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Imaging features of intestinal metastasis from pulmonary sarcomatoid carcinoma

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► ***Original article***

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ABSTRACT

Background: The aim of this study was to examine the imaging features of patients diagnosed with pulmonary sarcoma (PSC) exhibiting small bowel metastases, utilizing magnetic resonance imaging (MRI) and computed tomography (CT), and to report the clinical outcomes of surgical resection in conjunction with duvacizumab drug therapy. ***Materials and Methods***: Clinical data and CT imaging markers of patients with pathologically confirmed primary pulmonary sarcoma from January 2020 to April 2021 were retrospectively assessed. ***Results***: Immunohistochemical analysis of lung tissue samples indicated Galectin-3(+), PAS(-), Myoglobin(-), F8(-), CD31(-), TTF(+), P40 (-), D2-40(-), HMB45(-), AE1/AE3(+), MC(-), and CD68(-). PD-L1 positive cell count, as determined through immunohistochemical evaluation, was 50%. Immunohistochemical findings of the patient's small intestine tissue revealed AE1/AE3 (+), CD117(-), CD34(-), Desmin(-), SMA(-), Vimentin(+), S-100(-), CK7(-), CK20(-), CEA(-), EMA(-), PAS(-), CD45(-), with a Ki-67 positivity rate of approximately 40%. Following 11 cycles of duvacizumab drug therapy, the volume of the patient's left upper lung mass decreased from 7.1 cm × 5.7 cm to 2.8 cm x 3.3 cm. ***Conclusion***: The combination of surgical resection and duvacizumab drug therapy demonstrated clinical efficacy in patients with PSC and holds promise as a potential treatment option for patients suffering from PSC.

INTRODUCTION

Sarcomatoid carcinoma (SC) constitutes a group of poorly differentiated epithelial malignancies featuring mixed carcinoma and sarcomatous or sarcomatoid components. These malignancies can emerge in various sites, including the liver, lung, and central nervous system [(1)]. SC encompasses five subtypes: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pneumoblastoma, all characterized by poor differentiation, frequent metastasis, and high invasiveness. However, the gastrointestinal tract is a less frequent site of metastasis for patients with PSC, and no consensus exists regarding treatment options for PSC patients who develop gastrointestinal tract metastases [(2)].

The diagnosis of PSC primarily depends on the pathological findings of surgically resected tissue [(3)]. Most PSC patients receive an intermediate to advanced disease diagnosis [(4)], and their prognosis is generally poor [(5)]. Thus, early detection and diagnosis of PSC are crucial. Advancements in technology have allowed CT scans, with their brief examination time, exceptional image quality, and sensitivity to lesion calcification, to play a vital role in examining and diagnosing pulmonary diseases. Meanwhile, MRI's multi-directional imaging capabilities help reveal structural features and tumor spread staging and are often employed for qualitative diagnosis after CT findings. Identifying MRI and CT imaging features of PSC can enable early disease stage intervention and improve patient prognosis. National and international literature on PSC and PSC metastases is relatively scarce, with some reports presented on a case-by-case basis and even fewer accounts of PSC CT imaging and MRI.

The high malignancy of PSC and its significant resistance to conventional cytotoxic chemotherapy (e.g., platinum-based chemotherapy) have resulted in a much lower chemotherapy response rate for PSC compared to other cancers [(6-9)]. This necessitates the urgent development of effective treatment options. Immunotherapy has become the most rapidly growing treatment strategy in oncology, thanks to medical technology advancements [(10-11)]. Most patients with advanced tumors benefit from immunotherapy in this era. Current PSC-related research literature emphasizes higher dominant expression of programmed death ligand-1 (PD-L1) and tumor mutational load (TMB) as co-factors [(6, 12)], which suggests the potential for higher response rates and survival benefits when treating PSC with PD -L1 inhibitors [(13)]. Durvalumab (MEDI4736) is a humanized anti-G1 -kappa immunoglobulin that blocks programmed cell death ligand 1 (PD-L1)

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binding to PD-1 and CD80 (B7.1), which can lead to increased T cell activation and promote tumor cell death. Durvalumab has demonstrated success in clinical studies of various tumor types, including NSCLC. When platinum-based chemotherapy and radiotherapy fail to eradicate a patient's stage III non-small cell lung cancer (NSCLC) and the tumor is too advanced for surgical resection, duvacizumab often serves as the subsequent treatment [14]. To date, no information exists on the efficacy of dulcamaximab alone in PSC, nor is there evidence on the efficacy or safety of dulcamaximab alone in PSC treatment. In this article, the focus is on further characterizing this innovative and promising PSC treatment strategy by examining, for the first time, the treatment course impactology for patients with PSC presenting with small bowel metastases.

