Deciduoid mesothelioma of the thorax: a comprehensive review of the scientific literature.

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Abstract

Objective. Deciduoid mesothelioma is a rare variant of malignant epithelioid mesothelioma. It often involves the peritoneum, but also thoracic cases have been reported. The aim of the present review is to describe the demographic, clinical, radiological, and pathological features of such a rare variant of thoracic mesothelioma, and the state of the art regarding the therapeutic approaches currently available. **Data source.** English-language articles published from 1985 to June 2016, and related to thoracic deciduoid mesothelioma cases were retrieved using the Pubmed database. **Study selection.** The search terms were "mesothelioma", "thoracic mesothelioma", "epithelial mesothelioma", "pleural mesothelioma", and "deciduoid mesothelioma". **Results** Forty-four cases included in 16 papers, published in the period under investigation, were analyzed in detail. **Conclusions.** The mean age of the patients was 63 years, and the male to female ratio 1.7:1. Approximately 58% had exposure to asbestos, and 73% had a smoking history; familiarity was rarely reported. The most common anatomical site of origin was the right pleura, and the most frequent clinical manifestation were chest pain, dyspnea, cough, and weight loss. Thoracic X-ray and computed tomography were the imaging techniques most employed for diagnosis and surgical planning. The pathological diagnosis was obtained by examination of surgical or biopsy specimens in most cases. The best treatment strategy of deciduoid mesothelioma is a matter of debate; nevertheless a multidisciplinary approach is currently the best option for the choice of the adequate therapeutic scheme.

Key words: thorax, pleura, cancer, mesothelioma, deciduoid.

Introduction

Malignant mesothelioma (MM) is a rare form of cancer derived from mesothelial cells of serous membranes, principally the pleura and the peritoneum[1,2]. In most industrialized countries, more than 80% of pleural mesotheliomas in men are related, principally for occupational reasons, to asbestos exposure, particularly to amosite and crocidolite fibres[3]. Actually, high incidence rates are observed in western countries as a result of asbestos exposure in the 70's and the long latency of the disease (20 to more than 50 years)[4].

On the basis of their local evolution, MM can be divided in localized and diffuse, with the majority of the latter being malignant. Diffuse MM (DMM) is an extremely aggressive neoplasia characterized by a high local diffusion rate, with early involvement of the pericardium and the diaphragm, and by high recurrence rates after radical surgical treatment[2,3]. Median survival time from diagnosis without treatment ranges from 4 to 12 months; nevertheless better results have been reported in patients with favorable biological and clinical parameters, undergoing a multidisciplinary treatment[2,5,6].

There are four main histological types of MM: epithelial, representing about 50% of all cases and having a better prognosis, sarcomatoid, mixed or biphasic, and desmoplastic[7]. Epithelial mesotheliomas classically present a papillary or tubular pattern, but some may be solid and, infrequently, examples with microcystic, clear cell, signet ring, small cell have been described[7,8]. Occasionally it is possible to reveal patterns of mesenchymal differentiation (chondroid, osteoblastic, fibrosarcomatous etc) or lymphomas[1]. Differential diagnosis has to be made with pleurisy, lymphoproliferative disorders, mesenchymal pleural neoplasias, as well as adenocarcinoma and other consistently more frequent types of lung cancer[1-3]. The deciduoid histotype (MDM) is a very rare variant of epithelioid mesothelioma. It was firstly described by Talerman et al. in 1985, and it was initially believed to involve exclusively the peritoneum of female patients[9,10]. Indeed, numerous cases in literature confirm a frequent involvement of the peritoneal serosa; nevertheless, some cases of thoracic MDM have been reported. The aim of the present review is to detect all the cases of thoracic MDM reported in the scientific literature to date, and describe their demographic, clinical, radiological, and pathological features, as well as the therapeutic approaches employed, and the results obtained.

Data source

English-language articles published from 1985 (when the first case of deciduoid mesothelioma was described) to June 2016, and related to thoracic deciduoid mesothelioma cases were non systematically retrieved using the Pubmed database.

Study selection

The search terms were "mesothelioma", "thoracic mesothelioma", "epithelial mesothelioma", "pleural mesothelioma", and "deciduoid mesothelioma". Titles and abstracts were evaluated in order to include the most relevant studies. References of the selected articles were cross-checked in order to detect papers missed by the search engine.

