MANAGEMENT OF MALIGNANT PLEURAL EFFUSION

Effective Date: October, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Lung Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

A pleural effusion is defined as an abnormal collection of fluid between the thin layers of tissue lining the lung and the wall of the chest cavity.[1] There are a number of different causes for pleural effusions, one of which is the spread of cancerous cells to the pleural cavity. A malignant pleural effusion (MPE) may have positive pleural fluid cytology and/or pleural biopsy for malignant cells,[2] although a MPE does not require cytopathological confirmation in all cases. Approximately 50 percent of patients with metastatic malignancy will develop a pleural effusion. In order of decreasing frequency, lung cancer, breast cancer, lymphoma, ovarian cancer and gastric cancer are the most common etiologies for MPE. These cancers account for 80% of all MPE. The most common primary pleural malignancy associated with a pleural effusion is malignant mesothelioma. Approximately 80–95 percent of patients with malignant mesothelioma have a large pleural effusion at diagnosis. The presence of MPE usually indicates advanced stage cancer, thus prognosis of patients with MPE is poor. Median survival following diagnosis of MPE ranges from 3 to 12 months depending on the site of origin, the histological type and stage.[2]The shortest survival time is observed in malignant effusions secondary to lung cancer and the longest in ovarian cancer. In lung cancer patients the median survival is approximately 4 months, but may be as short as 30 days depending on patient performance status (PS).[3] Unfortunately, no reliable predictors exist to determine which patients will develop a MPE and why.[4]

The most common symptom associated with MPE is progressive dyspnea, which may be associated with chest pain or heaviness and a dry cough.[2] MPE patients suffer from symptoms that significantly diminish their quality of life; this coupled with a short life expectancy warrants delivery of timely care with minimal inconveniences to the patient.

This guideline was developed to outline treatment recommendations for patients with a MPE.

GUIDELINE QUESTIONS

- What diagnostic and baseline investigations are recommended for patients with suspected or confirmed malignant pleural effusions?
- What are the recommended treatment options for patients with asymptomatic malignant pleural effusions?
- What are the recommended treatment options for patients with recurrent symptomatic malignant pleural effusions?
- What is the recommended follow-up after treatment for a malignant pleural effusion?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Lung Tumour Team with input from members of the Respiratory Health Strategic Clinical Network. Members of the Alberta Provincial Lung Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, respirologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Lung Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in October, 2014.

SEARCH STRATEGY

PubMED, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews electronic databases were searched to March 27, 2014 for literature on the management of malignant pleural effusions. The following search terms were used: *pleural effusion, malignant* (MeSH [Medical Subject Heading]); results were limited to literature published since 2009, human subjects (19+ years), published in English, clinical trials, guidelines, meta-analysis, practice guidelines, randomized controlled trials (RCTs), and systematic reviews. Reference lists were scanned for relevant literature.

The National Guideline Clearinghouse was also searched for guidelines on malignant pleural effusions, as well as other prominent guideline developer websites.

TARGET POPULATION

The recommendations outlined in this guideline are intended for adults over the age of 18 years with malignant pleural effusions. Different principles may apply to pediatric patients and patients with different types of cancer.

RECOMMENDATIONS

The Alberta Provincial Lung Tumour Team has adapted the recommendations from the British Thoracic Society[5] and the American College of Chest Physicians[6], with modifications to fit the Alberta context.

Key Points:

- All treatment decisions should be guided by patient preferences.
- Selection of a treatment approach is largely dependent on the patient's anticipated duration of survival and the availability/appropriate utilization of local resources.

1. The management of a MPE should be individualized and may sometimes need to be discussed at a multidisciplinary Tumour Board.

2. The management of a MPE is palliative and therefore all treatment decisions should consider the type of malignancy (e.g., lung versus ovarian), patients' symptoms, life expectancy, functional status, quality of life, and goals of therapy.
    a. Palliative therapy goals should improve patients' quality of life through:
        - Relief of dyspnea
        - The need for reintervention
        - Reduced hospitalizations and length of stay

Diagnostic and Baseline Investigations

3. All patients with a suspected MPE should have an initial clinical history and physical examination. A MPE should be considered as a cause of breathlessness in patients with diagnosed cancer.

4. A chest radiograph should be used to detect the presence of a pleural effusion. A lateral decubitus chest radiograph may be used to differentiate pleural liquid from pleural thickening.

