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Pulmonary blastoma: a comprehensive overview of a rare entity

Abstract

Introduction: Pulmonary blastoma is a rare malignancy, accounting for less than 0.5% of primary lung tumors. It belongs to the group of pulmonary sarcomatoid carcinomas, and it is typically characterized by a biphasic pattern of an epithelial and a mesenchymal component. Only a few hundred cases have been reported worldwide. The aim of this study is to review and critically assess the literature regarding pulmonary blastoma.

Material and methods: A narrative literature review of PubMed database from the inception of the database up to January 2021, limited to the English language, was conducted, using combinations of the following keywords: "pulmonary blastoma", "biphasic pulmonary blastoma", "sarcomatoid carcinoma".

Results: Pulmonary blastoma is composed of an epithelial and a mesenchymal malignant component. Regarding pathogenesis, the origin of the biphasic cell population remains elusive. Characteristic immunohistochemical stains are supportive of diagnosis. Clinically, the symptomatology is non-specific, while 40% of the cases are asymptomatic. It is diagnosed at a younger age compared to other types of lung cancer, and it is often non-metastatic at diagnosis allowing for surgical treatment. Data on management and survival are scarce and mainly come from isolated cases. Advances on targeted therapy may provide novel treatment options. Given the rarity of the cases, multicenter collaboration is needed in order to establish therapeutic guidelines.

Key words: pulmonary blastoma, sarcomatoid lung carcinoma, biphasic pulmonary blastoma

Adv Respir Med. 2021; 89: 511–519

Introduction

Pulmonary blastoma (PB) is a rare malignancy that is estimated to account for 0.25 to 0.5% of all pulmonary neoplasms. It was seminally described in 1945 by Barrett and Barnard and was referred to as "embryoma"; however, in 1961, Spencer termed the tumor "blastoma" due to its histologic resemblance to the fetal lung at the 10–16-week stage of development (paraadenomal stage of lung development) [1]. Koss *et al.* (1991) classified pulmonary blastoma into 3 different subtypes: a) classic biphasic pulmonary blastoma (CBPB), b) pleuropulmonary blastoma (PPB) and c) well-differentiated fetal adenocarcinoma (WDFA) [2]. Pleuropulmonary blastoma predominantly presents in children and represents the most common primary pediatric pulmonary malignancy [3]. Classic biphasic pulmonary blastoma is typically characterized by a biphasic pattern consisting of a primitive mesenchymal stroma along with an epithelial component of fetal adenocarcinoma, while well-differentiated fetal adenocarcinoma is a monophasic tumor, presenting with immature adenocarcinoma as histologic characteristics [2]. Of note, since the WHO classification of lung tumors in 1999, pleuropulmonary blastoma is grouped with mesenchymal tumors, while fetal adenocarcinoma is classified as a subtype of lung adenocarcinoma [4]. Pulmonary blastoma is separately categorized as a type of sarcomatoid carcinoma of the lung

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DOI: 10.5603/ARM.a2021.0085 | Received: 05.04.2021 | | ISSN 2451–4934 | e-ISSN 2543–6031

[4, 5]. No significant changes have been made in the following versions, and therefore, the same terminology and categorization are adopted in the current WHO classification of lung tumors [6].

Only a few hundred cases of PB have been reported in the literature worldwide [7, 8]. Data on pathogenesis, epidemiology, management, and survival of pulmonary blastoma is scarce, and most evidence comes from case reports and case series. Additionally, the changes in the nomenclature of the tumor have led to confusion regarding the interpretation of earlier studies. Recently, the interest in rare pulmonary tumors has increased regarding both the pathogenetic and the clinical perspectives. To this end, the aim of this narrative review is to summarize updated data on pathogenesis, epidemiology, management, and outcome of pulmonary blastoma.

Pathogenesis

As far as the etiology is concerned, a correlation with smoking has been proposed with some cases demonstrating p53 mutation [9, 10]. Mutations in the gene of β-catenin have also been detected, similarly to other blastomas occurring in extrapulmonary sites, and those mutations are associated with the formation of morules in the tissue [11, 12]. Beta-catenin presents with a characteristic pattern of nuclear accumulation, which is unveiled with immunohistochemistry [11]. Of note, the mutations in β-catenin indicate a possible implication of the Wnt signaling pathway in the pathogenesis of PB [11]. In addition, a pathologic and molecular analysis of sixteen cases of PB demonstrated mutations in nine cancer-associated genes, namely *BRCA2*, *ERBB4*, *ALK*, *MET*, *BRAF*, *RAF1*, *PTEN*, *EGFR*, and *PIK3CA* [7].

