THYMIC NEOPLASMS

Effective Date: December, 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Tumour Team 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

Thymic neoplasms represent the most common tumours of the anterior mediastinum in adults, and include both thymomas and thymic carcinomas. Thymomas account for approximately 20 percent of mediastinal tumours, with incidence rates of 0.18 per 100,000 for men and 0.10 per 100,000 for women.[1] Thymic carcinomas are rare tumours, accounting for less than one percent of mediastinal tumours; these tumours are more invasive than thymomas, and often have a higher rate of relapse and a poorer prognosis.[2-4] The existing literature on treatments for thymic neoplasms consists of relatively small studies of multimodality treatments, mostly in the form of retrospective case series reports. No randomized controlled study has been reported to date on any treatment modality in this disease. Total resection of the tumour has been repeatedly reported to be the most important factor affecting the rate of survival.[5] In partially resected or unresectable tumours, there is a growing body of literature suggesting that neoadjuvant and adjuvant radiotherapy and chemotherapy combinations provide varying degrees of benefit to patients with thymic neoplasms.

GUIDELINE QUESTIONS

- What are the recommended treatments for patients with a stage I or IIA thymic neoplasm?
- What are the recommended treatments for patients with a resectable stage IIB or III thymic neoplasm?
- What are the recommended treatments for patients with a stage IIB or III thymic neoplasm that is initially unresectable?
- What are the recommended treatments for patients with an advanced-stage thymic neoplasm?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Tumour Team. Members of the Alberta Provincial Thoracic Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic 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 June, 2010 and subsequently updated in December, 2012.

SEARCH STRATEGY

Medical journal articles were searched using the PubMed (March 2009 to December 2012) and EMBASE (2009 to 2012) electronic databases, and the references and bibliographies of articles identified through the search were also scanned for additional sources. The update search strategy included the following terms: treatment, thymoma [MeSH heading], practice guideline, guideline, comparative study, multicentre study, meta-analysis, clinical trial, and randomized controlled trial. Articles were excluded from review if they: had a non-English abstract or were published prior to March 2009. A review of existing practice guidelines for thymoma and thymic carcinoma was also conducted from the following organizations: Cancer Care Ontario, National Comprehensive Cancer Network, British Columbia Cancer Agency, Scottish Intercollegiate Guidelines Network, New Zealand Guidelines Group, European Society for Medical Oncology, American Society of Clinical Oncology, and the National Institute for Health and Clinical Excellence. The guidelines were assessed for inclusion using portions of the AGREE tool.[6]

TARGET POPULATION

The recommendations in this guideline apply to adult patients over the age of 18 years diagnosed with thymoma or thymic carcinoma.

RECOMMENDATIONS

1. Whenever possible, patients should be considered for participation in ongoing clinical trials.

Early Stage Disease (Stages I – IIA)

2. Complete surgical resection is the standard of care for patients with an early stage thymic neoplasm.

Localized Disease (Stages IIB – III)

3. For patients with a resectable localized thymic neoplasm, complete surgical resection is the standard of care. Postoperative radiotherapy should be considered for patients with a resectable localized thymic neoplasm.
4. For patients with an initially unresectable localized thymic neoplasm, induction chemotherapy or chemotherapy plus radiation, followed by reassessment and consideration for surgery, is recommended. If the response is sufficient to permit surgery, surgical resection followed by adjuvant radiotherapy, if not administered pre-operatively, is recommended.
5. For patients with an unresectable localized thymic neoplasm, or for those who are medically ineligible for surgery, chemotherapy alone or in combination with radiotherapy is recommended.

Advanced Disease (Stages IVA – IVB)

6. For patients with an advanced thymic neoplasm, multimodality therapy should consist of induction chemotherapy followed by surgery for debulking or symptom control, where appropriate. Postoperative management should include chemotherapy and/or radiotherapy for local control and palliation.

Follow Up

7. Prolonged follow-up is recommended for patients who achieve a complete or partial response with either surgery or a multimodality approach. Surveillance should include an annual chest CT scan.