5. Computerized tomography (CT) scans, when clinically indicated, can detect very small pleural effusions (less than 10mL of fluid); intravenous administration of iodinated contrast material is recommended. A thoracic ultrasound can also be used to investigate small pleural effusions.

6. Undiagnosed effusions of more than 1 cm from the chest wall on a lateral decubitus chest radiograph should be diagnostically evaluated by ultrasound-assisted thoracentesis. Patients known to have advanced cancer do not need thoracentesis for small asymptomatic effusions.

7. If a thoracentesis is going to be performed, all effusions should be sent for cytology if a patient does not have a diagnosis of a MPE.
    a. A minimum 50 to 60mL of pleural fluid should be withdrawn for analysis
    b. The fluid should be analyzed for cell count and differential, gram stain and culture, pH, and glucose, as well as protein and lactate dehydrogenase (LDH), which can help to ascertain whether the fluid is a transudate or an exudate using Light's Criteria
    c. Consider sending larger volumes of fluid (100-200mL) for cell block and molecular testing (e.g., *epidermal growth factor receptor [EGFR])*.

8. All patients with a diagnosed MPE should be referred to respiratory medicine or thoracic surgery although initial thoracentesis should not be delayed in symptomatic patients. In Edmonton, referrals can be made to the Alberta Thoracic Oncology Program, and in Calgary/Southern Alberta, to the Tom Baker Cancer Centre Dyspnea clinic.

9. Availability of clinical resources should allow rapid assessment (within 1 week) of referred patient in order to avoid unnecessary emergency room visits and hospitalizations.

10. Chest ultrasonography, if available, is recommended at the point of care for any thoracentesis or percutaneous chest drain placement (including indwelling pleural catheter [IPC]).

Asymptomatic Patients

11. Asymptomatic patients do not require treatment but should be observed as MPEs may become symptomatic and require palliative treatment. Patients with a large MPE may be considered for a therapeutic thoracentesis.

Symptomatic Patients

12. Patients with symptoms may be considered for an initial therapeutic thoracentesis to relieve symptoms prior to further invasive treatments. The recommended total amount of fluid removed per session is 1000 to 1500mL although clinician judgment may be used to remove more if chest symptoms and/or pleural pressure are monitored. In some cases significantly less fluid should be removed if the patient develops chest discomfort or tightness during drainage or if pleural pressures decrease below -20cmH_20. The rate of reaccumulation of the pleural effusion, the patient's clinical and symptomatic response, and prognosis will help to guide the subsequent choice of therapy.

13. Outpatient therapeutic thoracentesis alone may occasionally be indicated for patients with a prognosis less than 1 month, and/or a poor PS, and/or a slow reaccumulation of the pleural effusion (i.e., more than 1 month) and should be performed as required to control symptoms.

14. Patients should be considered for more definitive interventions after the first or second thoracentesis. Treatment options include:
    a. Indwelling (i.e., tunneled) pleural catheter
        - Consider for patients with trapped lung who experience at least partial symptom relief following thoracentesis, or those with a shorter anticipated survival
        - Consider for any patient with a preference to avoid hospitalization and initial discomfort of pleurodesis.

    b. Talc pleurodesis via thoracoscopy:
        - Consider for patients with a longer anticipated survival
        - Consider if patient does not want indwelling catheter for lifestyle reasons
        - Contraindicated for patients with an irremediably entrapped or trapped lung

    c. Talc pleurodesis via chest tube:
        - Indicated for patients with a longer anticipated survival or contraindication to thoracoscopy
        - Contraindicated for patients with an irremediably entrapped or trapped lung

15. The source of talc should be taken into consideration when selecting a treatment option. In Alberta, uncertainty with currently available talc preparations has resulted in more frequent use of IPCs.

16. Chemotherapy may be considered as an adjunct treatment option. In particular, patients undergoing first line systemic treatment for tumours with typically rapid response rates (e.g., small cell lung cancer and lymphoma) may avoid the above definitive treatments.

17. Coordination with a palliative care team is recommended for patients with incomplete response to initial treatment.

Follow-up

18. All patients treated with an IPC should be managed and followed-up in the context of a specialist clinic, where accessible, such as the Dyspnea Clinic (Calgary) or Alberta Thoracic Oncology Program (ATOP) (Edmonton).

