REVIEW ARTICLE

The Treatment of Pleural Carcinosis With Malignant Pleural Effusion

Michael Ried, Hans-Stefan Hofmann

SUMMARY

Background: Pleural carcinosis is caused by tumors of the chest (e.g., lung and breast cancer) or elsewhere in the body (e.g., ovarian carcinoma) that metastasize to the visceral and/or parietal pleura. Recurrent malignant pleural effusion due to pleural carcinosis is one of the most common findings in oncology. It affects about 56 000 patients per year in Germany alone.

Methods: This review is based on pertinent literature retrieved by a selective search of the Medline database (key words: malignant pleural effusion, pleural carcinosis) and on the authors' clinical experience.

Results: Although many retrospective studies have been published, there has been only one randomized controlled trial of treatment, in which permanent pleural catheters were compared with talcum pleurodesis. Patients with pleural carcinosis have a median survival of less than 12 months. Many are suffering from progression of their underlying disease, with generalized tumor involvement; thus, the symptomatic treatment of pain and dyspnea is often the main therapeutic issue. The underlying tumor, usually an adenocarcinoma, can be diagnosed either by histology or by cytology. The main complication is progressive respiratory failure. The treatment is palliative, rather than curative. The main approaches are drainage of the effusion (by thoracentesis or with permanent pleural catheters) and pleurodesis (obliteration of the pleural space by causing the visceral and parietal pleura to adhere to each other).

Conclusion: Pleural carcinosis with symptomatic malignant pleural effusion is treated palliatively. The appropriate treatment in each case should be determined through discussion with the patient, with the goal of improving the patient's quality of life.

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With the exception of cardiovascular diseases, malignant neoplasia is the most common cause of death in Germany. Neoplasia is by far the most common cause of death in patients who die before the age of 65 (early deaths) (e1). Malignant pleural effusion is a sign of an advanced or generalized tumor stage (1). Evidence of malignant pleural effusion has been found at post-mortem in 15% of patients with malignant tumors and in 42% to 77% of cases causes an exudative pleural effusion (2, e2). Most patients can be offered only symptomatic and palliative treatment at this stage of their disease.

This article provides an up-to-date overview of the established treatments for pleural carcinosis with malignant pleural effusion and is intended to contribute to decisions regarding effective palliative care for this common disease pattern. To this end a selective search of the literature was performed in Medline, with the keywords “malignant pleural effusion” and “pleural carcinosis,” up to and including January 2013. Selection for this review article was based on the criteria of clinically relevant (emphasis on surgical options), up-to-date publications. Retrospective studies showed evidence of improved quality of life as a result of treatment for malignant pleural effusion for both pleurodesis and permanent pleural catheters. However, to date there has been only one prospective randomized trial comparing permanent pleural catheters to talc pleurodesis.

Incidence and pathogenesis

Malignant pleural effusion is identified on the basis of evidence of malignant cells in the pleural fluid or pleural tissue and is a very common diagnosis among patients with malignant tumors (approximately 50%) (1, 3). Almost all malignant tumors can affect the pleura at an advanced stage and thereby cause pleural carcinosis with pleural effusion (2). The frequency of pleural carcinosis with malignant pleural effusion in Europe is estimated at approximately 375 000 to 400 000 patients per year, with approximately 56 000 in Germany (2, 4). Because of the lungs' close anatomical proximity to the pleurae, lung cancer is the most common cause of malignant pleural effusion (accounting for approximately 40% of all cases) (Table 1) (5). The second-most common cause is metastatic breast cancer (approximately 25%), followed by lymphoma (approximately 10%),

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Figure 1:

Right-side pleural effusion in a patient with breast cancer

Figure 2:

Left-side pleural carcinosis with malignant pleural effusion and condition following primary insertion of chest drain

ovarian cancer (approximately 5%), and gastrointestinal cancers (approximately 5%) (6). For approximately 5% to 10% of malignant pleural effusions, no primary tumor can be found. These cases are described as CUP (cancer of unknown primary) (2). Differential diagnosis between malignant pleural effusion and malignant pleural mesothelioma can be difficult, as cytological testing yields positive results in only around 50% of these patients (7).

The parietal pleura seems to be more important to pleural fluid exchange than the visceral pleura, due to its proximity to microvessels and lymphatic openings to the pleural cavity (8). The average normal volume of pleural fluid is approximately 0.26 mL/kg body weight, with an hourly exchange of 11% (e3). A disruption to the balance between production and absorption leads to pleural effusion. The inflammation reaction associated with pleural carcinosis leads to increased formation of interstitial pleural fluid as a result of increased vessel permeability (e3, e4).