DISCUSSION

Clinical Presentation

Patients with thymic neoplasms will often present with an asymptomatic anterior mediastinal mass seen on chest imaging. The most common symptoms displayed by these patients include cough, dyspnea, chest pain, hemoptysis, dysphagia, hoarseness, superior vena cava syndrome, and phrenic nerve palsy.[7] Thymoma is associated with a variety of immune disorders, the most common being myasthenia gravis. In 30 to 50 percent of all cases of thymoma, the patient will also have myasthenia gravis; conversely, in 10 to 15 percent of all cases of myasthenia gravis, the patient will subsequently be diagnosed with thymoma.[8] In contrast to thymoma, myasthenia gravis is rare in patients with thymic carcinoma.[9] All patients suspected of having thymoma should be evaluated for signs and symptoms of myasthenia gravis, and these symptoms should be treated prior to surgery.

Diagnosis

The initial evaluation and workup of all patients with a suspected thymic neoplasm includes:[7]

- CT scan of the chest
- CBC and platelets
- Pulmonary function tests (PFT)
- Normal cardiac workup
- MRI and PET scans are optional, and are left to the discretion of the treatment team
- Serum α-fetoprotein and β-HCG, if appropriate
- A needle biopsy is not always indicated, and should only be performed if recommended by the thoracic surgeon

Staging

Thymic neoplasms are histopathologically described according to the World Health Organization (WHO) classification system, described in Table 1.[10] The most widely used system of clinical staging of thymic neoplasms is that of Masaoka and colleagues, recently updated as the Masaoka-Koga staging system, described in Table 2.[11, 12] This staging system is highly correlated with both the WHO classification system and with prognosis:[5, 13-15]

Table 1. WHO classification system for thymic neoplasms[10]

Type	Histologic Description
Type A	medullary; spindle-cell thymoma
Type AB	mixed thymoma
Type B1	predominantly cortical; lymphocyte-rich; lymphocytic, organoid thymoma
Type B2	cortical thymoma
Type B3	epithelial; squamous; atypical thymoma; well-differentiated thymic carcinoma
Type C	thymic carcinoma

Table 2. Masaoka-Koga staging system for thymic neoplasms[12]

Stage	Criteria
Stage I	Grossly and microscopically completely encapsulated tumor
Stage IIA	Microscopic transcapsular invasion
Stage IIB	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
Stage IVA	Pleural or pericardial metastases
Stage IVB	Lymphogenous or hematogenous metastasis

Treatment

Thymic neoplasms are uncommon and unpredictable; therefore all patients should be referred to and managed by a multidisciplinary treatment team with experience in the management of this disease. Whenever possible, patients should also be considered for inclusion in appropriate clinical trials (recommendation #1).

Early Stage Disease (Stages I – IIA). En-bloc surgical resection of the tumour and all surrounding tissues is recommended for all patients with an early stage thymic neoplasm (recommendation #2). The completeness of surgical resection has been reported to be the most important prognostic factor in early-

stage disease.[16, 17] In a thorough review of the literature, *Detterbeck et al.* reported average five- and ten-year overall survival rates of 92 and 88 percent, respectively, in studies of patients with stage I thymic neoplasms that were completely resected.[18] In addition, the authors reported that the average ten-year disease-free survival rates were as high as 92 percent for completely resected stage I disease.[18] Similar results for patients with stage II thymic neoplasms were recently reported by *Rena et al.*[19] In their retrospective review, the authors compared the outcomes of 58 patients with completely resected stage IIA or IIB thymic neoplasms who underwent only resection (n=32), or resection followed by postoperative adjuvant radiotherapy (n=25). Overall disease-free survival rates at five and ten years were 94 and 87 percent, respectively, and there was no statistically significant difference between the disease-free survival rates of patients who had surgery alone versus patients who had surgery and radiotherapy (p=0.432). The available evidence indicates that adjuvant radiotherapy does not have any added survival benefit for patients with a completely resected early stage thymic neoplasm[20], and therefore adjuvant radiotherapy is not recommended for early stage disease.[18, 19, 21-23]

Some recent studies advocate the use of limited thymectomies, minimally invasive thymectomies or video-assisted thoracoscopic surgeries in the surgical treatment of early stage I & II thymomas. *Onuki et al* reported that 10-yr overall survival and disease-free progression did not differ between individuals who underwent total thymectomy and those that underwent limited thymectomy which included resection along with surrounding tissue only.[16] *Jurado et al* observed similar results with 77 cases of minimally invasive thymectomies compared to 186 cases of open thymectomies although in this study long-term overall survivals were not assessed.[24] Other groups have observed similar results.[25, 26] However, at this time minimally invasive surgical procedures are not recommended for early stage disease until further prospective, controlled studies examining long term overall survival are conducted. This is in agreement with other Canadian guidelines on thymic neoplasms such as those from Cancer Care Ontario and British Columbia Cancer Agency.

