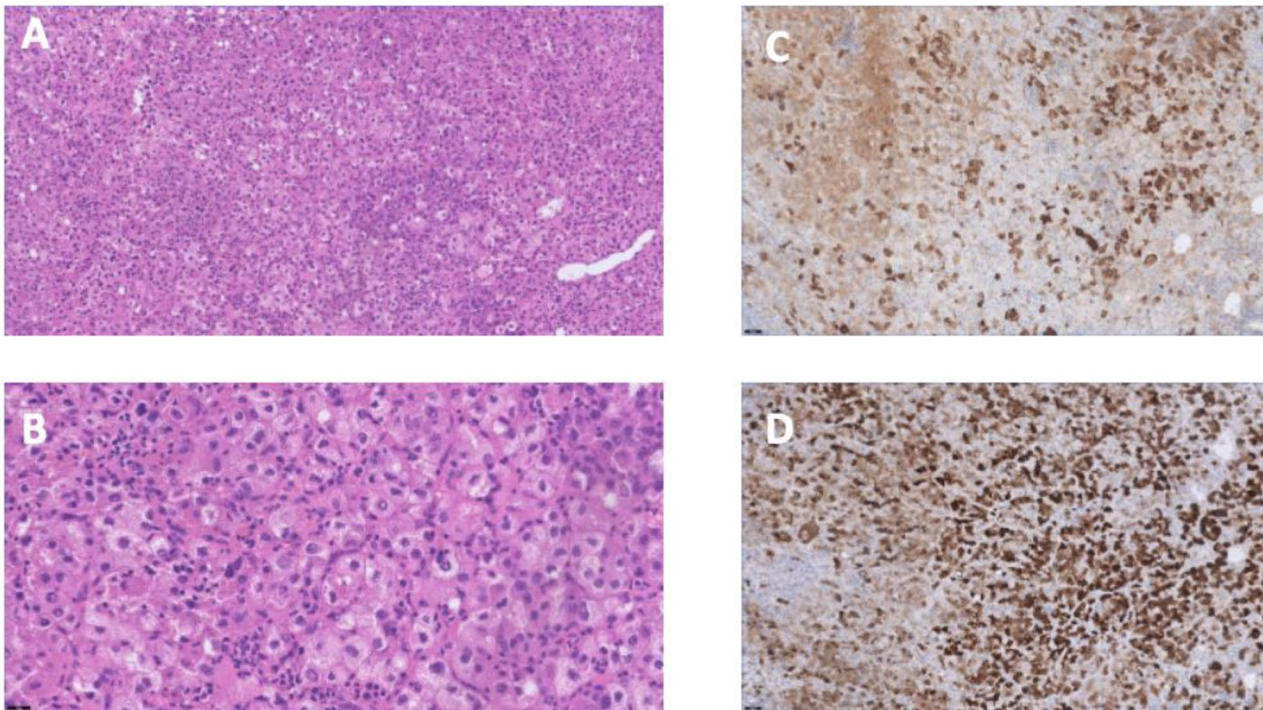


Fig. 5 Histopathology of the pleural yolk sac tumor: (A-B) hematoxylin and eosin staining of a malignant tumor with a hepatoid aspect. (C-D) SALL4 and alpha-fetoprotein staining of the tumor cells proving the germ cell origin. These elements together plead for a hepatoid variant of a yolk sac tumor