PB belongs to the group of pulmonary sarcomatoid carcinomas, which are poorly differentiated non-small cell lung cancers (NSCLC), including a part of sarcoma-like elements or true sarcomatous areas [5, 6]. An interesting question regarding the pathogenesis of sarcomatoid carcinomas is whether the biphasic population of cells derives from a single ancestor cell or not. Two hypotheses have been proposed; the convergent hypothesis, suggesting that the different cancer cell types arise from different stem cells of epithelial and mesenchymal origin, and the divergent hypothesis proposing a single totipotential stem cell origin [13]. Moreover, the pathogenesis of sarcomatoid carcinomas has gained interest due to the potential involvement of the epithelial-mesenchymal transition (EMT) resulting in the formation of a mesenchymal component in an otherwise epithelial tumor [5]. Regarding pulmonary blastoma, evidence supportive of a single cell origin has been derived from genetic studies [11, 14]. Additionally, a study exploring whole-genome allelic imbalance in a case of pulmonary blastoma demonstrated common alterations in both epithelial and mesenchymal components of the tumor [15].

Histology

Histologically, the tumor is composed of an epithelial and a mesenchymal component (Figure 1A, B). The epithelial element is morphologically characterized by irregularly branching glandular structures, lined by pseudostratified columnar cells with clear cytoplasm and little nuclear atypia. The appearance is similar to the gestational lung in the pseudoglandular phase [2]. An embryonic stroma with oval cells with a high nuclear-to-cytoplasmic ratio is present, but up to one-quarter of the cases contain foci of osteosarcoma, chondrosarcoma, and rhabdomyosarcoma [5]. Areas of necrosis and hemorrhage are commonly observed within the tumor [2]. Tissue sampling from multiple areas is essential to confirm the presence of both epithelial and mesenchymal malignant components and establish the diagnosis [16]. Formally, a definite diagnosis is not possible based on small biopsy or cytology specimens because it requires a sarcomatoid/sarcomatous component in at least 10% of the neoplasm. However, a diagnosis of "NSCLC with sarcomatoid/sarcomatous component, possible sarcomatoid carcinoma" is reasonable [6].

Due to diagnostic dilemmas, immunohistochemistry is largely used, and it is supportive in reaching the diagnosis of PB. On the one hand, epithelial components stain positive for Cytokeratin, CEA, epithelial membrane antigen (EMA), thyroid transcription factor-1 (TTF-1), and surface protein alpha [17]. On the other hand, the stromal components stain positive for vimentin, desmin, muscle-specific actin, myoglobin, and S-100 [14, 18–20]. It has been proposed that b-catenin accumulation in the nucleus could be used as an additional criterion for the diagnosis of pulmonary blastoma [21] (Figure 1C, D).

Clinical and radiographic characteristics

PB has both a local growth pattern invading adjacent structures and a hematogenous metastatic spread. The most common symptoms