MATERIALS AND METHODS

Materials

Patients with pulmonary sarcoma-like carcinoma admitted to our hospital from January 2020 to April 2021 were selected as study subjects. Inclusion criteria: ①Patients were all eligible for pathological biopsy or imaging examination to confirm the diagnosis of pulmonary sarcoma-like carcinoma. (ii) Those with complete clinical data and imaging data. (iii) Patients with sarcomatoid carcinoma of the lung presenting with intestinal metastases. Exclusion criteria: ①those with contraindications to CT examination; ②those who did not undergo CT examination. The study passed the ethical review of the medical paper by the ethics committee of Shishang City People's Hospital. Patients were informed of the study and voluntarily participated in the study.

Equipment and examination methods

Tissue pathology was firstly monitored by staining (name of reagent: revert blue staining solution, company name: Agilent Technologies Singapore (International) Pte Ltd. Ltd., manufacturing address: 2090 Commerce Drive Mckinney Texsa 75069 USA), followed by immunohistochemistry (reagent name: Ki-67 antibody reagent, company name: Fuzhou Meixin Biotechnology Development Co. (Production address: Building 12, Innovation Park, Haixi Hi-Tech Industrial Park, Fuzhou High-Tech Zone).

CT equipment: Siemens SOMATOM Definition 128 -row spiral CT, patient's breathing pattern trained before CT examination, CT scan range: thoracic inlet to 5 cm below the diaphragm, bed entry mode: head first, then foot, CT parameter settings: voltage 120 kV, tube current 60-80 mA, scan layer thickness 10 mm, layer spacing 10 mm, MRI: Magnetom Aera 1.5T, recording information during the examination performed by the patient.

Image measurement and analysis

Independent analysis of the patient's CT images by two senior radiologists. Observed indicators: number, location, morphology, size, mode of enhancement, degree of enhancement, presence or absence of adjacent lymph nodes and distant metastases of the tumor. When the physicians disagreed, the results of the joint discussion were used as the final conclusion.

Data and image processing

Data export was carried out under the supervision of two people. Image processing was performed using Photoshop V7.0.1.

RESULTS

Patient admission examination

The patient, a 65-year-old male with a 30-year history of heavy smoking, was admitted to the hospital with abdominal pain as the first presentation. After performing a CT of the chest and abdomen, the images suggested that the patient had a lung occupancy (figure 1A, 1B), a small bowel tumor (figure 1C, 1D), and intestinal obstruction (figure 1E), which did not exclude the possibility of intussusception. After the patient underwent pulmonary puncture and resection of the small bowel tumor, pathological testing was performed. The postoperative pathological findings showed multiple neoplasms in parts of the small intestine of some patients, of indeterminate type, not excluding high-risk gastrointestinal mesenchymal tumor totalling four, approximately 2-4 cm in diameter, the largest of which involved the plasma membrane layer and the remaining three involved the deep muscular layer; no tumor involvement was seen at each surgical margin or in any of the five lymph nodes of the intestinal wall. The immunohistochemical results of the small bowel pathology (figure 2) suggested AE1/AE3(+), CD117(-), CD34(-), Desmin(-), SMA(-), Vimentin(+), S-100(-), CK7(-), CK20(-), CEA(-), EMA(-), PAS(-), CD45(-), Ki -67 positivity rate was approximately 40%. Immunohistochemical results in the lungs (figure 2) suggested Galectin-3(+), PAS(-), Myoglobin(-), F8(-), CD31(-), TTF(+), P40(-), D2-40(-), HMB45(-), AE1/AE3(+), MC(-), CD68(-). Immunohistochemical detection of PD-L1 positive cell counts 50%.