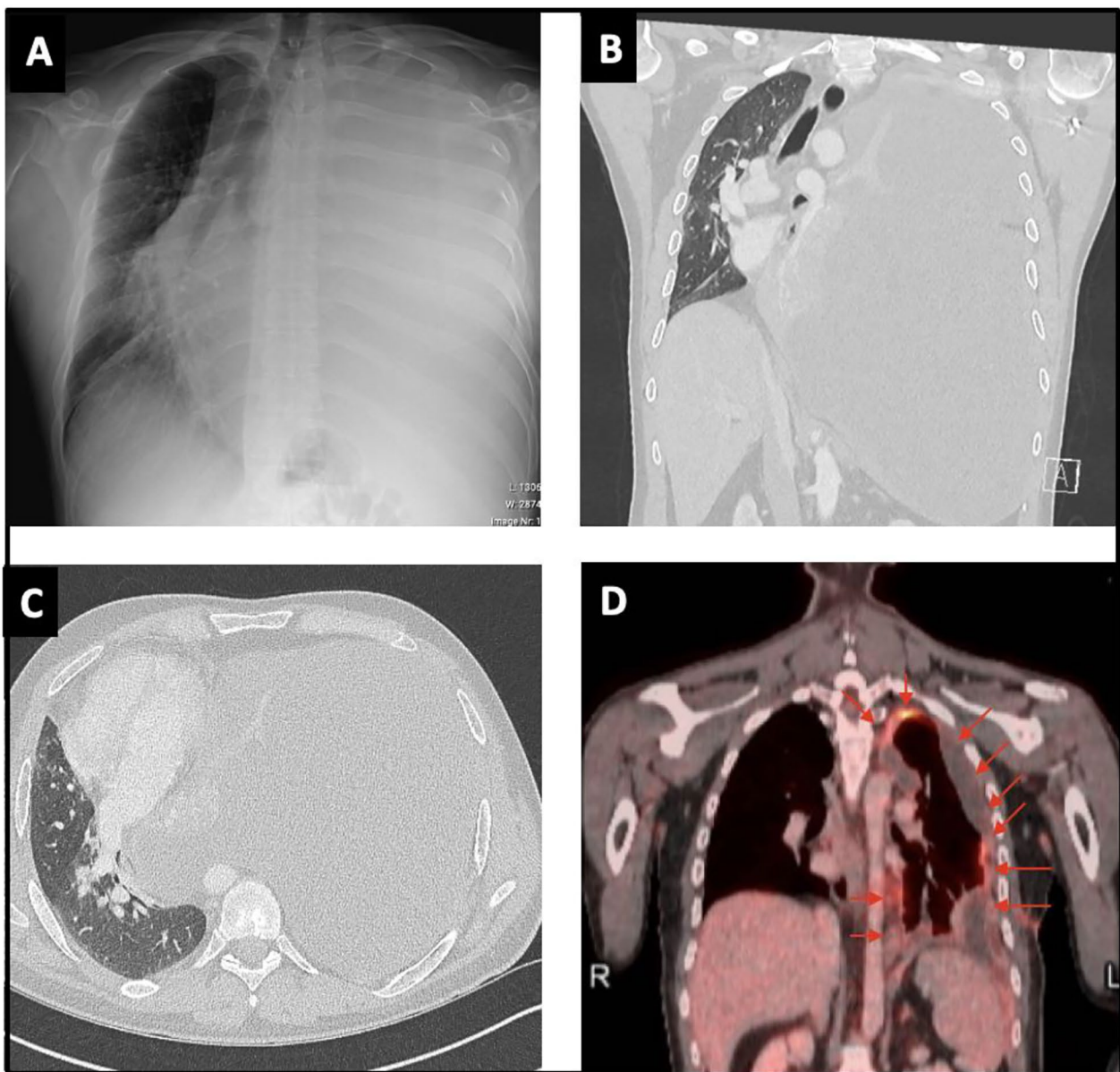


Fig. 6 (A, B, C) Chest x-ray and CT scan showing a large left-sided pleural effusion with abnormal pleural thickening; (D) PET-CT prior to neoadjuvant chemotherapy showing diffuse pleural thickening (partially due to a recent talcage), but without extra-thoracic disease

because synovial sarcomas are generally more chemo sensitive, doxorubicin and ifosfamide chemotherapy was initiated in an attempt to reduce tumoral load, and increase the chance of obtaining a complete resection in the future [6–8]. Chest CT after 6 cycles of chemotherapy showed stable disease but no signs of tumor reduction (Fig. 7a-c). A preoperative functional work-up was performed, myocardial perfusion scintigraphy and cardiac ultrasound were normal. VO_2 max during cyclo-ergometry was only 43%. Pulmonary function tests revealed a decreased VO_2 max of 43%, FEV1 of 46%, and FVC of 51%. V/Q scan showed a normal right lung but an important reduction in ventilation (20%) and perfusion (9%)

of the left lung. Preoperative oncological work-up with chest CT and MRI showed unchanged tumor dimensions with signs of mediastinal fat involvement but without invasion of the chest wall or mediastinal structures (Fig. 8a&b), PET-CT confirmed residual hypermetabolic pleural disease without arguments for extra-thoracic disease (Fig. 8c-e).

After a negative diagnostic laparoscopy to exclude peritoneal involvement and transdiaphragmatic growth, we performed an extrapleural pneumonectomy (EPP) (Fig. 9a&b), with excision of the thoracoscopy ports, a partial pericardial resection, resection of the left hemidiaphragm, and resection of the 6th rib and anterolateral

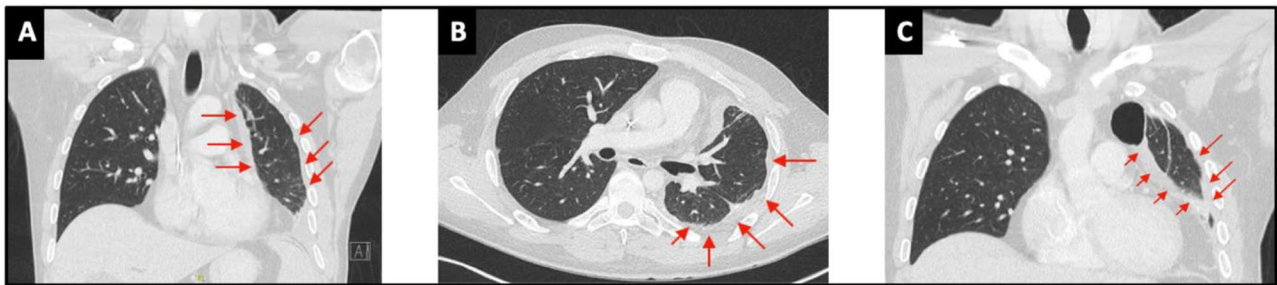


Fig. 7 (A, B, C) Chest CT-scan after 6 cycles of neoadjuvant chemotherapy showing stable disease