Results

Forty-four cases included in 16 papers, published in the period under investigation, were analyzed in detail[8,11-27]. The description of two cases was included in two different articles; demographic and clinical information was retrieved from both papers[20,28]. The main demographic features, and the localizations of the tumors in the enrolled patients are summarized in Table 1. The age of the patients was available in all cases, while information about their sex was not available in one case. The mean age of the patients was 63 (13 – 78) years, and the male to female ratio 1.7:1. Only 3 patients (6.8%) were younger than 30 at the time of diagnosis. The most common anatomical site of origin of the tumor was the pleura; the right parietal and/or visceral pleura was involved in 27 (61%) cases, while the left pleura was involved in 12 (27%) cases, and in one case bilateral lesions were found. Information about the side of the tumor was lacking in 3 (6.8%) cases; the tumor originated from the pericardium in 1 (2.3%) patient. Information reporting the involvement of the mediastinum was available in 4 (9%) cases, the lungs in 6 (13.6%), and the chest wall in 5 (11.3%).

Table 2 summarizes the main risk factors and clinical manifestations observed. Information about asbestos exposure was available in 43 cases; among them 25 (58.1%) had a previous exposure to asbestos for professional or other reasons. Regarding tobacco smoking, data were available for 15 patients, and 11 (73%) of them had a smoking history or were active smokers. Only Scattone et al. included data about familiarity in the six cases of deciduoid mesothelioma reported: 2 patients presented a familiar form, and the remaining 4 a sporadic form[20]. The most frequent clinical manifestation observed in the 24 cases in which signs and symptoms were described was chest pain (13 cases, 54%), dyspnea (12, 50%), cough (6, 25%), and weight loss (3, 12.5%). Interestingly, two clinically silent cases have been described, and the thoracic lesions have been discovered during radiological evaluations for pathologies of other anatomical districts. In one of those cases, the tumor involved also the peritoneum. In the case described by Henley et al, the tumor appeared as a mediastinal mass, while in the case reported by Tsai et al. the deviation of the ipsilateral hemithorax, a rare clinical manifestation, was reported[14,21].

Information about the radiological methods employed was available in 22 cases (Table 3). The traditional chest X-ray was used in at least 10 (45.4%) of them, while the computed tomography (CT) scanning was employed in 21 (95.4%). Further radiological techniques were rarely used; positron emission tomography (PET) scans were performed in 2 (9%), and magnetic resonance imaging (MRI) in 1 (4.5%) case. Most diagnoses were obtained by examinations of

surgical specimens (23, 52.3%, Table 3), or surgical biopsies (15 open and thoracoscopic, 34.1%). Only in 3 (6.8%) cases the diagnosis was obtained by needle biopsy, and in 1 (2.3) case by pleural fluid cytology (Table 3). Finally, in 2 (4.5%) instances the diagnosis was post-mortem. Immunohistochemical evaluations, in addition to the gross and histopathological examination of the specimens, was carried out in all the cases. Table 4 depicts the immunostainings most frequently used and the results obtained in the cases in which such analyses were performed; the cases reported by Ordonez et al. in 2012 are not included as no distinction between pleural and abdominal cases was made in reporting the immunohistochemical results[24]. Nevertheless, in this report, immunostaining for calretinin was positive in all cases[24].

Several therapeutic strategies have been employed in the cohort of patients under investigation. Surgery, chemotherapy and radiotherapy have been used alone or in various chronological, quantitative, or qualitative combinations, and described in 41 of the cases reviewed (Table 5). Surgery alone was performed in 9 (20.4%) patients, chemotherapy alone in 6 (13.6%), and radiotherapy alone in 1 (2.3%). A combination of two or all of these therapeutic approaches was used in 24 (54.5%) cases, indicating that a multidisciplinary approach, when feasible, is generally preferred. The surgical technique most commonly employed was pneumonectomy (extrapleural or not, 20 cases), while Pemetrexed was the chemotherapeutic agent most frequently administrated. Despite such therapeutic efforts, the survival rates were poor (Table 5). Excluding six cases without available data, and two patients who died immediately before or after surgery, the patients who were alive at the time of the publication of the article reporting their clinical case were 7 (19.4%), and their mean survival time was 17.2 months. On the other hand, 29 (80.6%) patients were dead, and in this case the mean survival time was 19 months. Only 7 (24.1%) out of the 29 dead patients survived more than 24 months, and only 1 (3.4%) lived more than 5 years.