Localized Disease (Stages IIB – III). The optimal combination of multimodality therapy to maximize resectability and minimize surgical mortality and morbidity for patients with localized thymic neoplasms remains unclear at the present time. Due to the relative rarity of thymic neoplasms, prospective clinical trials are lacking, and therefore published recommendations are based largely on results from case series and retrospective reviews, in combination with expert consensus.

Resectable: For patients with a resectable localized thymic neoplasm, complete surgical resection is the standard of care. In addition, the Alberta Provincial Thoracic Malignancies Tumour Team recommends that postoperative adjuvant radiotherapy should be discussed with the multidisciplinary treatment team as well as the patient (recommendation #3).

There is a growing body of literature supporting the role of postoperative adjuvant radiotherapy for patients with *incompletely resected* localized disease.[18, 27-31] In their early retrospective series, *Curran et al.* reported a five-year mediastinal recurrence rate of 21 percent in patients with stage III disease who underwent an incomplete resection and postoperative adjuvant radiotherapy compared with 100 percent for patients who did not receive adjuvant radiotherapy.[27] Similar results were reported in a larger and more recent retrospective review by *Ströbel et al.*[28] In their analysis of 228 patients with incompletely resected thymic neoplasms, of the 75 patients with stage III disease, the five-year relapse rate was lower in patients who received postoperative radiotherapy compared to those who did not (34% versus 78%).[28] *Detterbeck et al.* also concluded that the use of adjuvant radiotherapy in patients with incompletely

resected tumours is supported by the very low rates of mediastinal recurrence in the patients with gross residual disease who were treated with adjuvant radiotherapy (range 16 – 21%).[18]

The role of radiotherapy in patients with *completely resected* disease is less clear. Several case studies and retrospective reviews have reported an association between postoperative radiotherapy and a increased rate of local tumour control in patients with completely resected stage II or III tumours.[21, 27, 32-34] *Chang et al* conducted a single-centre, retrospective study on the efficacy of adjuvant radiotherapy for stage II and III thymomas in 76 patients. They reported increases in 5-yr DFS from 80% to 97.8% and in 10-yr DFS from 70% to 92.7% when comparing surgical resection only versus surgical resection and adjuvant 50 Gy radiotherapy, respectively.[17] However, the literature is currently conflicted as other reports have concluded that there is no significant survival advantage of postoperative radiotherapy for patients with completely resected stage II or III thymic neoplasms.[21, 23, 35-37]

The Alberta Provincial Thoracic Tumour Team recommends that postoperative radiotherapy should be used for all patients with stage II or III thymic neoplasms who have undergone an incomplete resection or have positive surgical margins. Postoperative adjuvant radiotherapy should also be considered for patients with stage II or III disease who have undergone a complete resection. The recommended adjuvant radiation dosage is between 45 Gy and 50 Gy for negative margins, between 50 and 54 Gy for microscopically positive margins, and 60 Gy for grossly positive margins, in 1.8 Gy to 2.0 Gy per daily fraction.[38] A total dose of 60 Gy to 70 Gy may be needed for patients who have gross residual disease following surgery. Extensive nodal irradiation to the entire mediastinum is not recommended.[38]

A large retrospective, multi-centre study of 249 patients by *Marulli et al* examined the effectiveness of multimodal treatment on stage III thymomas. All patients underwent surgery with 94 patients also undergoing induction chemotherapy and 205 patients undergoing adjuvant treatments. Three different chemotherapy regimens were assessed; all of which contained cisplatin. The majority of the patients (53.4%) had WHO B2 or B3 histology. The authors reported 10 year OS rates of 64% and 10 year DFS rates of 74%. Prognostic indicators of poor survival included R2 resection, recurrence, absence of myasthenia gravis, thymic carcinoma, age greater than 50 years and vascular invasion. The authors concluded that multimodal treatment of stage III thymoma achieves good survival outcomes.[20]