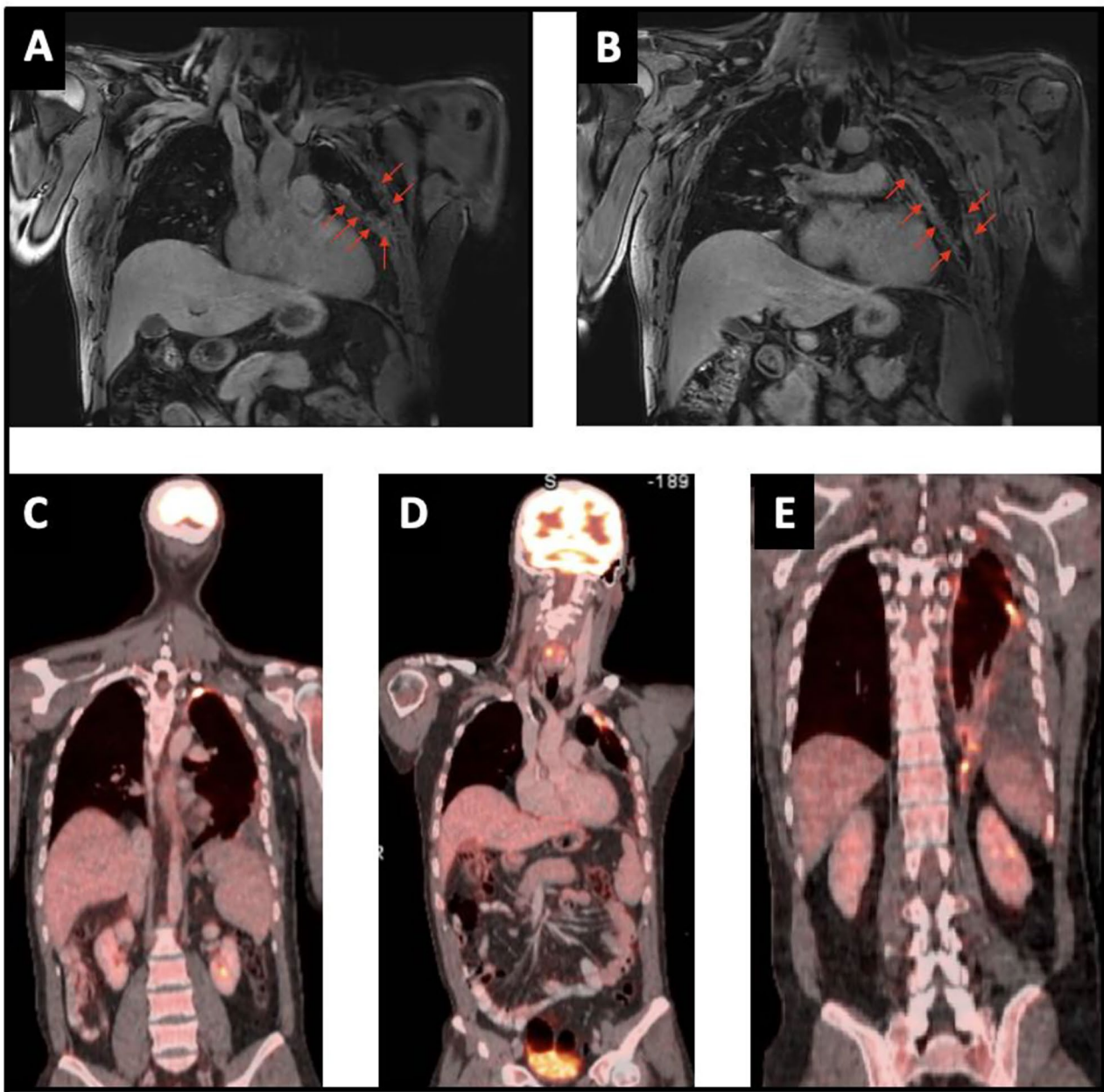


Fig. 8 (A, B) Preoperative chest MRI showing residual pleural disease after chemotherapy; (C, D, E) Preoperative thoracic PET-CT showing residual active pleural disease after chemotherapy

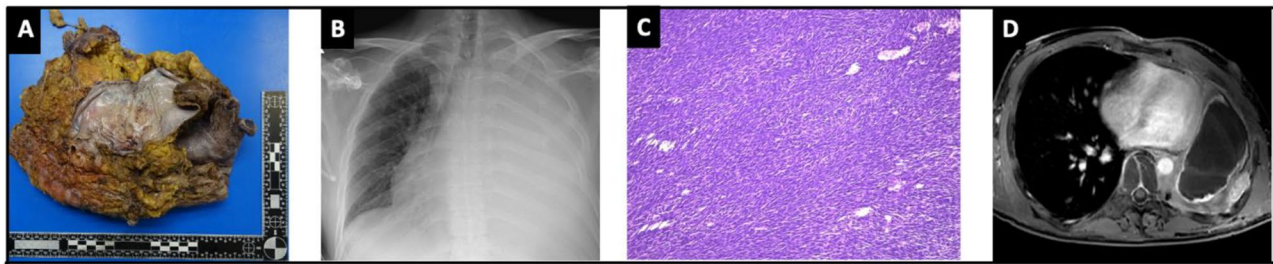


Fig. 9 (A) Extrapleural pneumonectomy resection specimen; (B) Chest x-ray 1 month post extrapleural pneumonectomy; (C) Hematoxylin & eosin stain showing the typical fascicular and herringbone growth pattern of a monophasic synovial sarcoma; (D) Tumor recurrence on chest MRI after 9 months

parts of ribs 4 and 5. Our EPP procedure is performed via a standardized protocol, starting with an extrapleural and mediastinal dissection, after which the internal mammary chain and thymus are resected. A minor challenge we encountered during the extrapleural dissection was the presence of multiple adhesions posteriorly where the thoracoscopic biopsies were taken. After this, the diaphragm was resected while leaving the peritoneal lining intact, and a dissection plane around the aorta and esophagus was followed upwards and the pulmonary hilum was transected. After the resection, the thoracic cavity is scrubbed with povidone-iodine to remove any residual malignant cells. Finally, a pericardial and diaphragmatic reconstruction was performed using a Gore-Tex patch. During the several steps of this procedure, multiple frozen sections were analyzed to ensure complete resection.