Patient's chest CT imaging results during treatment

The patient started immunotherapy with PD-L1 "Duvalyol monoclonal antibody 500mg ivgtt q2w" on April 15, 2020 for a total of 11 courses. CT imaging of the patient's lungs at the beginning of treatment showed a symmetrical thorax with a centralized

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tracheal mediastinum on both sides. There was an increase in translucency in both lung fields. A soft tissue density mass measuring approximately 7.1cm × 5.7cm was seen outside the hilum of the upper lobe of the left lung, with bronchial occlusion in the upper lobe focal segment and pleural thickening adjacent to the mass. Multiple enlarged lymph nodes were seen in the left hilum and mediastinum. A few cords in both lungs are present. Calcification of the left coronary artery. There is a small accumulation of fluid in the left pleural cavity. Mass in the upper lobe of the left lung with multiple enlarged lymph nodes in the left hilum and mediastinum. Little chronic inflammation in both remaining lungs. Calcification of the left coronary artery. There was a small accumulation of fluid in the left pleural cavity. The patient was subsequently reviewed every 2-3 months as prescribed by the doctor.

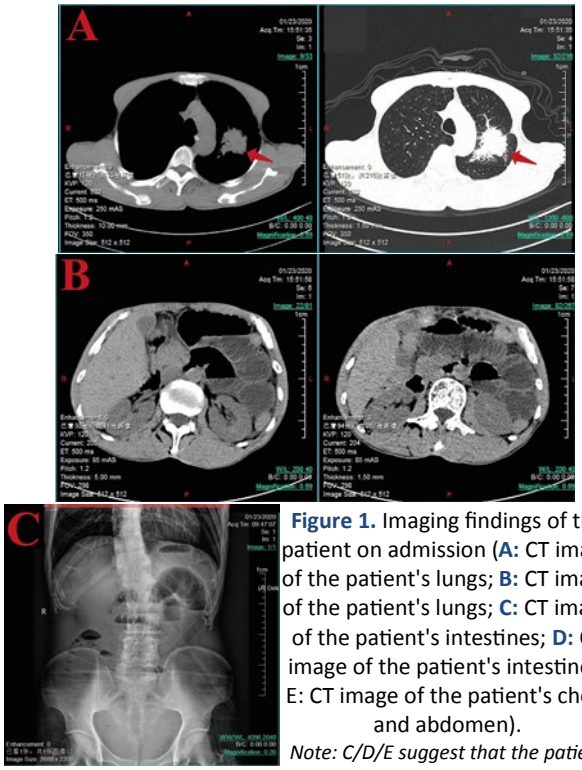


Figure 1. Imaging findings of the patient on admission (**A:** CT image of the patient's lungs; **B:** CT image of the patient's lungs; **C:** CT image of the patient's intestines; **D:** CT image of the patient's intestines; E: CT image of the patient's chest and abdomen).

Note: C/D/E suggest that the patient has signs of small bowel obstruction and the small intestinal canal in the right lower pelvic cavity appears to have concentric circles, which does not exclude the possibility of intussusception. A/B thoracic and abdominal CT suggests 1. a mass in the upper lobe of the left lung, with a high probability of cancer, please combine with clinical and related investigations; 2. a small nodule in the posterior basal segment of the lower lobe of the right lung, the nature of which is undetermined, follow-up is recommended; 3. a striped shadow in the middle lobe of the right lung, considering chronic inflammatory changes.

The patient's follow-up imaging data from 2020-2021 are shown in order in figure 3. There was normal translucency in both lung fields and coarse bronchovascular bundles in both lung fields. In the upper lobe of the left lung, an irregular mass with irregular shape and uneven density was seen, surrounded by cords. The remaining lung has a few patches and cords. The trachea and bronchioles are patent. There are no enlarged lymph nodes in the mediastinal space. There is no abnormal density in the pleural cavity on either side. There is no thickening of the pleura or pericardium on either side. Several low density nodules are seen in the liver on scan. A soft tissue mass in the upper lobe of the left lung does not exclude the possibility of a neoplastic occupancy and further strengthening scans are recommended. There is a little chronic inflammation in both lungs. Coronary artery calcification. Several hypodense shadows in the liver are detected on scan, the nature of which is to be investigated.