Initially unresectable: For patients with an initially unresectable localized thymic neoplasm, induction chemotherapy, alone or in combination with radiation, followed by reassessment and consideration for surgery, is recommended. If the response is sufficient to permit surgery, surgical resection followed by adjuvant radiotherapy, if not administered pre-operatively, is recommended (recommendation #4). In a prospective phase II study, *Kim et al.* reported the results of a long term follow up of 22 patients with stage III or stage IV thymic neoplasms.[39] The patients, who all had initially unresectable tumours, received three courses of induction chemotherapy consisting of cisplatin- doxorubicin-cyclophosphamide (PAC) plus prednisone and were then reassessed for surgery; 21 of the patients underwent subsequent surgical resection followed by postoperative radiation and chemotherapy. The overall survival rate was 95 percent at five years (95% CI, 87 - 100) and 79 percent at seven years (95% CI, 55 - 100). In addition, the progression-free survival rates were 77 percent at both five and seven years (95% CI, 58 - 100). Similar results were reported in a smaller prospective study by *Venuta et al.* in 2003.[40] Fifteen patients who had stage III tumours that were initially unresectable underwent neoadjuvant chemotherapy with either cisplatin-epirubicin-etoposide (n=8) or PAC (n=7). Thirteen of these patients subsequently underwent surgical resection followed by adjuvant chemoradiation, and the ten-year overall survival rate was 90 percent.[40] A more recent phase II clinical trial by *Lemma et al* evaluated the efficacy of a carboplatin and paclitaxel regimen for stage III-IV unresectable thymoma and thymic carcinoma in 45 patients. The

researchers used dosage schemes of carboplatin (AUC, 6) and paclitaxel (225 mg/m^2) every 3 weeks for a 6 cycle maximum. For the patients with thymoma, median PFS was 16.7 months (7.2-19.8 months [95% CI]) and almost half of all patients achieved stable disease. The authors concluded that the regimen has moderate clinical activity and may be a good option for individuals with unresectable thymoma.[41] *Grassin et al* observed similar results when using an etoposide, ifosfamide and cisplatin regimen for patients with stage III or IV thymoma.[42]

Neoadjuvant chemotherapy plus radiation is also sometimes used for patients with a localized thymic neoplasm; current evidence to support this practice is limited, however.[8, 43] In a small retrospective report of ten patients treated with neoadjuvant chemotherapy plus radiotherapy (range 33-49 Gy), *Wright et al.* reported that this regimen was well tolerated and resulted in a partial radiographic response in four patients, and an estimated five-year survival of 69 percent (95% CI, 32 - 100).[8] The results of a multi-centre, phase II clinical trial currently underway in the United States and Canada (NCT00387868) should provide further information on the role of neoadjuvant chemotherapy plus radiotherapy in this setting.

For patients with localized disease who are medically ineligible for surgery or whose tumour remains unresectable following induction therapy, the Alberta Provincial Thoracic Tumour Team recommends that chemotherapy alone or in combination with radiotherapy should be administered (recommendation #5). *Girard et al.* recently reviewed the efficacy of prospectively evaluated chemotherapy regimens for the treatment of inoperable tumours.[5] For single-agent therapies, the highest response rates were observed in controlled studies with cisplatin or ifosfamide, with response rates ranging from 10 to 62 percent. The most commonly used multi-agent chemotherapy regimens include: PAC, cisplatin-etoposide, cisplatin-doxorubicin-vincristine-cyclophosphamide (ADOC), and etoposide-ifosfamide-cisplatin (VIP).[7] Response rates between 32 and 92 percent have been reported with the use of these regimens for patients with unresectable or inoperable thymic neoplasms.[5, 7]

Following chemotherapy, radiotherapy should be used for local control. As in cases with gross residual disease following surgery, a total dose between 60 and 70 Gy may be needed for patients with inoperable or unresectable disease, as lower doses have been associated with higher rates of disease recurrence or progression.[38] In a phase II clinical trial published in 1997, *Loehrer et al.* reported the results of 23 patients with localized inoperable thymoma or thymic carcinoma.[44] Patients were treated with the PAC regimen followed by 54 Gy of radiotherapy to the primary tumour and regional lymph nodes and then up to six cycles of additional chemotherapy. The authors reported an overall response rate of 69.6 percent (95% CI, 47.1 – 86.8), and a five-year survival rate of 52.5 percent.