Histopathological examination confirmed the diagnosis of an R0 resected pleural synovial sarcoma. (Fig. 9d) Surprisingly, in contradiction to what was seen on imaging, the pathological examination revealed a good response to neoadjuvant chemotherapy with only limited viable residual tumor foci present in the resection specimen. The estimated viable tumor load after neo-adjuvant chemotherapy was around 2–3%. The patient experienced an uneventful postoperative recovery and was discharged on POD 8. (Fig. 8c) Due to the young age of the patient, the aggressive nature of the disease, and the high recurrence risk, regular follow-up visits were scheduled with 3 monthly PET-CT scans. During the first follow-up three months after surgery, the PET-CT scan did not show any signs of tumor recurrence. Furthermore, the patient was recovering well both physically and mentally. Unfortunately, PET-CT scan and chest MRI 6 months post-surgery showed a fulminant early tumor recurrence on the chest wall (biopsy proven) for which treatment with trabectedin is ongoing. One year after the operation, the patient is alive.

Discussion

In this case series we report the management and follow-up of two rare primary pleural neoplasms treated by a multimodal approach consisting of induction chemotherapy and radical surgical resection.

Our first case is a unique report of a primary pleural yolk sac tumor in a previously healthy female. While in literature only one case was published in 2002 with a postmortem diagnosis in a 14-year-old patient, we report, to our knowledge, a first case including diagnosis and treatment of a pleural yolk sac tumor in a living patient [9]. Our approach was based upon the management of other extragonadal yolk sac tumors [10] consisting of neo-adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP-chemotherapy) [10–12]. Bleomycin was omitted in this case due to potential pulmonary toxicity. The response to neo-adjuvant chemotherapy was mainly followed by α -FP levels, as they appear to be a good predictor for the response of yolk sac tumors to chemotherapy, although levels might be influenced by several factors [10]. The initial response to (B) EP-chemotherapy was excellent with a good reduction of α -FP levels from 68.300 μ g/l to 3159 μ g/l after two cycles. After the third cycle however, a reduced response was noted with a further reduction to only 2543 μ g/l. Because of the reduced tumoral response a switch was made to a TIP-chemotherapy regimen (paclitaxel, cisplatin, and ifosfamide), this choice was based upon its use as a second line chemotherapeutic in testicular germ cell tumors [13, 14] as well as a second line chemotherapeutic in other extra-gonadal germ cell tumors [11, 15]. Chemotherapy was followed by surgical resection, and HITHOC. In this case we opted for ePD as there were no arguments for lung invasion. Current literature regarding surgical resection of MM also suggests favorable outcomes in selected patients treated with ePD (\pm HITHOC) compared to EPP [16–18].

Concerning HITHOC, there is growing evidence for its use after the resection of pleural neoplasms like MM, disseminated thymoma, and thoracic pseudomyxoma peritonei, and it is generally considered a feasible and safe approach resulting in additive local tumor control

[17, 19–23]. Furthermore, hyperthermic intraperitoneal chemotherapy (HIPEC) has previously been described in the treatment of ovarian yolk sac tumors [24, 25]. In our HITHOC protocol we opted for oxaliplatin, based on our previous experience with HITHOC for disseminated thymoma [19, 20], the immediate cytotoxic effect of Oxaliplatin, and its favorable side effect profile [19]. In our recent cases of disseminated thymoma and thoracic pseudomyxoma peritonei treated with HITHOC, no relevant HITHOC-related morbidity or mortality was observed and both patients remained free of disease during oncological follow-up [19, 20]. Currently, we cannot compare our results to other cases because this is the very first case of a pleural yolk sac tumor published in literature. However, other cases on pulmonary and mediastinal yolk sac tumors have been published. Generally considered as rare and aggressive, thoracic yolk sac tumors typically exhibit unfavorable outcomes, and treatment usually consists of a combination between neo-adjuvant chemotherapy and/or surgery and/or adjuvant chemotherapy [11]. Notably, in many cases, authors choose a similar approach as in our case, with neo-adjuvant chemotherapy (most often BEP-regimen), followed by complete surgical resection [11, 26–29]. More recently a meta-analysis was published on mediastinal yolk sac tumors revealing a poor prognosis with a median time to survival of 23 months for adult patients, 3-year overall survival of 24.4%, and 5-year overall survival of 23% [30]. On multivariate analysis the main predictors for favorable outcome were: undergoing surgery, receiving chemotherapy, and a more anterior localization of the tumor [30]. Furthermore, the authors claim that the most important cornerstones of the successful treatment of such malignancies are (1) early diagnosis (2) neoadjuvant chemotherapy and (3) surgical resection [30].

The second case describes the treatment of a pleural synovial sarcoma in a young adult male. Pleural sarcomas are rare and aggressive tumors, accounting for less than 1% of all primary pulmonary malignancies [31]. The first case of a pleural synovial sarcoma was published in 1996 by Gaertner et al. [32] Since then, few cases have been reported by others [31, 33–43]. A range of treatments have been suggested for pleural synovial sarcoma including extensive surgical resection, (neo)adjuvant chemotherapy (with ifosfamide and doxorubicin), and radiotherapy [33, 38–40, 42–45]. In our case, the patient was initially deemed borderline inoperable due to the diffuse intrathoracic involvement. Although controversial and with limited evidence, an attempt was made at downstaging the tumor with ifosfamide and doxorubicin to facilitate a potential R0 resection in the future [4, 46–48]. While current ESMO guidelines state that the role of neo-adjuvant chemotherapy in the treatment of synovial sarcoma's remains uncertain, other authors agree that

neoadjuvant chemotherapy can offer a benefit in selected cases who were initially not/borderline eligible for resection [7, 47–49]. The choice of chemotherapeutic agents was based upon (neo-)adjuvant and palliative chemotherapy regimens used in other synovial sarcomas [7, 8, 46, 47]. Achieving a complete surgical resection is crucial when treating sarcoma's because it is directly associated with improved survival outcomes [45]. In our case we opted for a radical resection with an EPP because of the young age of the patient, the favorable V/Q scan, and the limited response to chemotherapy. Adjuvant radiotherapy is most often used when complete resection is not feasible or where residual disease is anticipated after surgery [33, 50].