DISCUSSION

MPE is not curable and therefore all treatment options are palliative; optimal management strategies should aim to improve patient-related outcome measures[4] and consider patient preferences given the distress and morbidity from a MPE. Palliative therapy goals should include: relief of dyspnea, permanent control of fluid accumulation, prevent the need for reintervention, and limit/avoid the need for hospital stay.

Diagnostic and Baseline Investigations

All patients with suspected MPE should have an initial clinical history and physical examination. A MPE should be considered as a cause of breathlessness in patients with a diagnosed lung cancer. A chest radiograph and a CT scan are the primary imaging methods used to detect a MPE, although ultrasound and magnetic resonance imaging (MRI) are also indicated in certain clinical circumstances.

A MPE diagnosis can be established by thoracentesis, which is a simple bedside procedure that rapidly samples fluid for visual and microscopic examination. Effusions of more than 1 cm from the chest wall on a lateral decubitus chest radiograph, or those that do not have a definitive diagnosis should be diagnostically evaluated by thoracentesis. A thoracic ultrasound, if available, is recommended to help guide the placement of the thoracentesis needle. A study of 941 pleural procedures assisted by ultrasound found pneumothorax, pain, and breathlessness in 2.5, 2.7, and 1 percent of procedures, respectively.[7] In comparison, approximately 30% of thoracentesis performed without ultrasound guidance are associated with complications.[3] A minimum of 50 to 60mL of pleural fluid should be withdrawn for analysis of cell count, pH, and glucose, as well as protein and lactate dehydrogenase (LDH), which can help to ascertain whether the fluid is a transudate or an exudate using Light's Criteria.[8] Light's Criteria is a method that measures serum and pleural fluid protein and LDH to diagnose an exudate such as a MPE. If at least one of the following three criteria is fulfilled, the fluid is exudative: (1) pleural fluid protein/serum protein ratio greater than 0.5, or (2) pleural fluid LDH/serum LDH ratio greater than 0.6, or (3) pleural fluid LDH more than two-thirds the upper limits of the laboratory's normal serum LDH. Studies have shown that when evaluating for possible malignancy, increasing the volume of fluid withdrawn for analysis above 60mL does not significantly increase the yield of pleural fluid cytology. In one prospective study of 44 patients, 31 of whom had a known malignancy, both 50mL and 890mL pleural fluid samples were analyzed and yielded identical results.[9] In another study of 102 patients, sampling less than 60mL of pleural fluid appeared to reduce the diagnostic yield for a MPE. Given these study results, the recommended volume of pleural fluid required to diagnose a MPE is a minimum of 50 to 60mL.[10] However, consideration should be given to sending more fluid (e.g., 100-200mL) for cytological examination in case additional analyses are required (e.g., *EGFR*).

Asymptomatic Patients

Asymptomatic patients do not require treatment but should be observed as MPEs may become symptomatic and require palliative treatment. Patients with a large MPE may be considered for a therapeutic thoracentesis (see below).

An Alberta-specific study of 113 new lung cancer patients found that 30 percent had radiologic evidence of a pleural effusion and 12 percent were asymptomatic.[11] Of these asymptomatic patients, only one progressed and required palliative treatment. Although evidence is limited, the results of this study suggest that small asymptomatic MPE do not progress and therefore treatment does not appear warranted in this patient population.

Symptomatic Patients

There are several treatment options for symptomatic MPE patients, all of which need to be considered in the context of the patient's symptoms, life expectancy, functional status, quality of life, and goals of therapy. Other considerations include patient and caregiver/family acceptability of an intervention, cost,

and avoidance of invasive procedures and complications that remove the patient from their home and disrupt the course of their terminal cancer. Clinician experience and resource availability is also a factor. Pleurodesis and IPCs remain the mainstay treatment options for MPE and a recent RCT has shown both to be equally effective.[12]

Therapeutic Thoracentesis. A therapeutic thoracentesis involves the removal of a large volume of pleural fluid through a catheter that is percutaneously advanced into the pleural space under sterile conditions. Symptomatic MPE patients should be considered for a therapeutic thoracentesis prior to any definitive pleural procedures to ensure that the patient benefits from pleural fluid drainage.[2] The rate of reaccumulation of the pleural effusion, the patient's clinical and symptomatic response, and prognosis will help to guide the subsequent choice of therapy. Multiple repeat therapeutic thoracentesis is indicated for patients with a prognosis of less than 1 month, and/or a poor PS, and/or a slow reaccumulation of the pleural effusion (i.e., more than 1 month) and should be performed by experienced clinicians as required to control symptoms. However, repeated thoracentesis is not an optimal management option for most patients.