Discussion

Malignant deciduoid mesothelioma is a rare tumor, with only a few cases described since its first description in 1985[9]. Ordóñez in a recent report reviewed approximately 650 mesotheliomas from the files of the Department of Pathology at the University of Texas MD Anderson Cancer Center, and he detected 21 deciduoid cases[24]. The thoracic cases were 17 accounting for the 2.7% of all cases, and 80.9% of the total deciduoid cases found[24]. Nascimento et al. advocated in the past that the disease affects only the peritoneum of young female patients, because his two cases and the case previously published by Talerman were observed in young women, without asbestos exposure and hormonal immunoreactivity in the neoplastic cells[9,10]. Nevertheless, subsequent reports by Ordóñez and Shanks et al. definitely evidence that the disease can also affect the pleura, as well as male patients[8,11].

Our review of the literature evidenced 44 cases of decidouid mesothelioma involving the thoracic region to date. Most of the patients were males (male:female ratio 1.7:1), and the mean age was 63 years, as opposed to cases of

peritoneal involvement which mostly affect women in a younger age; this pattern resembles the general epidemiological behavior of MM of the pleura which is consistently more frequent in males[3]. We also found out that the right hemithorax is significantly more involved than the left side, as occurs in cases of the extremely more frequent non-small cell lung cancer (NSCLC), and the mechanism may be similar, depending on the anatomy of the tracheal tree and the greater dimensions of the right lung that allows a higher amount of asbestos and other pollutants to reach this anatomic region[29].

The role of asbestos is well established in the pathogenesis of MM. Nevertheless, such a relation could not be initially established with the deciduoid subtype[9,10]. Our results evidence that approximately 58% of the patients with thoracic MDM have been exposed to asbestos prior to diagnosis. Such a percentage is lower than that reported for all forms of DMM, and may indicate that asbestos may be less influential on the pathogenesis of MDM, and other risk factors and pathophysiological mechanisms should be investigated. To this purpose, Scattone et al. performed a study with the aim to identify peculiar genetic changes responsible for critical phases in the pathogenesis of MDM and their prognostic relevance with a comparative genomic hybridization (CGH) approach in 2006[c]. The Authors found that genetic abnormalities in all the tumors, the most frequent being chromosomal gains at 1p, 12q, 17, 8q, 19 and 20 and losses at 13q, 6q and 9p. Survival was found to be longer in those patients who presented a smaller number of losses ($\leq$2) in the neoplastic chromosomes. They concluded that certain chromosomal regions are preferentially affected, and that the clinical outcome is predicted by the number of losses[20]. Also, the role of tobacco smoking seems to be relevant, as 73% of the 15 patients with available data were former or current smokers.

The study of the clinical manifestations of the disease evidenced absence of a specific clinical picture. The most common clinical manifestations were pain, dyspnea, cough, and weight loss, as in other thoracic, neoplastic and non-neoplastic diseases, including the epithelial forms of mesothelioma. This often makes the diagnosis challenging. Particular clinical manifestations were also described, as in the case reported by Henley et al; the patient was diagnosed with an anterior mediastinal mass, which was surgically resected and pathologically examined, with the diagnosis being thymic carcinoma[14]. Interestingly, the patient was affected also by myasthenia gravis. A few months later a right pleural thickening was evidenced, and the case was further reviewed pathologically. The final diagnosis was MDM. The Authors underlined the particularities of the case: first, the clinical presentation as an anterior mediastinal mass, simulating a thymic primary tumor. The tendency of thymic tumors to spread along the pleura in a mesothelioma-like fashion is well-known; however, the converse situation, in which mesothelioma presents initially as a mediastinal mass that mimics thymic neoplasia is very unusual[14]. Furthermore, the Authors highlighted that the tumor arose in a field of prior radiation therapy for Hodgkin's disease, as in the case described by Puttagunta et al[13]. There are several descriptions of MM arising in patients with a history of radiation therapy, but the real association is not yet clear[30,31].

Tsai et al. reported a pediatric case manifested with chest pain, and retraction of the right hemithorax, with ipsilateral deviation of the spine[21]. The occurrence of MM in the pediatric group age is very rare, and this represents the only case of MDM reported to date.

The chest X-ray and CT scan were the imaging techniques most frequently employed, and the most common findings were pleural effusion, lung atelectasis, and pleural thickening, followed by signs of invasion of the neighboring anatomic structures. These radiological signs are indistinguishable from those observed in other epithelial mesotheliomas. Complementary imaging techniques (PET, MRI) were rarely used, and only in recent reports; this may be due to clinical reasons, but also due to the poor accessibility to such techniques in the past, as opposed to their recent wider availability.