As shown in previous cases of pleural synovial sarcoma's, the mainstay treatment is complete surgical resection when feasible, often combined with other (neo-)adjuvant treatment modalities. Nonetheless the prognosis of pleural synovial sarcoma's remains poor, with a median time to recurrence or metastasis of 8.5 months according to a 26-patient case series of pleuropulmonary synovial sarcoma's [45]. A more recent study with 20 cases reports a 2-year overall survival of 51% and a 5-year overall survival of 22%, a median overall survival of 25 months, and a median disease-free interval of 8.5 months [48]. Notably, as seen in our case, other authors also report a good response of pleural synovial sarcoma's to neo-adjuvant chemotherapy [51, 52].

A variety of options are available when a recurrence of a pleural sarcoma occurs. When feasible, recurrences can be treated with radiotherapy [53] or secondary resections [37, 39, 40, 54]. Adjuvant or salvage chemotherapy can be considered for metastatic disease, local recurrences, or locally inoperable cases [39]. Nonetheless, the exact choice of chemotherapeutic drugs remains a subject of debate [40, 45, 53]. Alternative adjuvant therapies, such as rh-endostatin combined with ifosfamide or pemetrexed, as well as the use of sunitinib as maintenance therapy, have been suggested in the treatment of recurrent disease [36]. In our case an early fulminant local recurrence occurred. Because of the fulminant nature of the recurrence, re-resection or radiotherapy were not considered reasonable options. Therefore we opted for trabectedin as a second line agent after treatment with Ifosfamide and Doxorubicin [55]. Trabectedin has shown acceptable results in a retrospective multicenter trial looking at metastatic synovial sarcoma's, with an overall response rate of 15%, a tumor control rate of 50%, and a median progression free survival of 7 months in responders [55]. Further options in case of recurrent/non-resectable/metastatic disease are dacarbazine and pazopanib [55].

HITHOC was not considered in the sarcoma case because of the limited response to systemic

chemotherapy. Currently, there are no reports on the use of HITHOC for pleural synovial sarcoma. The first choice of chemotherapeutic drug would be ifosfamide or doxorubicin. However, ifosfamide is not suited due its need for metabolic activation [56]. Doxorubicin on the other hand can be a viable option for HITHOC and has already been successfully administered in HIPEC cases, and in HITHOC for disseminated thymoma and MM [19, 57–60].

Repeated cycles of chemotherapy and extensive thoracic surgery affected the physical condition of both patients, requiring intense physical rehabilitation with extended recovery times.

During the follow-up of our first case, no signs of tumor recurrence have been found up to 6 months after surgery, and the patient remained in good general health during follow-up. Our second patient, although asymptomatic and in good general health, experienced an early limited local tumor recurrence 6 months after surgery for which further treatment with trabectedin is ongoing. Due to the high risk for recurrence in these cases, a strict and multidisciplinary follow-up is essential, with routine PET-CT scans and additional MRI imaging and CT guided biopsies in case of doubt.

Because both cases are rare and at least some parts of the chosen treatment protocols are novel, with limited evidence on the efficacy of certain treatment choices, both patients were extensively informed about the unique therapeutic approach. The potential risks, benefits, and expected outcomes were carefully explained to the patient and informed consent was achieved in both cases. Both cases were also followed by a multidisciplinary oncological advisory board which supported the clinical decision.

Conclusion

In this case series we describe the treatment of two rare pleural neoplasms, one involving a pleural yolk sac tumor treated with extended pleurectomy decortication and hyperthermic intrathoracic chemotherapy, the other involving a pleural synovial sarcoma treated with an extrapleural pneumonectomy. Our findings confirm that neo-adjuvant chemotherapy (+/- HITHOC) followed by extensive surgical resection is a feasible strategy for non-mesothelioma primary pleural neoplasms, with the potential of favorable short-term oncological outcomes in selected cases. Nonetheless, strict follow-up is crucial due to the high risk for recurrence and the need for timely reintervention.

Abbreviations

MM	Malignant Mesothelioma
NYHA	New York Heart Association
α-FP	Alpha-fetoprotein
ePD	Extended Pleurectomy Decortication

POD	Postoperative day
EPP	Extrapleural Pneumonectomy
HITHOC	Hyperthermic Intrathoracic Chemotherapy

Acknowledgements

The authors would like to thank all members of the Department of Thoracic Surgery and the Lab (BREATHE), perfusionists, anesthesiologists, oncologists and intensive care physicians involved in the Thoracic Surgery Program at the University Hospitals Leuven, Belgium, for their contribution.

Author contributions

TV, JVS, and LC. were responsible for the conception, design, and drafting of the manuscript. TV, JVS, AB, AP, PN, and LC were responsible for adding and reviewing the surgical details of this manuscript. TV was responsible for all surgical and radiological images. PS and HD were responsible for adding and reviewing the oncological details of this manuscript. BW and RS were responsible for adding and reviewing the pathology details and pictures in this manuscript. KV was responsible for reviewing the details on hyperthermic intrathoracic chemotherapy. YD and SB were responsible for reviewing the details on the postoperative management of both patients described in this manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Disclosures

Laurens J. Ceulemans is supported by a KU Leuven University Chair funded by Medtronic, a research project from the Research Foundation Flanders (FWO) Belgium (G090922N) and is appointed senior clinical researcher for FWO (18E2B24N).