Clinical symptoms and diagnosis

In most cases patients complain of progressive dyspnea, which may be accompanied by chest pain and reduced general wellbeing or symptoms of the underlying malignancy. Clinical presentation depends on the extent of the effusion, how long it has been developing, and the patient's overall physical condition (2).

If there are clinical grounds for suspecting pleural effusion, a conventional two-view chest X-ray should be performed (*Figure 1*). This shows fluid volumes of 200 mL or more. Patients with pleural carcinosis usually have medium to large pleural effusions (500 to 2000 mL); only 10% of effusions are less than 500 mL in volume. Pleural ultrasound can be used to diagnose significantly smaller fluid accumulations (2, 5). In many cases computed tomography (CT) and magnetic resonance imaging of the chest provide additional information on possible tumors. These examinations should not be performed until after an initial thoracentesis, as pleural and pulmonary changes are usually concealed if the effusion is massive (*Figure 2*) (1).

Conclusive evidence of a malignant pleural effusion can only be provided by cytological or histological evidence of tumor cells. The diagnostic accuracy of cytological evidence of tumor cells in a pleural effusion varies a great deal (between 50% and 90%) and depends on the expertise of the examiner, as well as on the extent of the tumor and type of material used for examination (9, e5). Diagnostic accuracy can be increased by examining a tissue sample taken by thoracoscopy (*Figure 3*), as this type of sample can be used for additional testing for treatment targets (e.g. hormone receptor status for breast cancer), in addition to histology (10). In most cases there is histological evidence of an adenocarcinoma (11).

Progression and treatment

The prognosis of patients with pleural carcinosis is very limited, with a mean survival of approximately four months and a one-year survival rate of around 18% (4, 5, e6). By way of comparison, the survival of patients with a primary lung, stomach, or ovarian tumor is only a few months, and that of patients with breast cancer several months to years (*Table 1*) (2, 12). In addition to limited survival, patients with pleural carcinosis also often suffer significantly reduced quality of life, with multiple medical interventions as a result of recurring pleural effusions (13). The primary aim of treatment for patients with pleural carcinosis is usually palliative care in the form of a reduction in clinical complaints (14). Treatments range from conservative treatment with short-term monitoring to surgical intervention and depend on the patient's overall condition and prognosis for survival (15).

The aim of treatment for patients with a malignant pleural effusion is drainage of the pleural effusion

and subsequent pleurodesis (joining of the visceral and parietal pleurae), in order to prevent a recurrence of the effusion (3). Possible treatment options are thoracentesis, temporary or permanent pleural catheter insertion, and thoracoscopic pleurodesis (16–18). In addition to reducing tumor mass, pleurectomy also obliterates the pleural cavity. Cytoreductive surgery with intraoperative local chemotherapy, as used for peritoneal carcinosis, has not been shown to be of clinical value in the treatment of pleural carcinosis to date but will still be discussed in the following (19).

Thoracentesis

Thoracentesis leads to the correct diagnosis in approximately two-thirds of cases of pleural carcinosis with pleural effusion and relieves any dyspnea (2, 12). The time and scale of thoracentesis depend on the primary disease pattern and the overall condition of the patient. At an initial stage (no complaints), smaller perfusions can remain untreated but must be monitored in the short term. Progressive effusions with increasing dyspnea must be adequately drained as they may lead to an irreversible reduction in lung capacity (trapped lung syndrome).

Following successful thoracentesis of an effusion, an imaging examination (chest X-ray or CT) should always be performed for monitoring purposes, to identify an iatrogenic pneumothorax and/or hemothorax or trapped lung syndrome (20). If a large pleural effusion is drained too quickly (effusion aspirate >1.5 L), there is a risk of unilateral re-expansion edema, which has a mortality rate of up to 20% (21). Patients with evidence of a malignant pleural effusion and complete postinterventional pulmonary expansion are eligible for future pleurodesis (6).

Chemotherapy and radiotherapy

Systemic chemotherapy may also be used in patients with a malignant pleural effusion if there is a chemosensitive primary tumor (e.g. lung, breast, or prostate cancer, lymphoma) (22, e7). Systemic chemotherapy is first-line treatment for small-cell lung cancer, as in many cases the pleural effusion resolves with no surgical intervention (2). Simultaneous radiotherapy may further improve survival for such patients (e8).