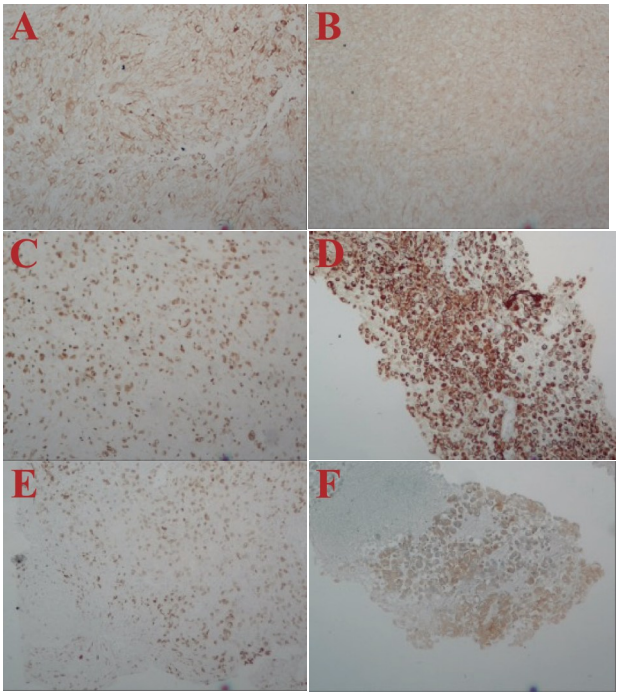


Figure 2. Immunohistochemistry results of the patient (**A:** small bowel immunohistochemistry AE1/AE3 (+); **B:** small bowel immunohistochemistry Vimentin (+); **C:** small bowel immunohistochemistry Ki67 positivity rate 40%; **D:** lung immunohistochemistry Galectin-3 (+); **E:** lung immunohistochemistry TTF (+); **F:** lung immunohistochemistry AE1/AE3 (+)).

The patient's CT findings of 21 October 2020 show increased translucency in both lung fields and increased and disturbed bronchial vascular bundles in both lung fields. An irregular mass was seen in the upper lobe of the left lung, measuring approximately 2.8 × 3.3 cm, with an irregular pattern and uneven density, surrounded by cords and bronchial shadowing, with some bronchial narrowing and adjacent pleural thickening and adhesions. A small subpleural nodule of 4mm in diameter was seen in the lower lobe of the right lung. A few patches and cords in the remaining lung, with localised pleural thickening and adhesions on the right side. The hilar shadow is small in both lungs and the trachea and bronchi are patent. No enlarged lymph nodes are

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seen in the mediastinal space. Several hypodense nodules are seen in the liver. The gallbladder is normal in size, shape and position. The wall of the gallbladder is unclear and there is no abnormal density in the lumen. The common bile duct is not dilated. The spleen is not large, normal in shape and position, with no abnormal density. The pancreas is normal in size and shape with clear margins. The pancreatic ducts are not dilated. The kidneys on both sides are not abnormal in position and size, with regular morphology and well-defined margins. There is no abnormal density in the parenchyma of the two kidneys. There is no filling of the bladder, no significant enlargement of the prostate, no significant abnormal parenchymal density, a slightly blurred abdominopelvic fatty space, a collection of intestinal shadows in the pelvic region, some suspicious thickening of the intestinal wall and scoliosis. There is an irregular mass in the upper lobe of the left lung, the nature of which is undetermined, with the possibility of a neoplastic lesion. A little chronic inflammation in both lungs. Coronary artery calcification. Small subpleural nodular shadow in the lower lobe of the right lung of undetermined nature. A few patches and cords in the remaining lung, with localised pleural thickening and adhesions on the right side. The abdominopelvic fatty space is slightly obscured and there is an aggregation of intestinal shadows and suspicious thickening of part of the intestinal wall in the pelvic region.