Ethical approval

This study was approved for publication after internal ethical review by the UZ Leuven department of thoracic surgery.

Consent to participate

A written consent to participate was obtained from both patients included in this case series.

Consent to publish

A written consent to publish was obtained from both patients included in this case series.

Received: 12 December 2023 / Accepted: 28 March 2024

Published online: 16 April 2024

References

1. Laura Granville ACL, Timothy C, Allen M, Dishop VL, Roggli A, Churg DS, Zander. Philip T. Cagle. Review and update of uncommon primary pleural tumors. *Archives of pathology & laboratory medicine*; 2005.
2. Layek A, Rajpoot A, Joshi P, Mishra M. Primary pleural liposarcoma: a rare differential for an opaque hemithorax. *BMJ case Rep.* 2022;15(2).
3. Attanoos RL, Pugh MR. The diagnosis of Pleural Tumors Other Than Mesothelioma. *Arch Pathol Lab Med.* 2018;142(8):902–13.
4. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, et al. Malignant pleural mesothelioma: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol.* 2022;33(2):129–42.
5. Stang A, Trabert B, Wentzensen N, Cook MB, Rusner C, Oosterhuis JW, et al. Gonadal and extragonadal germ cell tumours in the United States, 1973–2007. *Int J Androl.* 2012;35(4):616–25.
6. Eilber FC, Dry SM. Diagnosis and management of synovial sarcoma. *J Surg Oncol.* 2008;97(4):314–20.