Temporary pleural/chest drains

A chest drain is always recommended for rapidly-recurring pleural effusions, as repeat thoracenteses are associated with an increased risk of infection. Pleurodesis should be used only in patients with fully expanded lungs (5). Both antineoplastics (e.g. bleomycin) and non-antineoplastics (e.g. talc) are used as sclerosing agents for chemical pleurodesis (Table 2). Of the drugs listed in Table 2, only bleomycin has been licensed for palliative intrapleural treatment in patients with malignant pleural effusion.

Figure 3: Thoracoscopic evidence of pleural carcinosis in a cytologically-confirmed malignant pleural effusion prior to scheduled talc pleurodesis

TABLE 1

Incidence of pleural carcinosis with malignant pleural effusion*

Tumor entity (all stages)	Patients with pleural carcinosis (%)	Primary tumor according to cytology (%)	Estimated median survival (months)
Lung cancer	Approx. 8 to 15	25 to 52	6 to 8
Breast cancer	Approx. 2 to 12	3 to 27	6 to 48
Lymphoma	Approx. 7	12 to 22	6 to 7
Other tumors	–	29 to 46	–

*Modified according to (2, 4, 6, 14, e3, e4)

The advantages of talc (medicinal product) are its high success rates (up to 93%) and low costs (23). In addition to the suspension used for chest drainage, talc can also be used as a spray powder for thoracoscopy. The most common side effects of the local inflammation reaction to chemical pleurodesis are pain and fever (24). Pain can also be reduced using local application of lidocaine as a sclerosing agent (12). To ensure pleurodesis is successful, suction (–20 cm H₂O) should be applied to the chest drain for at least 48 hours. Nonresponders to chemical pleurodesis are usually patients with very rapidly- and strongly-recurring pleural effusion, as this leads to rapid suspension of both sclerosing agents and cytokines and chemokines formed by the pleura. The chest drain should not be removed until the lungs have expanded (without suction) and the aspirate is less than <100 mL.

Indwelling pleural catheters

Long-term tunneled pleural catheters have become established for the palliative treatment of chronic pleural effusion in recent years (25, 26). This type of indwelling pleural drain is recommended in particular for absent lung expansion, recurrent pleural effusion, and compromised overall condition (17,

TABLE 2

Success rates and adverse effects of sclerosing agents*

	Dose	Success rate (%)	Side effects (%)	
			Pain	Fever
Tetracycline	500 mg	67	14	10
Doxycycline	500 mg	72	40	31
Talc	2.5 to 10 g	93	7	16
Bleomycin	60 mg	54	28	24
Doxorubicin	10 to 40 mg	24	29	15
Cisplatin	100 mg/m ²	27	55	-
Mitomycin C	8 mg	41	7	11

*Modified according to (23)

Figure 4:
Indwelling
subcutaneous
tunneled pleural
catheter

e9). A significant improvement in quality of life and reduction in dyspnea have been demonstrated (27). This particular type of catheter system allows patients to be treated less invasively, and very satisfactorily on an outpatient basis (28, 29).

The subcutaneously tunneled site of the catheter (Figure 4) reduces the risk of infection (20). Multiple studies have shown these catheters to be safe, effective (primary success rate: 91%), and low in complications when used long-term (4.8%) (17). Length of hospital stay is significantly shorter than after surgical pleurodesis (e10). In 26% to 58% of cases the use of this type of catheter even achieves spontaneous pleurodesis, so in many cases it has been possible to remove them (17, 30, 31). The rate of further effusion-related hospital stays is low (32). In most cases removal causes no problems, and complications (e.g. catheter fracture) have been reported only in isolated cases (e11). Additional treatments such as chemotherapy or radiotherapy can be performed even if a pleural catheter has been fitted (e12).

To date there has been one randomized trial that has compared the efficacy and safety of indwelling tunneled pleural catheters and traditional doxycycline pleurodesis (33). This trial showed that it was difficult to compare the two procedures for this

indication. However, it also demonstrated the advantages of an indwelling pleural drain (short hospital stays and low recurrence rates) (33).

Video-assisted thoracic surgery (VATS)

Thoracoscopy is indicated for pleural effusion of unclear etiology or urgent suspicion of pleural carcinoma with negative cytological findings. It can be performed either as medical thoracoscopy under local anesthesia or as VATS under general anesthesia with one-lung ventilation (double-lumen tube) (10). In addition to aspirating a pleural effusion, both procedures can be used diagnostically, to look into the pleural cavity and remove tissue for biopsy in a targeted way (2). VATS can also be used to remove marked partial adhesions of the visceral and parietal pleurae (adhesiolysis). If scar tissue is preventing the lung from expanding, VATS can remove it at an early stage (decortication). In addition to a diagnostic pleural biopsy, pleurodesis can also be performed in the same session (e13).