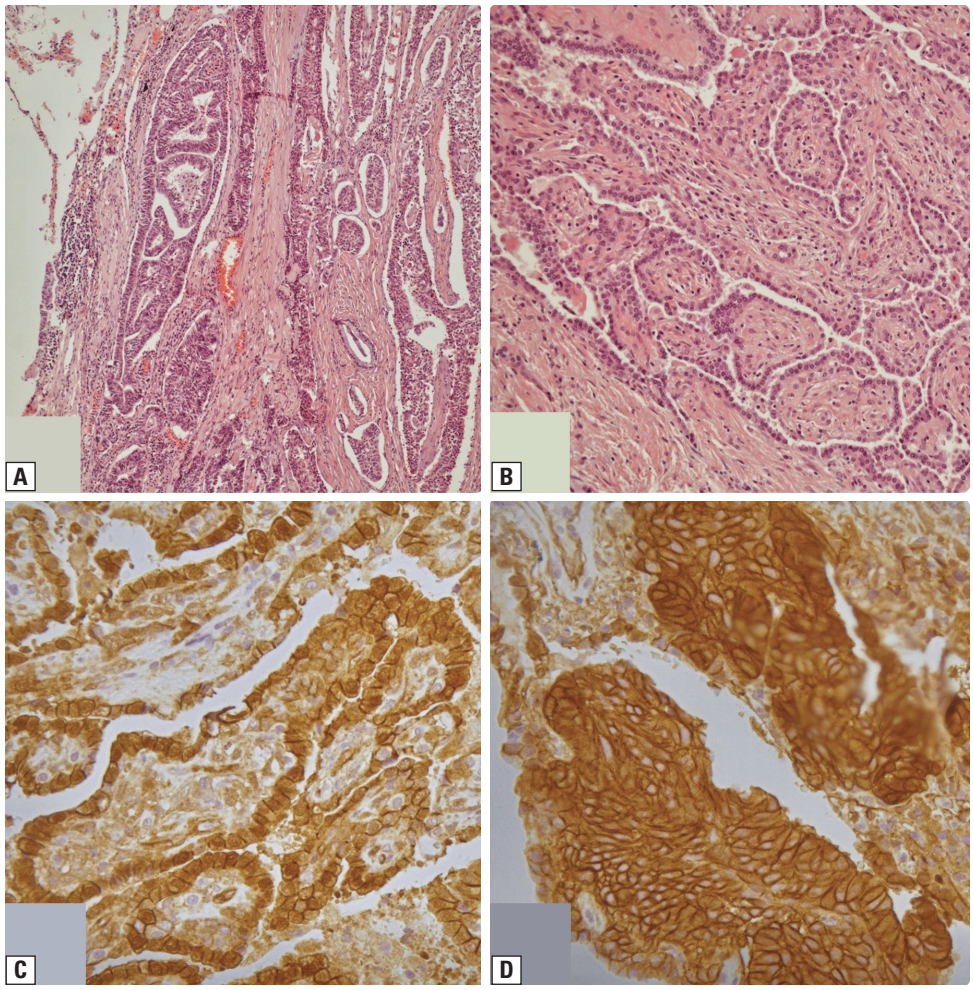

Figure 1. Biphasic tumor consisting of areas of fetal adenocarcinoma (**A**) and a mesenchymal fibroblastic-like cells (**B**). Both epithelial and mesenchymal blastematous cells show accumulation of β-catenin (**C, D**)

that occur are cough, hemoptysis, shortness of breath, recurrent pneumonia, fever, and weight loss, but asymptomatic tumors, accounting for 40% of cases, may also be detected incidentally [22–25]. There is a similarity in the anatomical presentation of these tumors. Involvement of the upper lobes, restriction to only one lung, and mean tumor size of 7–10cm are some of them [8, 26–28]. Hematogeneous metastases in the brain, bones, and liver, similar to NSCLC, but also in the breast, ovaries, peritoneum have been reported [8, 29]. There is no established biomarker indicating the diagnosis of PB, however, alpha-fetoprotein (AFP) increase has been identified in a few cases [30, 31].

In computed tomography of the chest, PB is characterized by well-circumferenced lesions, with dense and vesical elements with varying contrast uptake and central necrosis. Invasion of the pleura is possible and endobronchial growth is present in 25% of cases [16, 22]. The proximity to the pleura renders the bronchoscopy and biopsy difficult in the majority of the cases. A CT-guided transthoracic biopsy may be more convenient for diagnosis [32].

Table 1 summarizes typical histologic, immunohistochemical, clinical, and radiographic characteristics of pulmonary blastoma.

Epidemiology

Pulmonary blastoma is typically diagnosed at a younger age compared to NSCLC, as the majority of the patients are diagnosed before 50 years old [33–59]. A bimodal age distribution with peaks of incidence in the 4th and 7th decade of life has been reported [18], however, this has not been confirmed in a recent epidemiological study [60]. Regarding the gender predilection of the neoplasm, the results are ambiguous. Some studies report a male predominance [18, 40, 61], while others describe equal prevalence or even predominance of female gender [32, 60]. It should

Table 1. Histologic, immunohistochemical, clinical, and radiographic characteristics of pulmonary blastoma