The pathological diagnosis was obtained by examination of surgical or biopsy specimens in most cases. This reflects the intrinsic to the disease difficulties to characterize and differentiate it from other pathological processes. The classic cytological picture of MDM was well described by Nascimento et al in 1994: "a proliferation of large, round, ovoid, and polygonal cells that had sharp cellular outlines, abundant glassy eosinophilic cytoplasm, and round vesicular nuclei with prominent eosinophilic nucleoli. Binucleated forms were occasionally present"[10]. Mitotic figures can be rare or common, the cytoplasm can be pale, and, at higher magnification, the membrane appears covered by microvilli[8]. The cells are generally arranged in anastomotic sheets or small clusters. The deciduoid pattern can involve the lesions diffusely, or be limited in focal areas, and this sometimes makes the diagnosis challenging. Areas with papillary pattern, and features commonly seen in epithelioid mesotheliomas can be intermixed, and this may be useful for the differential diagnosis with primary or metastatic adenocarcinomas and other tumors[8].

The ultrastructural pattern of the disease is characterized by clusters of neoplastic cells which lay on a basal lamina, and are connected to each other by well-formed desmosomes. Their apical and lateral surfaces are covered by long, branching microvilli, and their endoplasmic reticulum is generally well developed. Bundles of intermediate filaments can be seen around the nucleus, and most cells contain electron-dense membrane-bound inclusions, some of which display a fibrillar or lattice configuration, and occasionally small intracytoplasmic lumina or pools of glycogen[8]. The voluminous cytoplasm and its rich content is the cause of the typical deciduoid appearance, the intermediate filaments are responsible for the glassy appearance of the cytoplasm, while the glycogen pools may contribute to make it clearer[8,11].

An immunohistochemistry panel is generally useful for the differential diagnosis of MDM, as no single pathognomonic markers exist. Positivity for calretinin, cytokeratin 5/6, cytokeratin 7, and vimentin, as well as negativity for CD 15, MOC 31, and TTF1 are highly suggestive of thoracic MDM. Also negativity for CEA and

BerEP4 may contribute to the diagnosis[11]. Thrombomodulin has been demonstrated to be reactive in 80% of mesotheliomas; nevertheless, it reacts also with adenocarcinomas in up to 77% of cases[11,32].

The pathological features of MDM described, reflect the difficulty to establish such a diagnosis in needle biopsy and/or cytological preparations; furthermore, the evolution of the modern minimally-invasive video-thoracoscopic techniques frequently allow the obtainment of histology specimens[33]. Only one diagnosis by pleural fluid cytology has been described in the literature, and was reported by Ordonez in 2000[8]. The microscopic examination of the sections showed large polygonal cells with abundant, eosinophilic, dense cytoplasm, with round or oval nuclei containing a small nucleolus. Binucleated cells were seen frequently. The cell membranes were covered with prominent microvilli, that were better demonstrated on sections stained for thrombomodulin. In the latter preparations, the cell membranes appeared thick, with spiky outlines showing the dense covering of microvilli. The neoplastic cells exhibited strong reactivity for cytokeratin 5/6 and calretinin, but no reaction was seen for CEA, Leu-M1 (CD15), B72.3, or MOC-31[11].

Not only the diagnosis of MDM is challenging, but also its treatment. There is not a clear therapeutic strategy established, and several combinations of treatments have been proposed in the literature. Our analysis demonstrated that multimodality approaches are preferred to single modality treatments, especially in recent years. Surgery, chemotherapy, and radiotherapy have been combined in various ways, and in several dosages; nevertheless, no specific and diriment studies exist. For this reason, no valuable guidelines can be proposed for this specific histotype. Nevertheless, guidelines for the treatment of epithelial MM are available, and can be used as far as no survival differences are evidenced in the subgroup of patients with MDM[34]. What appears reasonably evident is that a multidisciplinary approach in reference centers would be preferable for the sufferers[2,34]. The surgical approach most employed is pneumonectomy, but its advantages among less invasive techniques, especially pleurectomy-decortication are not clear. Pemetrexed based regimens are the most commonly used for adjuvant chemotherapy. Neoadjuvant treatment is accepted as standard therapy in stage IIIA, and is being investigated as therapy in earlier stages. Despite some encouraging results with cisplatin and gemcitabine, the combination that provided greater survival benefit was pemetrexed with cisplatin[7,35]. Radiotherapy has been beneficial in the prevention of recurrence after surgery, forming part of trimodal therapy[25]. Intrapleural or local therapies, such as photodynamic therapy, hyperthermic intrapleural chemotherapy and immunotherapy are currently under investigation[22].