The recommended total amount of fluid removed per session is traditionally 1000 to 1500mL[13] although a threshold volume of pleural fluid removal has not been identified and some suggest that no upper limit is necessary as long as the procedure is terminated if the patient develops dyspnea, cough, or chest discomfort or the pleural pressure drops below -20 cm H_20.[2] Drainage should be halted if these endpoints occur even if less than 1000mL has been drained. Thoracentesis is associated with a small risk of re-expansion pulmonary edema, which occurs in approximately 1 percent of patients, but it is independent of the volume of fluid removed, pleural pressures, and pleural elastance.[14]

IPC. An IPC procedure involves the insertion of a tunneled small catheter into the pleural cavity which allows intermittent drainage of fluid with a vacuum bottle.[2] IPC can be considered as first-line treatment for MPE patients along with pleurodesis. IPCs can also be used as a second-line treatment when pleurodesis has failed or is contraindicated (in the case of lung entrapment).[4] A recent RCT found that both treatments are equally effective at relieving patient-reported dyspnea[12] and therefore, IPC is a feasible alternative to pleurodesis, particularly if the patient prefers a minimally invasive procedure.[15]

Van Meter *et al.* conducted a systematic review of 19 studies with 1,370 MPE patients treated with IPCs and found that this procedure is well tolerated and resulted in symptomatic improvement in 95 percent of cases and spontaneous pleurodesis in 45 percent of cases.[16] In an Alberta/Canadian prospective cohort of 82 MPE patients, Sabur *et al*. found similar results; IPCs were associated with a significant improvement in global health status, quality of life, and dyspnea at two weeks.[17]

A retrospective analysis of 223 Albertan MPE patients treated with an IPC reported complete symptom control in 39 percent of procedures and partial control in 50 percent of procedures.[18] The study authors found that spontaneous pleurodesis occurred in 43 percent of the successful IPC procedures. The overall median survival time for this study population was 144 days and complication rates were low. The study authors concluded that MPE treatment with IPC is effective and allows for outpatient management with low complication rates and should be considered as a first-line treatment option in the management of MPE patients.[18]

In a prospective study of 160 MPE patients, total hospital days from any cause were significantly fewer for those patients treated with IPCs compared to those treated with pleurodesis (median 6.5 versus 18 days,

p=0.002).[19] Effusion-related hospital days were also significantly fewer with IPCs (median 3 versus 10 days, p<0.001). Furthermore, the study authors found that fewer patients with IPCs required further pleural procedures as compared to those treated with pleurodesis (13.5 percent versus 32.3 percent) although safety profiles and symptom control between the two treatment options were comparable.[19] It should also be noted that IPC requires a regular outpatient drainage schedule, which may be burdensome for the patient or caregiver, therefore, patient preferences must be considered when balancing the requirements for hospitalization in the case of pleurodesis (discussed below) versus IPC in an ambulatory and outpatient setting.[2]

Complications from IPCs are uncommon. One multicentre study of 1,021 MPE patients reported an infection rate of 5 percent from IPCs, of which 54 percent could be treated with antibiotics without removal of the catheter.[20] A systematic review of IPC safety found that both serious and minor complications were rare and that their use was without complications in 87.5 percent of patients.[16] Specifically, the following complications were reported: empyema (2.8 percent), pneumothorax requiring a chest tube (5.9 percent), unspecified pneumothorax (3.9 percent), cellulitis (3.4 percent), obstruction/clogging (3.7 percent), and unspecified catheter malfunction (9.1 percent).[16]

A recent cost-effectiveness analysis of managing MPEs found that IPC was the most cost-effective and least expensive option overall in comparison to thoracentesis and pleurodesis, although cost was dependent on the patient's length of survival.[21] For patients with longer survival, pleurodesis was the most cost-effective treatment option given the cost of replenishing treatment supplies and ongoing home care for IPC therapy versus hospital-based pleurodesis.