Pulmonary blastoma	Characteristics
Pathology	**Epithelial component**: irregularly branching glandular structures, lined by pseudostratified columnar cells with clear cytoplasm and little nuclear atypia (fetal adenocarcinoma). **Mesenchymal component:** oval cells with a high nuclear-to- cytoplasmic ratio is present by definition, but up to one-quarter of the cases contain foci osteosarcoma, chondrosarcoma, and rhabdomyosarcoma
Immunohistochemistry	**Epithelial component**: Cytokeratin, CEA, epithelial membrane antigen (EMA), thyroid transcription factor-1 (TTF-1), and surface protein alpha **Mesenchymal component**: stromal components stain positive for vimentin, desmin, muscle-specific actin, myoglobin, and S-100
Clinical presentation	Cough, hemoptysis, shortness of breath, recurrent pneumonia, fever, and weight loss Asymptomatic tumors (40% of cases)
Radiographic presentation	Well-circumferenced lesions, with dense and vesical elements with varying contrast uptake and central necrosis

be noted that earlier studies may have included fetal adenocarcinomas within the term of pulmonary blastoma, which may differ concerning the epidemiological features and thus, it needs to be considered when interpreting the data [55].

Prognosis of pulmonary blastoma has been considered poor, based on the reported survival of isolated case reports and case series [2, 39, 29]. Nevertheless, in the most recent epidemiological study, with data deriving from the Surveillance, Epidemiology and End Results (SEER) database of the US population, it has been demonstrated that nearly half of the PB patients achieved long-term survival [60]. In fact, the 5- and 10-year survival rates in all PB patients were 58.2 and 48.5% [60].

Management and outcome

The majority of the patients with pulmonary blastoma are diagnosed at earlier stages, which allows for surgical treatment [29]. Similar to NSCLC, lobectomy is the most frequent procedure performed [8, 27, 47]. A study of 5 patients with PB by Liman *et al*. between 1987 and 2000 reported long-term survival after radical surgery, in patients with small size tumors (< 5 cm) without nodal involvement [47]. Specifically, in this study, one patient presented with stage T1N0M0, one individual with T2N0M0, and three patients with T2N1M0. As it was anticipated, the subjects without nodal involvement had the most favorable outcome [47].

The efficacy of adjuvant therapy has not been established with clinical trials; however, several published cases are reporting good outcomes with the use of adjuvant chemotherapy with or without radiotherapy [29, 62, 32]. Cisplatin combined with etoposide has been proposed as a regimen for adjuvant chemotherapy based on a review of the literature [63]. In a more recent report by Lewis *et al*. (2018), two patients underwent surgical treatment and they received adjuvant cisplatin-based chemotherapy for four cycles followed by thoracic radiation. Both patients achieved long-term survival [62].

Additionally, a few reports have described cases in which the patients received neoadjuvant therapy for downstaging before surgical resection. Bosch-Barrera *et al.* (2015) reported a 25-year-old patient with unresectable locally advanced pulmonary blastoma who received neoadjuvant chemoradiotherapy with two induction cycles of cisplatin plus etoposide, followed by concurrent weekly cisplatin and radiotherapy treatment. The tumor size significantly decreased, allowing for complete resection by pneumonectomy [59]. In another case, a 17-year-old male with a large tumor (12cm) with adjacent chest wall infiltration, which was considered unresectable initially, received preoperative chemotherapy with cisplatin plus etoposide. The reevaluation with chest CT scan after 3 cycles of chemotherapy demonstrated good regression of the mass. Therefore, the man underwent right upper and middle lobectomy followed by adjuvant local irradiation [57]. Moreover, in a patient who presented disease recurrence with a large mass, and although the original plan was for definitive radiation therapy with concurrent cisplatin and etoposide, the tumor regressed considerably after 2 weeks of treatment. Therefore, a preoperative course of radiation therapy and chemotherapy was decided and three weeks after completing therapy, he was reassessed with a chest CT showing impressive regression of disease, allowing for surgical treatment with right pmeumonectomy [67].

Regarding metastatic disease, treatment mainly includes chemotherapy; however, guidelines on regimens do not exist. Cutler *et al*. (1998) [63] and more recently Lewis *et al*. (2018) [62] have reviewed reports of patients who received chemotherapy. Historically, single-agent chemotherapy was initially tried with no clinical or objective response [62]. Vila *et al*. were the first to use combination chemotherapy with chlorambucil plus methotrexate in 1973 [33]. Over the following decades, oncologists applied various cytotoxic regimens, namely cisplatin-etoposide with or without ifosfamide and cyclophosphamide- and vincristine-based regimens. Other chemotherapeutic drugs that have been commonly used are carboplatin, doxorubicin, and paclitaxel [34, 52, 58, 65]. Moreover, two reports have been published of patients who received sorafenib; in one case the patient had a renal metastasis which responded well to sorafenib allowing for surgical treatment with radical nephrectomy [29, 50]. Interestingly, other four cases of metastasectomy have been reported, two of them involving metastatic tumors in the brain, in one case, a metastatic lesion in the breast, and finally, a case of metastatic PB to the ovary [48, 34, 62].