Advanced Disease (Stages IVA – IVB). Surgery is an important therapeutic measure that can prolong survival, even when it is for debulking purposes only.[45] This is particularly true for thymomas, which are slow-growing tumours. In patients with large bulky masses or advanced disease, however, surgical resection may not be initially feasible. Because both thymoma and thymic carcinoma appear to be sensitive to chemotherapy, many publications and consensus statements recommend delivering preoperative or induction chemotherapy to patients with advanced thymic neoplasms, in an attempt to shrink the tumour and reduce the morbidity of the surgery or the fields of radiotherapy.[5, 43, 45-48] Chemotherapy with platinum-based regimens has been associated with durable remissions in patients with unresectable, advanced, or metastatic disease.[42, 49] The chemotherapy regimens used most often, either alone or as part of multimodality therapy, in advanced disease include PAC with or without prednisone, VIP, cisplatin-etoposide, and ADOC.[3, 39, 45, 50-58]

Several small studies have demonstrated the importance of a multimodality approach in prolonging disease-free survival for patients with advanced thymic neoplasms. Response rates in these studies range from 60 to 100 percent, and resectability rates following induction chemotherapy range from 30 to 70 percent.[3, 39, 45, 50-52, 55, 56] In the study by *Kim et al.*, described earlier, 11 patients with stage IV disease were included in the analyses, and multimodality treatment resulted in five- and seven-year overall survival rates of 95 and 79 percent, respectively.[39] In a retrospective report by *Huang et al.*, 18 patients with stage IVA tumours underwent induction chemotherapy with PAC (n=10), VIP (n=3), carboplatin-paclitaxel (n=3) or cisplatin-etoposide (n=2).[50] Complete resection was achieved in 12 (67%) patients, and four patients received postoperative hemithoracic radiotherapy. Five- and ten-year survival rates were 78 and 65 percent, respectively. A more recent prospective study by *Yang et al* evaluated the safety of en bloc total thymectomy and EPP for stage IVA thymoma in 7 patients. They observed no operative mortalities. They also reported a median OS of 30.6 months and a Kaplan-Meier 2-year OS of 100% and concluded that en bloc extended total thymectomy and EPP can be safely performed on certain patients with stage IVA thymoma.[59] Similar conclusions were drawn by *Gonzalez et al* in a study of 4 cases evaluating EPP and venous confluence resection for patients with stage IVA thymoma.[60]

For recurrent or metastasized thymic neoplasms, two prospective phase II trials of chemotherapy alone have been reported. In the US Intergroup trial, 30 patients with thymoma or thymic carcinoma that had metastasized following radiotherapy were treated with the PAC regimen.[57] The authors reported an overall response rate of 50 percent, which included three complete responses and twelve partial responses; ten patients had stable disease. The median duration of response was 11.8 months, and the median survival time was 37.7 months. In the European Organization for Research and Treatment of Cancer (EORTC) trial, 16 patients with recurrent or metastatic malignant thymoma were treated with a combination of cisplatin and etoposide.[58] The authors reported five complete responses and four partial responses, with a median response duration of 3.4 years. The median progression-free survival time was 2.2 years, and the median overall survival time was 4.3 years.