The patient's CT findings on 14 November 2020 showed increased translucency in both lung fields and increased and disorganized bronchial vascular bundles in both lung fields. An irregular mass was seen in the upper lobe of the left lung, measuring approximately 2.8 × 3.3 cm, with an irregular pattern and uneven density, surrounded by cords and bronchial shadowing, with some bronchial narrowing and adjacent pleural thickening and adhesions. A small subpleural nodule of 4mm in diameter is seen in the lower lobe of the right lung. The remaining lung has a few patches and cords, and the right pleura is partially thickened and adherent. The hilar shadow is small in both lungs and the trachea and bronchi are patent. There are no enlarged lymph nodes in the mediastinal space. A few hypodense nodules in the liver were detected. The patient has an irregular mass in the upper lobe of the left lung, the nature of which is undetermined and not significantly changed from the previous (CT of 2020-10-21). Little chronic inflammation in both lungs. Coronary artery calcification. Small subpleural nodular shadow in the lower lobe of the right lung, with insignificant changes from the previous. Localized pleural thickening and adhesions on the right side.

Patient's repeat chest CT on 28/01/2021 suggested that the patient had an irregular mass in the upper lobe of the left lung, nature to be determined, measuring approximately 2.8*3.3 cm, with insignificant changes in the mass compared to the findings on 2020-11-14. The patient's repeat chest CT findings on 06/03/2021 suggested the presence of an irregular mass in the upper lobe of the left lung, of a nature to be determined, measuring approximately 2.8*3.3cm.

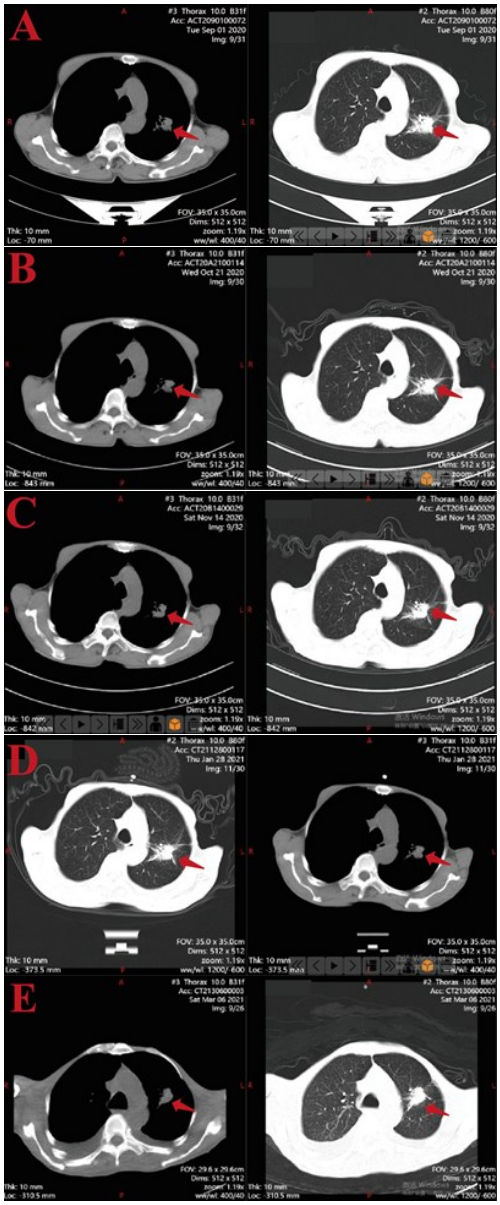


Figure 3. CT images of the patient's lungs during treatment (**A:** CT images of the patient's lungs at 2020_09_01; **B:** CT images of the patient's lungs at 2020_10_21; **C:** CT images of the patient's lungs at 2020_11_14; **D:** CT images of the patient's lungs at 2021_01_28; **E:** CT images of the patient's lungs at 2021_03_06).

*Note: A: Total mAs: 1496, Total DLP:197mGycm, 120KV, 76mAs, CTDIvol:5.84L, DLP(Thorax):192mGycm, TI:0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512; B: Total mAs : 3880, Total DLP:517mGycm, Chest:120KV, 87mAs, CTDIvol:6.63L, DLP (Thorax):208mGycm, TI:0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512 Abdomen:120KV. 100mAs, CTDIvol: 7.68L, DLP (Abdomen):300mGycm, TI: 0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512; C: Total mAs: 1870, Total DLP:250mGycm, 120KV, 92mAs CTDIvol: 7.08L, DLP (Thorax):244mGycm, TI: 0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512; D: Total mAs: 1741, Total DLP:232mGycm, 120KV, 93mAs, CTDIvol: 7.11L, DLP (Thorax):227mGycm, TI:0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512; E: Total mAs:1135, Total DLP:148mGycm, 120KV, 67mAs, CTDIvol:5.17L, DLP (Thorax):144mGycm, TI:0.5s, cSL:0.6mm. FOV:51.2*52.1cm, Dims:512*512.*

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MRI findings of the patient's brain during treatment

The patient's MRI brain findings during treatment showed no significant changes (figure 4).