Only a few reports exist on the molecular alterations detected in PB, and even fewer that qualify for targetable therapies. Two cases have been published in which the tumor carried a ROS1 rearrangement. In the first case, fluorescence *in situ* hybridization (FISH) demonstrated a *ROS1* rearrangement in 7/50 tumor cells (14%) [20]. In the other case, the patient had a detectable CD74– ROS1 rearrangement and responded to crizotinib, providing a novel option for the treatment of PB [66]. The evidence remains scarce with regards to other molecular alterations; however, in the absence of established therapies and given the adenocarcinoma component of the tumor, it is reasonable to search for possible targetable mutations [26]. Finally, regarding immunotherapy, high expression of PD-L1 has been reported in some cases of PB, but no study has been published yet with the use of an immunotherapeutic agent [59].

Our literature review of recent (2000–2020) cases of patients with pulmonary blastoma who received chemotherapy in any setting (neoadjuvant, adjuvant, or metastatic) is shown in Table 2 [26, 28–30, 45, 47, 49, 50, 64, 66–71, 52, 54, 57–59, 62, 72–75]. Only English literature is included. Demographics characteristics, chemotherapeutics regimens, as well as reported survival, are summarized in the table.

Conclusion

Pulmonary blastoma is a rare tumor with unknown pathogenesis and aggressive behavior. It is diagnosed at a relatively young age, and it is frequently non-metastatic at diagnosis, allowing for surgical treatment. No guidelines exist regarding neoadjuvant or adjuvant therapy and concerning the optimal management of metastatic tumors. Due to the rarity of the cases, multicenter

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Bini *et al*. [67]	2001	53/M	LL Lobectomy	After recurrence: Chemotherapy cisplatin-etoposide × 3 cycles	12 m
Zaidi *et al*. [68]	2002	24/F	LU Lobectomy	Neoadjuvant vincristine, dactinomycin, ifosfamide, doxorubicin, etoposide, carboplatin	Alive at 35 m
Zaidi *et al*. [68]	2002	23/M	No	Vincristine, dactinomycin, cyclophosphamide, cisplatinum, doxorubicin	8 m
Walker *et al*. [45]	2005	21/F	Thoracotomy with decortication	Chemotherapy due to residual disease after surgery	6 m
Liman *et al*. [47]	2006	27/F	RU Lobectomy	Vincristine and cyclophosphamide followed by ifosfamide and etoposide	17 m
Liman *et al*. [47]	2006	54/M	RL Lobectomy	Vincristine and cyclophosphamide	10 m
Oshika *et al*. [49]	2007	58/M	RU Lobectomy and mediastinal LN dissection	Adjuvant chemotherapy with cisplatin and etoposide; Radiation after recurrence	Alive 70 m postop