Regarding prognosis, MDM was thought to be a more aggressive variant in comparison to other forms of mesothelioma[16]. The issue is not clear, as recently some authors reported that it may not be so aggressive[24]. Our review evidenced that approximately 80% of the patients included died, with the mean survival time being 19 months; only 7 survived more than 24 months, and only 1 lived more than 5 years, evidencing that the prognosis of the disease is

similar to that reported for other epithelial mesotheliomas. Further scientific efforts should be performed, and further cases should be reported, preferably in a multicenter, prospective, well designed fashion.

Conclusion

Our review evidenced that MDM more frequently involves the right pleural of male patients, generally in their sixth decade of life. Asbestos and tobacco exposure was documented in most cases, while the most common clinical manifestations were pain, dyspnea, cough, and weight loss. Chest X-rays and CT scans represent the most useful imaging tool, but surgical exploration is generally necessary to obtain the final diagnosis. No precise therapeutic protocols have been yet identified, and the prognosis of the disease remains extremely poor. Further scientific efforts should be done in this field, and further well designed studies should be reported.

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Tables

Table 1. Demographic data of the patients, and anatomical localization of the tumors found in the current literature.

Article	Cases	M:F	Age (years)	Anatomical position (side)
Ordonez, 2000[8]	4	3:1	46,64,60,78	Pleura (3R, 1L)
Shanks et al, 2000[11]	1	M	52	Pleura (R)
Gloeckner-Hofmann et al, 2000[12]	1	F	40	Pleura and mediastinum (R)
Puttagunta et al, 2000[13]	1	M	41	Pleura (L)
Henley et al, 2001[14]	1	F	30	Mediastinum + pleura (R)
Monaghan et al, 2001[15]	1	M	66	Pleura (R)
Shia et al, 2002[16]	3	1:2	69, 71, 65,	Pleura (2R, 1L)
Reis-Filho et al, 2002[17]	1	F	71	Pericardium
Asioli et al, 2004[18]	1	M	62	Lung + pleura (L)
Mourra et al, 2005[19]	1	F	41	Pleura + rib + dermis (NA)
Scattone A, 2006[20]	6	3:3	23,73,71,32,52,74	Pleura (4R, 1L,1Bil) + chest wall in 1 (R).
Tsai et al, 2010[21]	1	M	13	Pleura (R)
Santos et al, 2012[22]	1	F	40	Pleura (R)
Solterman et al, 2011[23]	1	M	75	Pleura (L), multiple metastases
Ordonez, 2012[24]	17	12:5	46,60,57,71,50,74, 43,61,51,73,50,62, 66, 61,67,56,68	Pleura (11R, 4L, 2NA), lung 4, pericardium 2, diaphragm 4, chest wall 3
Arnago-Tomàs et al, 2013[25]	1	NA	17	Pleura (L) + mediastinum
Alar et al, 2014[26]	1	M	64	Pleura (R)
Ushio et al, 2015[27]	1	M	73	Pleura (L)

M: male, F: female, NA: not available, R: right, L: left, Bil: bilateral.

Table 2. Main risk factors and clinical manifestations of thoracic deciduoid mesothelioma in the scientific literature.

Paper	Asbestos exposure	Smoke exposure	Initial clinical manifestations
Ordonez[8]	Y2, N2	Y2, N1, NA1	Dyspnea 4, cough 3, pain 3, weight loss 1
Shanks et al[11]	Y	Y	Cough, dyspnea, lethargy, weight loss
Gloeckner-Hofmann et al[12]	N	Y	Dyspnea
Puttagunta et al[13]	N	NA	Dyspnea, pain
Henley et al[14]	N	Y	Mediastinal mass
Monaghan et al[15]	Y	NA	Night sweats, lethargy,
Shia et al[16]	Y1, N1, NA1	Y2, NA1	Dyspnea 1, NA2
Reis-Filho et al[17]	N	Y	Dyspnea, weight loss
Asioli et al[18]	N	Y	Asymptomatic
Mourra et al[19]	N	NA	Abdominal pain, asymptomatic in thorax
Scattone A[20]	6Y	NA	Pain 5, dyspnea 2, cough 2
Tsai et al[21]	N	N	Pain, thoracic deviation
Santos et al[22]	N	N	Pain
Solterman et al[23]	Y	Y	NA
Ordonez[24]	Y11, N6	NA	NA
Arnago-Tomas et al[25]	N	N	Cough
Alar et al[26]	Y	NA	Dyspnea, pain
Ushio et al[27]	Y	Y	Dyspnea, pain

Y: yes, N: no, NA: not available.