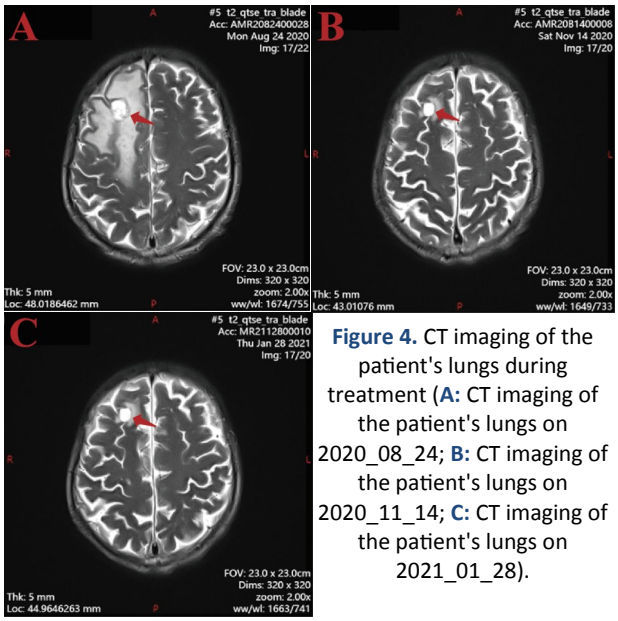


Figure 4. CT imaging of the patient's lungs during treatment (**A:** CT imaging of the patient's lungs on 2020_08_24; **B:** CT imaging of the patient's lungs on 2020_11_14; **C:** CT imaging of the patient's lungs on 2021_01_28).

*Note：TR:5000.0ms; TE:101.0ms; TA:1600000.00ms; Thickness:5.00mm; Spacing:6.5; Image Size:320*320; FOV. read:23.0*23.0cm, FOV phase:100%, Dims:320* 320.*

DISCUSSION

Although distant PSC metastases have a high incidence, few studies describe their clinicopathological features. To the best of current knowledge, this is the first report of PSC with small bowel metastases treated with durvalumab in combination with surgical resection of a localized tumor in the small bowel. PSC exhibits biphasic histopathological features, displaying both cancerous and sarcomatous components [15]. The origin of the sarcomatous element of PSC remains uncertain, but clonal development has been hypothesized in previous research [16, 17]. Some patients exhibit metastatic PSC of the small intestine with unknown primary lesions. As the PSC subtype is rare, lacks typical presentation and imaging signs, and has a significantly worse prognosis than other forms of non -small cell lung cancer [1], it is clinically important to understand how treatment in the event of metastasis to the small intestine or other sites can maximize patient quality of life and extend survival.

Previous studies have demonstrated that PSC cases can confirm bright discoloration for epithelial markers (CK and EMA) and mesenchymal markers (Vimentin), while Ki67 positivity suggests tumor cell proliferation invasiveness and TTF-1, CK, and CK7 positivity indicates a pulmonary origin [18, 19]. Immunohistochemical results in the reported patient's case showed positive results for AE1/AE3, Vimentin, Ki-67, Galectin-3, TTF, CK7, PCK, CK8/18, which, combined with an elevated percentage of PD-L1 positive cell counts, supported the clinical diagnosis. Surgical treatment for early-stage PSC patients prolongs survival, and surgical factors are independently beneficial aspects for PSC patients [20-23]. Ozkan *et al.* [24] conducted a retrospective cross-sectional study of 44 surgical patients with PSC, concluding that surgical excisional treatment could benefit patients, while postoperative adjuvant therapy had no effect on survival [25].