7. Blay JY, von Mehren M, Jones RL, Martin-Broto J, Stacchiotti S, Bauer S, et al. Synovial sarcoma: characteristics, challenges, and evolving therapeutic strategies. *ESMO Open*. 2023;8(5):101618.
8. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up(★). *Ann Oncol*. 2021;32(11):1348–65.
9. Vaideeswar PDJ, Jambhekar NA. Primary pleuro-pulmonary malignant germ cell tumours. *J Postgrad Med*. 2002;48(1):29–31.
10. Vilius Rudaitis UM, Justina Katinaitė J. Successful treatment of advanced stage yolk sac tumour of extragonadal origin a case report and review of literature. *ACTA Med Lituanica*. 2016;23:110–6.
11. Silva L, Vergilio FS, Yamaguti DCC, Cruz I, Queen JAG. Yolk sac primary tumor of mediastino: a rare case in a young adult. *Einstein (Sao Paulo)*. 2017;15(4):496–9.
12. Chen Y, Yang C, Huang C, Li S. Feasibility of resection after neoadjuvant chemotherapy for mediastinal yolk sac tumor. *Asian J Surg*. 2023;46(12):6008–9.
13. Kondagunta GV, Bacik J, Donadio A, Bajorin D, Marion S, Sheinfeld J, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol*. 2005;23(27):6549–55.
14. Motzer RJ, Sheinfeld J, Mazumdar M, Bains M, Mariani T, Bacik J, et al. Paclitaxel, Ifosfamide, and Cisplatin Second-Line therapy for patients with relapsed testicular germ cell Cancer. *J Clin Oncol*. 2000;18(12):2413–8.
15. Vanidassane I, Sharma V, Ramteke P, Yadav MK, Batra A. Primary yolk sac tumor of the liver in an adult man. *Am Coll Gastroenterol Case Rep J*. 2019;6(4):e00050.
16. Zhou N, Rice DC, Tsao AS, Lee PP, Haymaker CL, Corsini EM, et al. Extrapleural Pneumonectomy Versus Pleurectomy/Decortication for Malignant Pleural Mesothelioma. *Ann Thorac Surg*. 2022;113(1):200–8.
17. Klotz LV, Hoffmann H, Shah R, Eichhorn F, Gruenewald C, Bulut EL, et al. Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach. *Translational Lung Cancer Res*. 2022;11(11):2230–42.
18. Kanayama M, Mori M, Matsumiya H, Taira A, Shinohara S, Takenaka M, et al. Surgical strategy for malignant pleural mesothelioma: the superiority of pleurectomy/decortication. *Surg Today*. 2022;52(7):1031–8.
19. Vandaele T, Van Slambrouck J, Proesmans V, Clement P, Lambrecht M, Naftex P, et al. Hyperthermic Intrathoracic Chemotherapy (HITHOC) for Pleural disseminated Thymoma: a systematic literature review. *Ann Surg Oncol*. 2023;30(1):543–60.
20. Proesmans V, Vandaele T, Van Slambrouck J, Wolthuis A, A DH, Dekervel J, et al. Pleural decortication and hyperthermic intrathoracic chemotherapy for pseudomyxoma. *Int J Hyperth*. 2022;39(1):1153–7.
21. Aprile V, Bacchin D, Korasidis S, Nesti A, Marrama E, Ricciardi R, et al. Surgical treatment of pleural recurrence of thymoma: is hyperthermic intrathoracic chemotherapy worthwhile? *Interact Cardiovasc Thorac Surg*. 2020;30(5):765–72.
22. Dawson AG, Kutyywayo K, Mohammed SB, Fennell DA, Nakas A. Cytoreductive surgery with hyperthermic intrathoracic chemotherapy for malignant pleural mesothelioma: a systematic review. *Thorax*. 2023;78(4):409–17.
23. Bongiolatti S, Mazzoni F, Salimbene O, Caliman E, Ammatuna C, Comin CE et al. Induction chemotherapy followed by Pleurectomy Decortication and Hyperthermic Intraoperative Chemotherapy (HITHOC) for early-stage Epithelioid Malignant Pleural Mesothelioma-A prospective report. *J Clin Med*. 2021;10(23).
24. Yu HH, Yonemura Y, Hsieh MC, Lu CY, Wu SY, Shan YS. Experience of applying cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for ovarian teratoma with malignant transformation and peritoneal dissemination. *Ther Clin Risk Manag*. 2019;15:129–36.
25. Hayes-Jordan A, Lopez C, Green HL, Xiao LC, Huh W, Herzog CE. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric ovarian tumors: a novel treatment approach. *Pediatr Surg Int*. 2016;32(1):71–3.
26. Wu D, Zhang K, Zhang X. Primary mediastinal yolk sac tumor: a case report and literature review. *Clin Case Rep*. 2023;11(8):e7781. <https://doi.org/10.1002/ccr3.7781>. PMID: 37564606; PMCID: PMC10410121.
27. Darif K, Benbrahim Z, Acharfi N, Khacha A, Maaroufi M, Amaadour L, Oualla K, Arifi S, Mellas N. A primary mediastinal germ cell tumor of yolk sac type: case report. *Pan Afr Med J*. 2021;38:330. <https://doi.org/10.11604/pamj.2021.38.330.23730>. PMID: 34285753; PMCID: PMC8265249.
28. Zhu F, Wang L, Zhai X. Primary mediastinal yolk sac tumor: a case report and literature review. *Int J Clin Exp Pathol*. 2020;13(11):2772–7. PMID: 33284891; PMCID: PMC7716131.
29. Akasbi Y, Najib R, Arifi S, Lakranbi M, Smahi M, Mellas N, ELMesbahi O. Complete histologic response to chemotherapy in a patient with a mediastinal yolk sac tumor: a case report. *BMC Res Notes*. 2014;7:803. <https://doi.org/10.1186/1756-0500-7-803>. PMID: 25399910; PMCID: PMC4239375.
30. Dabsha A, Elkharbotly I, Yaghamour M, Badr A, Badie F, Khairallah S, et al. Survival difference among adult and pediatric mediastinal yolk sac tumors cases: a meta-analysis of case reports. *Eur J Surg Oncol*. 2024;50(3):108019.
31. Kumar S, Goyal K, Bhatt R, Bansal S, Mishra M. Primary pleural synovial sarcoma: a rare cause of hemorrhagic pleural effusion. *Adv Respiratory Med*. 2021;89(1):60–2.
32. Gaertner Erich ZH, Fleming, Marian. Colby Thomas, Travis William. Biphasic synovial sarcomas arising in the Pleural Cavity A Clinicopathologic Study of five cases. *Am J Surg Pathol*. 1996;20.
33. Yamaki M, Yonehara S, Noriyuki T. Large primary pleural synovial sarcoma with severe dyspnea: a case report. *Surg case Rep*. 2017;3(1):29.
34. Alejandra Duran-Mendicuti PC, Sara O, Vargas M. Primary synovial sarcoma of the Chest Radiographic and clinicopathologic correlation. *J Thorac Imaging*. 2003.
35. Atif Sharif TA, Mumtaz, Akhtar. Naeem Zia., Cystic pleural synovial sarcoma. *J Coll Physicians Surg Pakistan*. 2016.
36. Teng C, Li LI, Shen W, Li J, Liu Y, Jiang Q, et al. Pleural synovial sarcoma patient treated with combined chemotherapy and Endostar, plus sunitinib maintenance therapy: a case report and review of the literature. *Oncol Lett*. 2015;10(2):1141–4.
37. Katsurada N, Ohnishi H, Ikeda M, Jimbo N, Hatakeyama Y, Okamura K. Primary pleural synovial sarcoma with repeated resection leading to long-term survival. *Respirol case Rep*. 2019;7(8):e00480.
38. Takuma Tsukioka KI, Iwata T, Mizuguchi S, Morita R. Shigefumi Suehiro. Resected case of synovial sarcoma in the Pleural Cavity. *Japanese J Thorac Cardiovasc Surg*. 2006.
39. Noritoshi Nishiyama TI, Nobuhiro Izumi T, Tsukioka K, Nagano, Shigefumi Suehiro. Aggressive repeat surgery for a recurrent synovial sarcoma in the pleura. *Annals of Thoracic and Cardiovascular surgery*; 2009.
40. Siok Bian Ng QA. Sim Leng Tien, Christina Sivaswaren, Lai Ching Lau. Primary pleural synovial sarcoma. A case report and review of the literature. *Archives of pathology & laboratory medicine*; 2003.
41. Kang MK, Cho KH, Lee YH, Han IY, Yoon YC, Park KT, et al. Primary synovial sarcoma of the parietal pleura: a case report. *Korean J Thorac Cardiovasc Surg*. 2013;46(2):159–61.
42. Colwell AS, D'Cunha J, Vargas SO, Parker B, Dal Cin P, Maddaus MA. Synovial sarcoma of the pleura: a clinical and pathologic study of three cases. *J Thorac Cardiovasc Surg*. 2002;124(4):828–32.
43. Hung JJ, Chou TY, Sun CH, Liu JS, Hsu WH. Primary synovial sarcoma of the posterior chest wall. *Ann Thorac Surg*. 2008;85(6):2120–2.
44. Sanghyuk Song JP, Kim HJ, Kim IH, Han I, Kim H-S. Suzy Kim. Effects of Adjuvant Radiotherapy in patients with synovial sarcoma. *Am J Clin Oncol*. 2017.
45. Lan T, Chen H, Xiong B, Zhou T, Peng R, Chen M, et al. Primary pleuropulmonary and mediastinal synovial sarcoma: a clinicopathologic and molecular study of 26 genetically confirmed cases in the largest institution of southwest China. *Diagn Pathol*. 2016;11(1):62.
46. Mangla A, Gasalberti DP. Synovial Cell Sarcoma. [Updated 2023 May 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. <https://www.ncbi.nlm.nih.gov/books/NBK587366/>
47. Desar IME, Fleuren EDG, van der Graaf WTA. Systemic treatment for adults with synovial sarcoma. *Curr Treat Options Oncol*. 2018;19(2):13.
48. Pieropan S, Mercier O, Mitilian D, Pradère P, Fabre D, Ion DI et al. Feasibility and long-term outcomes of surgery for primary thoracic synovial sarcoma. *Interact Cardiovasc Thorac Surg*. 2022;35(4).
49. Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Pousa AL, Grignani G, Basso U, Blay JY, Tendero O, Beveridge RD, Ferraresi V, Lugowska I, Merlo DF, Fontana V, Marchesi E, Donati DM, Palassini E, Palmerini E, De Sanctis R, Morosi C, Stacchiotti S, Bague S, Coindre JM, Dei Tos AP, Picci P, Bruzzi P, Casali PG. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-ST5 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18(6):812–822. doi: 10.1016/S1470-2045(17)30334-0. Epub 2017 May 9. Erratum in: *Lancet Oncol*. 2017;18(6):e301. PMID: 28499583.