Table 3. Imaging and diagnosis of deciduioid mesothelioma in the cases examined.

Article	Imaging	Diagnosis by:
Ordonez[8]	CXray and CT in all cases	NB 1, OB 2, PFC 1
Shanks et al[11]	CT scan.	OB
Gloeckner-Hofmann et al[12]	CXray and CT scan	SS
Puttagunta et al[13]	CXray and CT scan	CB
Henley et al[14]	NA	SS
Monaghan et al[15]	NA	CB
Shia et al[16]	CT 1 case, NA 2	NB 1, SS 2
Reis-Filho et al[17]	CXray	Autopsy
Asioli et al[18]	CXray and CT scan	SS
Mourra et al[19]	CT scan	SS
Scattone A[20]	CT scan in all cases	CB
Tsai et al[21]	CXray and CT scan	CB
Santos et al[22]	CXray, CT and PET/CT	NB
Solterman et al[23]	NA	Autopsy
Ordonez[24]	NA	B 2, SS 15
Arnago-Tomas et al[25]	CXray, CT, MRI, and PET	SS
Alar et al[26]	CXray and CT scan	CB
Ushio et al[27]	CXray and CT scan	SS

Xray: chest X-ray, CT: computed tomography, B: biopsy, NB: needle biopsy, OB: open biopsy, CB: close biopsy (pleuroscopy or thoracoscopy, medical or surgical) PFC: pleural fluid cytology, SS: surgical specimen PET: positron emission tomography,

Table 4. Main immunohistochemical results in the cases under investigation.

Marker (n° cases)	Comment
Calretinin (27)	Positive in 24, focally positive in 3 cases.
CD15 (18)	Negative in 17 cases, positive in one.
Vimentin (17)	Positive in 13, focally positive in 2, negative in 2 cases.
Cytocheratin 5/6 (15)	Positive in 7, focally positive in 1, negative in 7 cases.
Cytocheratins (15)	Positive in 13 cases, focally positive in 2 cases
Mesothelin (8)	Positive in all cases
MOC-31 (4)	Negative in all cases
Thrombomodulin (3)	Focally positive in all cases
TTF1 (3)	Negative in all cases.
WT1 (3)	Positive in 2 cases, negative in 1 case.
Cytocheratin 7 (2)	Positive in all cases.

Table 5. Therapeutic approaches and outcomes in the cases reviewed.

Article	Treatment	Survival (months)
Ordonez[8]	EPP, CTH + PNEUM, PNEUM + RTH, one NA	6,8,5, one NA
Shanks et al[11]	NA	Alive after 8
Gloeckner-Hofmann et al[12]	CTH+RTH+Debulking	NA
Puttagunta et al[13]	RTH	21
Henley et al[14]	Surgical resection + CTH	NA
Monaghan et al[15]	NA	NA
Shia et al[16]	P/D (other NA), P/D, EPP+RTH	17, 4, alive after 12
Reis-Filho et al[17]	No treatment, dead 2 days after biospy	Dead before surgery
Asioli et al[18]	Lobectomy + chest wall resection	Alive after 20 months
Mourra et al[19]	Surgical resection	14
Scattone et al[20]	Pleurodesis - palliation in 2, CTH in 4	39,43,38,24,24,12
Tsai et al[21]	PNEU + P/D + Wedge esophagectomy + pre- and postoperative CTH	Alive after 24 months
Santos et al[22]	CTH + EPP	Dead after surgery
Solterman et al[23]	CTH + RTH	51
Ordonez,[24]	CTH in 2, PNEU in 2, PNEU+RTH in 6, PNEU+CTH in 1, CTH+PNEU in 1, PNEU+RTH+CTH in 2, Other in 3	6,5, 6,4,6,17, 18,6,8,4, 62,6,19, 35,18, 1 alive after 25, two cases NA.
Arnago-Tomas et al[25]	EPP + CTH	Alive after 21
Alar et al[26]	EPP + CTH	Alive after 12
Ushio et al[27]	Partial lobectomy + CTH	25

EPP: extrapleural pneumonectomy, PNEU: pneumonectomy, P/D: pleurectomy-decortication, CTH: chemotherapy, RTH: radiotherapy, NA: not available