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Mulamalla *et al*. [50]	2007	37/F	RU Lobectomy with LN dissection; Resection of local recurrence; Laparoscopic radical nephrectomy after response to sorafenib	Pemetrexed and bevacizumab × 3 in combination with radiation (4800 cGy) Sorafenib	NA
He *et al*. [69]	2008	47/F	The mass was removed en bloc through radical left intrapericardial pneumonectomy	Adjuvant chemotherapy (carboplatin/etoposide/isofosfamide) × 3 ;radiotherapy	3 y postop alive- disease free
Yu *et al*. [70]	2009	38/F	Lobectomy, metastasectomy (abdominal hysterectomy and bilateral salpingo-oophorectomy)	Adjuvant radiotherapy and chemotherapy (cisplatin and etoposide)	NA
Zagar *et al*. [64]	2010	24/M	RU Lobectomy, R pneumonectomy	Five years after lobectomy: Neoadjuvant radiation (60 Gy) followed by concurrent chemo-RT with cisplatin and etoposide (50 Gy total) in 2 Gy daily fractions; followed by adjuvant cisplatin and etoposide × 2 cycles	NA
Schwitter *et al*. [71]	2011	28/F	LU Lobectomy and LN dissection	Adjuvant Chemotherapy (initially ifosfamide, vincristin, actinomycin D and doxorubicin, later ifosmamide/cisplatin) Stereotactic Radiosurgery and whole brain RT (30 Gy)	Alive at 18 m
Van Loo *et al*. [29]	2011	77/M	RU Lobectomy with LN dissection	After recurrence: Sorafenib	12 m
Lindet *et al*. [52]	2011	22/F	R Pneumonectomy, pericardiectomy	After recurrence: 1st line: Ifosfamide, doxorubicin × 6 cycles then doxorubicin × 2 cycles followed by stereotactic radiotherapy (40 Gy); 2nd line: carboplatin, vincristine, 3rd line: cyclophosphamide; actinomycin-D, 4th line: docetaxel/gemcitabine	18 m
Sharma *et al*. [54]	2013	63/M	RL Lobectomy	After recurrence: Four cycles of cyclophosphamide, doxorubicin and vincristine (CAV)	NA
Muthu *et al*. [57]	2014	17/M	RU/RM Lobectomy; Tumorectomy along with excision of segments of fourth and fifth ribs	Neoadjuvant chemo with 3Cy Cis-VP Adjuvant RT, declined adjuvant chemo Declined chemo after 1st recurrence After 2nd recurrence → Cis-VP. The tumor was then de-bulked and its residue was irradiated; palliative radiation to the spine	24 m
Gallo *et al*. [72]	2015	43/M	No	Four cycles of cisplatin, ifosfamide, and etoposide (VIP) concurrently with 40 Gy external-beam radiation in 20 fractions	NA
Sakata *et al*. [58]	2015	63/M	LU Lobectomy and LN dissection	After recurrence: Carboplatin, Paclitaxel and bevacizumab	9.5 m
Bosch-Barrera *et al*. [59]	2015	25/F	Pneumonectomy (after neoadjuvant}	Neoadjuvant chemoradiotherapy based on two induction cycles of cisplatin plus etoposide, followed by concurrent weekly cisplatin to 50.4 Gy radiotherapy	Alive 8 m postop
Kilic *et al*. [73]	2016	68/M	LUL lobectomy, Cranial metastectomy	After recurrence: Radiotherapy and chemotherapy	6 m
Liu *et al*. [28]	2017	53/M	Left lobe resection plus mediastinal LN dissection	Adjuvant: Paclitaxel combined with nedaplatin × 4 Recurrence: RT 42 Gy/21 f pemetrexed + cisplatin + bevacizumab	18 m

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Caer *et al*. [74]	2018	71/F	RL Lobectomy	1st: Cisplatin-vepesid, 2nd: Carbo-etoposide; RT; Carbo-etoposide	Alive at 7 y postop
Meng *et al*. [66]	2018	44/F	No	Crizotinib first time used for PB (CD74–ROS1 rearrangement) → reduction in pleural effusion and 34.4% shrinkage of tumor size and improvement of symptoms, after 3m PD with enlarged L lung lesion and L pleural effusion	3 m PFS
Lewis *et al*. [62]	2018	38/F	LU Lobectomy with chest wall resection and mediastinal LN dissection, right parietal craniotomy, gamma knife radiosurgery (GKRS)	Adjuvant chemotherapy with cisplatin and vinorelbine , thoracic radiation with 50.4 Gy in 28 fractions.	Alive at 10 y postop
Lewis *et al*. [62]	2018	29/F	Thoracotomy and resection of the tumor Resection of the ovarian masses	Cisplatin, ifosfamide, vepesid, 59.49 Gy of radiation in 33 fractions	Alive at 10 y postop
Yang *et al*. [30]	2019	29/F	RM Lobectomy with LN dissection	Adjuvant Radiotherapy and nedaplatin	Alive at 6 m postop
Vossler *et al*. [75]	2019	66/F	Left Lobectomy	Palliative radiation and chemotherapy (cisplatin and etoposide)	6 m
Luo *et al*. [26]	2020	58/M	RU Lobectomy	Adjuvant: Nedaplatin plus paclitaxel After recurrence: two cycles of etoposide-cisplatin and six cycles of pemetrexed, bevacizumab, and carboplatin. The chemotherapy was stopped due to toxicity. The patient was finally administered anlotinib, a new oral multikinase inhibitor	Alive at 4 years

F — female; M — male; R — right; L — left; RU — right upper; RM — right middle; RL — right lower; LU — left upper; LL — left lower; m — months; y — years; Gy — Grey; NA — not available

collaboration is sorely needed in order to provide databases, allow large clinical trials, and establish therapeutic guidelines.

Conflict of interest

None declared.

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