50. Loscertales J, Trivino A, Gallardo G, Congregado M. Primary monophasic synovial sarcoma of the pleura: diagnosis and treatment. *Interact Cardiovasc Thorac Surg*. 2011;12(5):885–7.
51. Silva RG, Gross JL, Silva RA, Haddad FJ, Younes RN, Cruz VM, Avertano-Rocha AB. Primary monophasic synovial sarcoma of the pleura: Neoadjuvant chemotherapy followed by complete resection. *Thorac Cancer*. 2010;1(3):95–101. <https://doi.org/10.1111/j.1759-7714.2010.00019.x>. PMID: 27755799.
52. Balieiro MA, Lopes AJ, Costa BP, Veras GP, Perelson PS, Acatauassú Nunes R, Saito EH. The surprising outcome of a giant primary mediastinal synovial sarcoma treated with neoadjuvant chemotherapy. *J Thorac Dis*. 2013;5(1):94–6. <https://doi.org/10.3978/j.issn.2072-1439.2012.12.05>. PMID: 23372956; PMCID: PMC3547992.
53. Chen S, Zhang K, Wan X, Chen Y, Ma S, Deng Q. The use of apatinib in treating primary pleural synovial sarcoma: a case report. *Medicine*. 2019;98(51):e18382.
54. Yetisyigit T, Arpacı E, Seber ES, Kucukoner M, Kos FT, Sonmez OU, et al. Salvage treatment experience in advanced synovial sarcoma: a multicenter retrospective analysis of the anatolian society of medical oncology. *Asian Pac J Cancer Prev*. 2013;14(9):5185–8.
55. Sanfilippo R, Dileo P, Blay JY, Constantinidou A, Le Cesne A, Benson C, Vizzini L, Contu M, Baldi GG, Dei Tos AP, Casali PG. Trabectedin in advanced synovial sarcomas: a multicenter retrospective study from four European institutions and the Italian Rare Cancer Network. *Anticancer Drugs*. 2015;26(6):678–81. <https://doi.org/10.1097/CAD.000000000000228>. PMID: 25763543; PMCID: PMC4730787.
56. Bruce C, Baguley FAB, Elizabeth Barrett-Connor MR, Berger, Judy L, Bolton D, Eastmond, Maarten C, Bosland CW, Jameson, Joseph F, Buell J, Kaldor P, Karran, Anthony B, Miller, David G, Kaufman, Alfredo A, Molinolo S-H, Kim, Jørgen H, Olsen M, Matilde Marques, David H. Phillips, Charles A. Schiffer, Heinz H. Schmeiser, Linda Titus-Ernstoff, David B. Thomas, Hiroyuki Tsuda., IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals. International Agency for research on cancer. 2012.
57. Manzanedo I, Pereira F, Serrano A, Perez-Viejo E, Martinez-Torres B, Carrion L, et al. The use of cisplatin plus doxorubicin or paclitaxel in hyperthermic intraperitoneal chemotherapy (HIPEC) for stage IIIc or IV epithelial ovarian cancer: a comparative study. *Clin Translational Oncol*. 2019;21(10):1357–63.
58. Laura V, Klotz ML, Martin E, Eichhorn U, Grütznert I, Koch H, Winter T, Kauke T, Duell, Rudolf A, Hatz. Pleurectomy/decortication and hyperthermic intrathoracic chemoperfusion using cisplatin and doxorubicin for malignant pleural mesothelioma. *J Thorac Disease*. 2019.
59. van Rutha OvT S, Korseb CM, Verwaala VJ, Zoetmulder FAN. Pharmacokinetics of doxorubicin and cisplatin used in intraoperative hyperthermic intrathoracic chemotherapy after cytoreductive surgery for malignant pleural mesothelioma and pleural thymoma. *Anticancer Drugs*. 2003.
60. Eelco de Bree SvR, Baas P, Th EJ, Rutgers N, van Zandwijk AJ, Witkamp, Frans AN. Zoetmulder. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. *Chest*. 2002.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.