Despite the ongoing controversy regarding non-surgical treatment for PSC, immunotherapy has significantly improved the prognosis for PSC cases and may eventually become the standard therapeutic option for future PSC patients [3, 26]. Since the prevalence of PD-L1 positivity in PSC exceeds that in NSCLC overall [11, 27], immunohistochemical measurement of PD-L1 expression is the sole authorized biomarker in the National Comprehensive Cancer Network recommendations. Anti-PD-1/PD-L1 treatment is indicated as first-line therapy for advanced or metastatic NSCLC with positive PD-L1 expression [28]. Qin *et al.* [29] also supported investigation into PD-L1 as a potential therapy for patients with PSC. Durvalumab, a selective human immunoglobulin G1 monoclonal antibody against PD-L1, was enrolled in a multicenter, non-randomized, open-label phase 1b study in the USA (No. NCT02000947) involving 102 patients diagnosed with locally advanced or metastatic NSCLC. The study assessed the performance of durvalumab plus trametinib in individuals with progressive squamous or non-squamous NSCLC, observing complete inhibition of free SPD-L1 in all patients, suggesting effective target engagement of durvalumab and enhanced biological and antitumor activity when combined with trametinib [14]. No studies have investigated dosing alone in advanced small intestinal metastatic PSC. Q4w was chosen for efficacy assessment in patients due to the absence of significant pharmacological limitations during treatment and PK simulations showing near linearity of durvalumab at doses ≥3 mg/kg, indicating full target saturation.

Yuji Nishizawa *et al.* [30] reported an average survival of 7.7 months after bowel resection in individuals with lung cancer gastrointestinal metastases, with some patients achieving a survival history beyond 5 years [31]. Xie *et al.* [32] documented the first case of small bowel metastases from PSC using 18F-FDG PET/CT imaging, concluding that patients with small bowel metastatic PSC survived less than six months after the onset of black stool symptoms, potentially correlating with discomforts such as perforation, obstruction, and bleeding caused by small bowel involvement. In this study, the patient's survival after surgical resection of the mass combined with durvalumab extended to 14 months,

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exceeding the average survival but not achieving long -term survival. This outcome may be related to the patient already presenting with an acute abdominal emergency of small bowel obstruction at the time of presentation and not intervening early in the PSC.

Previous studies have demonstrated that the average age of PSC diagnosis is 60, and most men seeking treatment had a history of regular smoking, which is consistent with the case patient. PSC rarely metastasizes to the gastrointestinal system [31, 33-36], and gastrointestinal metastases may be asymptomatic in the early stages but carry a fatal risk when diagnosed late with severe complications such as intussusception, perforation, intestinal obstruction, hemorrhage, and acute appendicitis [37]. In a study including 934 patients with PSC cancer eligible for analysis, statistics revealed that 512 (54.8%) patients developed metastases at sites including bone (16.3%), brain (11.6%), liver, and lung [38], with individuals under the age of 60 representing a disproportionate share of those diagnosed with brain metastases. Gao *et al.* [39] concluded that common sites of metastases in PSC include lymph nodes, bones, adrenal glands, liver, brain, and reported cases of PSC with metastases to the epiglottis and ileum. The case data included MRI findings of the patient's brain, although the patient did not exhibit brain metastases. As PSC-related studies are limited, factors and patterns associated with metastasis are not currently well understood, which may warrant a large cohort study.

CONCLUSION

This study concludes that durvalumab combined with surgical resection of localized lesions therapy improved tumor response in patients with PSC with small bowel metastases. The significant reduction in tumor size and the absence of serious adverse effects demonstrated the clinical activity of the combination therapy. Thus, surgical excision of localized lesions followed by combination therapy with durvalumab represents a new paradigm for the treatment of PSC.

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***Ethical consideration*:** This article passed the ethical review of the medical paper by the Hospital Ethics Review Board.

***Author contributions*:** Conceptualization was done by H.WU and L.Y.; Methodology was done by H.WU and T.T.; H.WU completed the survey and formal report. H.WU, T.T.; H.WU did the survey and formal analysis; H.WU wrote the original manuscript H.WU and T.T. did the writing, review, and editing; H.WU, L.Y. obtained the resources; all authors reviewed the manuscript.

***Data availability*:** All of the data in this article was actually available.

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