Talc Pleurodesis via Thoracoscopy or Chest Tube. Although many sclerosing agents have been used in an attempt to create a pleurodesis, talc is most commonly used due to its well-known effectiveness. Pleurodesis refers to a procedure during which a sclerosing agent is injected into the pleural cavity causing chemical irritation that leads to pleuritis and eventually to pleural fibrosis and obliteration of the pleural space.[3] Pleurodesis cannot be achieved unless the lung is fully expanded to achieve visceral and parietal pleura apposition. If the lung is entrapped, pleurodesis is generally not indicated and patients should be treated with an IPC.

A meta-analysis of 36 RCTs including 1,499 patients found that talc was the most efficacious sclerosing agent.[22] The success rate of talc in preventing MPE recurrence ranges from 60 to 90 percent[6], although 50 percent of patients undergoing talc pleurodesis will experience inadequate fluid control at six months.[23]

The largest MPE trial to date (n=501) has shown that both pleurodesis via thoracoscopy or chest tube are equally effective in controlling MPE (30-day freedom from radiographic MPE recurrence: 78 percent versus 71 percent, respectively; actual success rate in eligible patients: 53 percent versus 60 percent, respectively).[23]Patient-related quality of life outcomes (e.g., comfort and safety) were also better for thoracoscopy, although there were no differences on convenience of the two procedures. The study authors reported fever, dyspnea, and pain complications, as well as respiratory failure in 4 percent and 8 percent of chest tube and thoracoscopy patients, respectively, which accounted for 11 toxic deaths in total.[23]

Length of hospital stay has been shown to be shorter for patients treated with IPCs than for patients receiving pleurodesis.[19] Therefore, patients with a shorter anticipated survival may prefer to be managed with IPCs to limit the amount of time spent in a hospital during their final stage of life. In addition to quality of life considerations, costs associated with the use of the two treatment types should be acknowledged

(e.g., costs for nursing and doctor time, drainage bottles, and dressing changes, etc.) Based on the results of one cost-effectiveness study, treatment with talc pleurodesis was less costly than IPC with similar effectiveness. IPC became more cost effective when life expectancy was 6 weeks or less.[24] Using data from a recent RCT comparing IPC w talc pleurodesis Penz *et al*. found no significant difference in mean cost of managing patients with IPC versus talc pleurodesis. However, for patients with limited survival (less than 14 weeks) IPC was significantly less expensive than talc pleurodesis.[25]

The most common adverse events associated with talc pleurodesis are fever, pain, and gastrointestinal symptoms; less common complications include arrhythmia, dyspnea, respiratory failure, systemic inflammatory responses, empyema, and talc dissemination.[22]

Ultimately, the choice between talc pleurodesis via thoracoscopy or chest tube is more dependent on medical circumstances rather than the efficacy of the two procedures. If the MPE is identified through a diagnostic thoracoscopy, then it is reasonable to proceed with talc pleurodesis via thoracoscopy during the diagnostic procedure. On the other hand, patients with a lower PS may prefer pleurodesis via chest tube because it is less invasive.

The source of talc should also be taken into consideration when selecting a treatment option. In Alberta, uncertainty with currently available talc preparations has resulted in more frequent use of IPCs.

Other Treatment Options. Certain cell types are responsive to chemotherapy and radiation therapy in the context of a MPE. MPEs in small-cell lung cancer patients in particular are responsive to systemic chemotherapy,[26] although further randomized trials are needed to compare this treatment option with the standard procedures. The British Thoracic Society recommends that patients with proven or suspected mesothelioma should be considered for prophylactic radiation therapy to the site of thoracoscopy or chest tube insertion.[5]