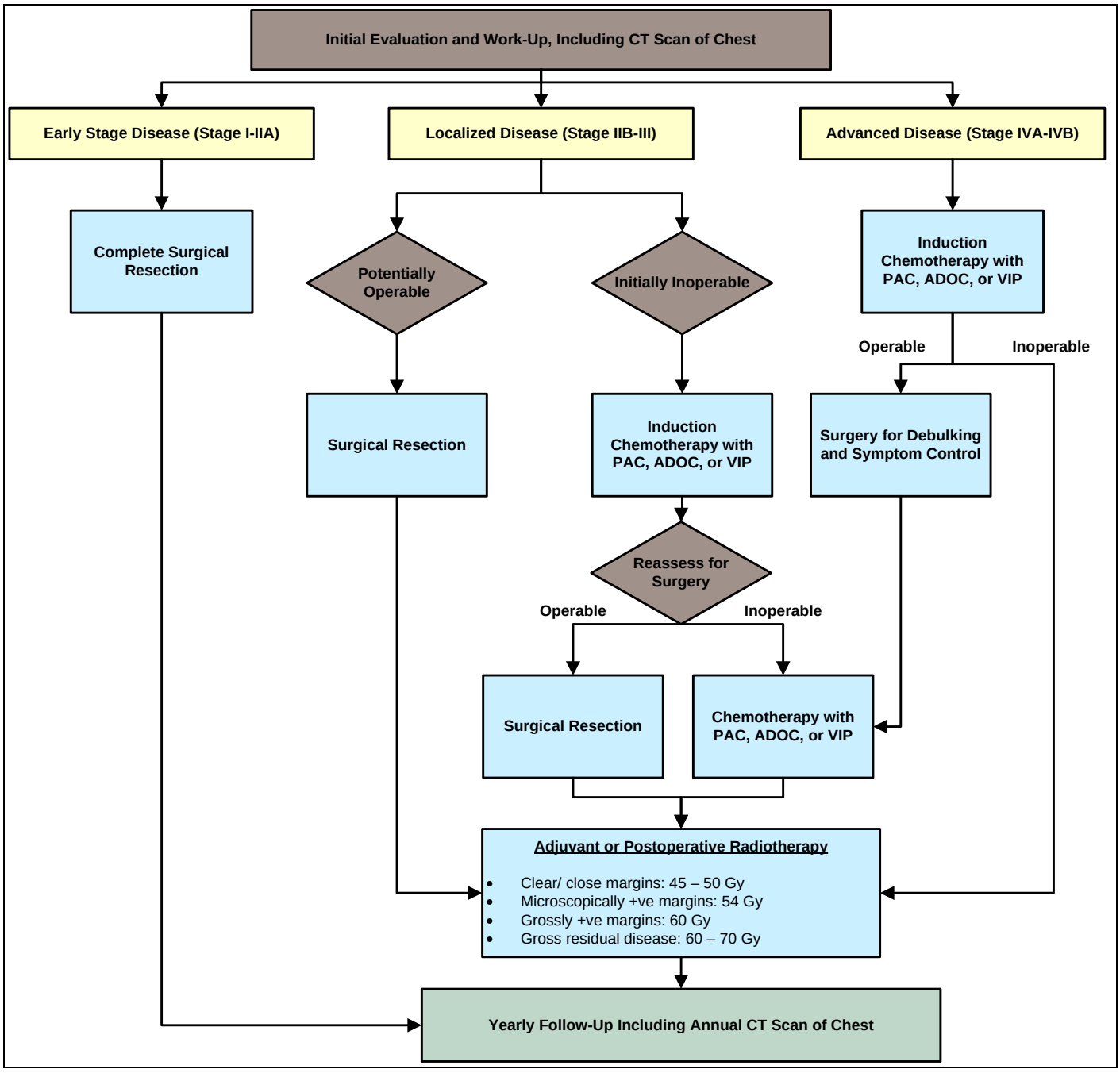
Radiotherapy for patients with advanced disease should be used for local control following induction chemotherapy and surgery, or as an adjuvant to chemotherapy for patients who are medically inoperable. A total dose of 60 to 70 Gy may be needed for patients with unresectable or gross residual disease.[38]

Based on the results of the studies to date, the Alberta Provincial Thoracic Tumour Team recommends multimodality therapy consisting of induction chemotherapy, with or without radiation, followed by surgery for debulking or symptom control, where appropriate, for patients with an advanced thymic neoplasm. Postoperative management should include chemotherapy and/or radiotherapy for local control and palliation (recommendation #6).

Follow-Up

Thymic neoplasms have been associated with an increased risk for secondary malignancies, as well as late recurrences.[1, 18, 61-63] In their comprehensive review, *Detterbeck et al.* reported that the mean time to recurrence for patients with early-stage disease was ten years, while the mean time to recurrence for patients with localized or advanced disease was three years.[18] Due to the high risk of a secondary malignancy and/or a late recurrence, the Alberta Provincial Thoracic Tumour Team recommends prolonged follow-up for patients who achieve a complete response with either surgery or a multimodality approach (recommendation #7). Surveillance should include an annual chest CT scan.
Figure 1 summarizes the treatment options recommended by the Alberta Thoracic Tumour Team for patients with thymic neoplasms.

TREATMENT ALGORITHM



GLOSSARY OF ABBREVIATIONS

Acronym	Description
ADOC	cisplatin + doxorubicin + vincristine + cyclophosphamide
BCCA	British Columbia Cancer Agency
CBC	complete blood count
CCO	Cancer Care Ontario
CT	computed tomography
EORTC	European Organization for Research and Treatment of Cancer
Gy	gray
HCG	human chorionic gonadotropin
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PAC	cisplatin + doxorubicin + cyclophosphamide
PET	positron emission tomography
PFT	pulmonary function test
VIP	etoposide + ifosfamide + cisplatin
WHO	World Health Organization

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 Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. 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 Thoracic 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. Alberta Health Services – Cancer Care 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 Thoracic 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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