The use of thoroscopic pleurodesis (talc spray/talc poudrage) is restricted to patients in whom full expansion of the lungs is achieved intraoperatively (34, 35). Thoroscopic talc poudrage and talc suspension have comparable success rates (36).

Pleurectomy

Pleurectomy has also been described in the treatment of malignant pleural effusion and includes resection of the parietal pleura. The extent of pleurectomy depends on how far the tumor has spread. Patients should be extubated immediately after surgery in order to achieve natural respiration and thereby minimize any air leakages caused by the pleurectomy. Complication rates (bleeding, empyema) and mortality rates are high, at 25% and 10% to 19% respectively (e14, e15).

Pleurectomy is indicated for selected symptomatic patients with better prognosis (e.g. breast cancer) in whom multiple chemical pleurodeses have failed.

However, pleurectomy is not yet a clear alternative to talc pleurodesis or an indwelling pleural catheter (12, e16).

Cytoreductive surgery and hyperthermic intrathoracic chemotherapy (HITHOC)

In patients with peritoneal carcinosis, multimodal treatment consisting of cytoreductive surgery (parietal and visceral peritonectomy) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is administered as curative therapy, where indicated (19). In the chest, cytoreductive surgery (radical pleurectomy/decortication) combined with HITHOC is used for primary pleural tumors (pleural mesothelioma) and secondary pleural tumors (e.g. thymoma with pleural involvement) (37, e17, e18). HITHOC has already been performed in individual patients with pleural carcinosis detected intraoperatively during elective lung cancer resection and resulted in improved survival (e19). To date, cytoreductive surgery and hyperthermic perfusion is not recommended as treatment for patients with secondary pleural carcinosis, unlike peritoneal carcinosis. This is because no curative approach exists, as tumor growth is usually advanced and generalized (e20). The significance of this combination therapy for pleural carcinosis might be demonstrated in the future.

Summary

The correct selection of and decision on palliative care for pleural carcinosis with symptomatic malignant pleural effusion is dependent on many factors, for both patients and physicians (12). Differentiated patient examination is vital, in order to guarantee the fewest possible complications and best possible chance of success (15). Adequate treatment of dyspnea is the primary treatment aim (14). Both talc pleurodesis and indwelling pleural catheters have been demonstrated to prevent recurrent effusion and thereby also reduce complaints (18, 28, e21). In addition to a number of retrospective studies, to date there is only one prospective randomized trial comparing treatment with an indwelling pleural catheter with talc pleurodesis (38, 39). However, the choice of talc pleurodesis (drain/thoracoscopy) and/or an indwelling pleural catheter depends mainly on morphological criteria (e.g. restricted lung expansion) and clinical criteria (e.g. general health).

The way in which talc is applied has very little effect on the success of pleurodesis (e22). The success rate of talc pleurodesis can range between approximately 85% and 93%, depending on the primary tumor (38, 40). Thoracoscopic talc pleurodesis is recommended mainly for patients with pleural effusion of unclear etiology and intraoperatively-detected pleural carcinosis (13, 16, e23, e24).

Pleurectomy should be performed only in patients with relatively good prognosis or those who do not respond to chemical pleurodesis (12). An indwelling

KEY MESSAGES

- Malignant pleural effusion resulting from pleural carcinosis is one of the most common findings in patients with malignant diseases.
- The average survival of patients with pleural carcinosis is less than 12 months.
- Any new-onset pleural effusion of unclear etiology should undergo thoracentesis and cytological examination.
- Therapy focuses on symptomatic treatment of dyspnea and pain to improve patients' quality of life.
- Depending on the patient's overall condition, talc pleurodesis or an indwelling tunneled pleural catheter may be appropriate palliative treatment options for malignant pleural effusion.

pleural catheter is now a good alternative for patients with limited lung expansion (25, 26, e10). An advantage of these catheters is their relative ease of implantation, very low complication rate (approximately 3%) and very good home handling by patients (39, e25).

Optimum treatment for pleural carcinosis with symptomatic malignant pleural effusion must be selected on the basis of palliative aims and in consultation with the patient, in order to improve the patient's symptoms and thereby quality of life.

Conflict of interest statement

Dr. Ried and Prof. Hofmann declare that no conflicts of interest exists. Manuscript received on 10 October 2012, revised version accepted on 17 February 2013.

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