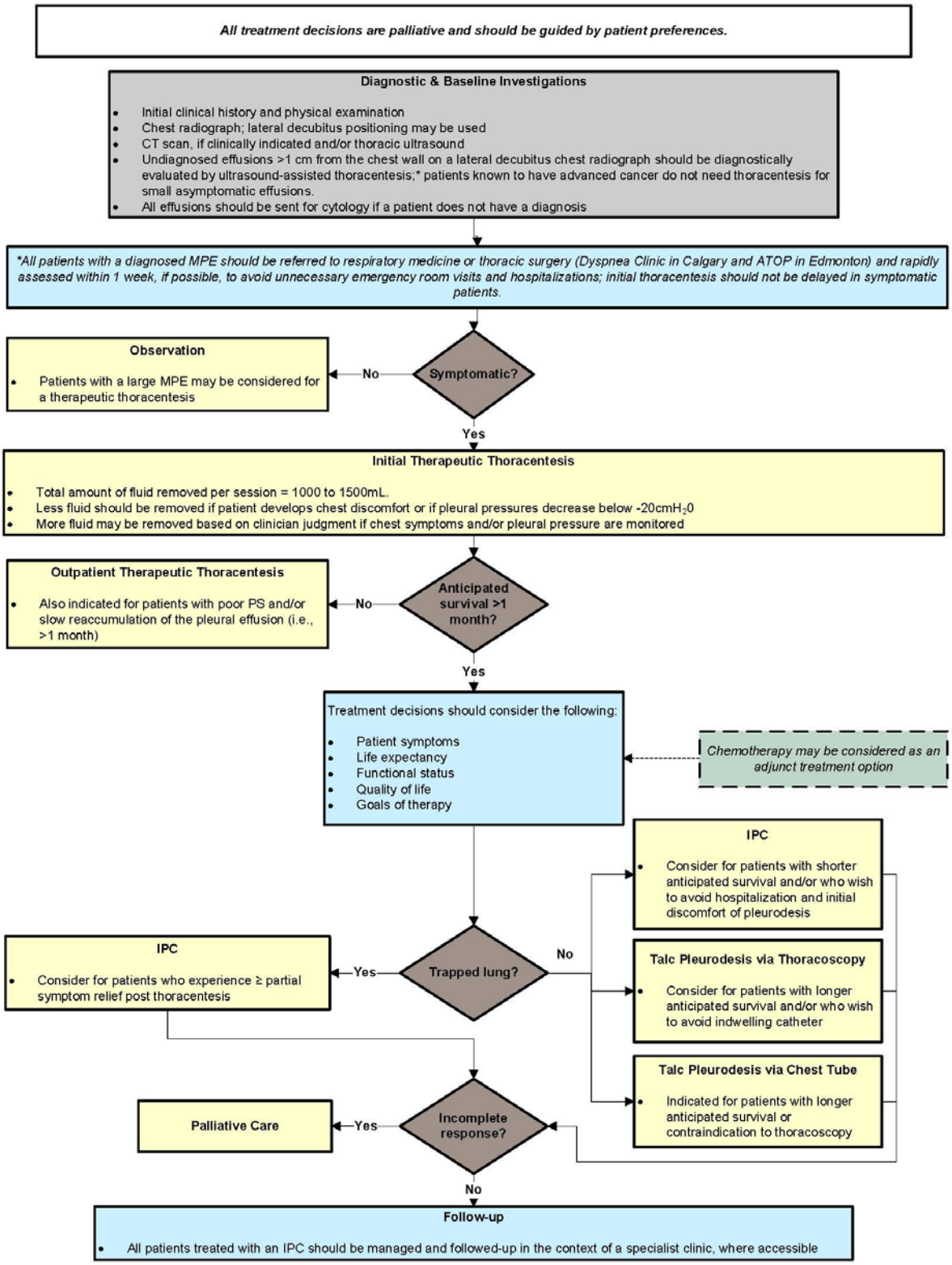
Although a pleurectomy has been described as a treatment option for MPEs,[27] to date there is insufficient evidence to recommend this as a treatment option over those that are currently recommended.

Patients who have an incomplete response to initial treatment should receive palliative care for pharmacological management of dyspnea symptoms.

Follow-up

Long-term follow-up is problematic in MPE patients due to the advanced stage cancer. Therefore, there is little empirical evidence to offer specific recommendations for follow-up care. Anecdotal evidence suggests that all patients with MPE and who are treated with an IPC should be managed and followed-up providers who are educated in managing MPE. Additionally, patients should be seen two weeks following catheter insertion and again three months later or as required until catheter removal or death.

TREATMENT ALGORITHM



GLOSSARY OF ABBREVIATIONS

Acronym	Description
ATOP	Alberta Thoracic Oncology Program
CT	computerized tomography
EGFR	*epidermal growth factor receptor*
IPC	indwelling pleural catheter
LDH	lactate dehydrogenase
MPE	malignant pleural effusion
MRI	magnetic resonance imaging
PS	performance status
RCT	randomized controlled trial

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Lung Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Lung Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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