Thymoma
A Focus on Current Therapeutic Management

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Abstract: Thymomas are rare intrathoracic malignant tumors. Commonly used staging system is the Masaoka classification, based on peroperative and histopathological findings. Surgery is the cornerstone of the management of thymomas, initially being useful for precise histopathological diagnosis and staging, and in most cases ensuring the first step of the therapeutics simultaneously. After tumor stage, complete resection is the most constant and significant prognostic factor for progression-free and overall survival. Postoperative radiotherapy is recommended in incompletely resected thymomas. Completely resected stage II and III tumors may also benefit from adjuvant radiotherapy to reduce local recurrence rates but without impact on survival. In primary unresectable thymomas, multimodal strategy nowadays includes neoadjuvant chemotherapy, extensive surgery, adjuvant radiotherapy, and in some cases, adjuvant chemotherapy. The most popular chemotherapy regimens combine cisplatin, adriamycin, etoposide, cyclophophamide, or ifosfamide.

The management of thymomas is a paradigm of cooperation between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the therapeutic strategy and evaluating the prognosis. As a consequence of their rarity, no prospective randomized trials are available and collaborative studies are warranted to evaluate and improve current therapeutic standards, taking into account recent improvements in techniques, such as robotic surgery, radiotherapy, and supportive treatments.

Key Words: Thymoma, Surgery, Radiotherapy, Chemotherapy.

(*J Thorac Oncol.* 2009;4: 119–126)

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/09/0401-0119

Thymomas are uncommon intrathoracic malignant tumors. As a consequence of their rarity, knowledge regarding these tumors is mainly based upon case reports or small retrospective series, most of which were published years ago. Even if sometimes difficult to interpret, these studies nevertheless provide a good overview of the results of surgical resection, and the role of radiotherapy and chemotherapy. Publication bias regarding the inclusion of patients (medical, surgical or pathologic studies) may hamper the estimation of the individual weight of each therapeutic option in the multimodal treatment of these tumors.

Thus, the objectives of this chapter are to (1) describe available therapeutic options for thymomas, (2) review their indications in adults, and (3) provide a comprehensive analysis of current treatment recommendations, using standard grading system.[1] As thymic carcinomas and carcinoids are extremely uncommon, they will not be considered for this review.

Thymoma: Clinical Staging Considerations

Thymomas are rare malignant epithelial tumors, accounting for less than 0.5% of all cancers. Their main pathologic characteristics include a wide range of cytologic patterns within thymic epithelial cells, and the association with a nontumoral lymphocytic component, whose relative proportion to neoplastic cells is the basis of the current World Health Organization (WHO) histopathological classification (Table 1).[2] The thymus gland induces the differentiation of T lymphocytes, what may provide an explanation for the wide spectrum of autoimmune manifestations associated with thymoma.

Even if the WHO classification has been designed to assume some prognostic value (Table 1), the most significant factor for survival is the invasiveness of the tumor.[3–15] Several staging systems have been described. The Masaoka and, especially in continental Europe, the French Groupe d'Etude des Tumeurs Thymiques (GETT) classifications are mostly used, as they are based on peroperative and histopathological findings, the latter offering the advantage of being clearly connected to therapeutic options (Table 2).[6,8] Moreover, the concordance between these 2 classifications is higher than 85%.[16] The unauthorized Tumor-Node-Metastasis system proposed in 1991 has never been formally adopted, even in recent studies.[17]

TABLE 1. The World Health Organization Histopathological Classification of Thymomas[1]

Type	WHO Classification-Pathological Features	Invasiveness	10-yr Disease-Free Survival
A	Spindle cell and medullary thymoma, lymphocyte-poor area	10–40%	100%
AB	Mixed pattern of type A (lymphocyte-poor) and type B (lymphocyte-rich) thymoma	30–40%	100%
B1	Thymoma resembling the normal thymus	45–50%	85%
B2		65–70%	85%
B3	Sub-types B1, B2, and B3 differentiated by an increasing epithelial/lymphocyte ratio and the emergence of atypia	85–90%	35%

WHO, World Health Organization.

TABLE 2. Correspondence Between the Masaoka and the Groupe d'Etude des Tumeurs Thymiques (GETT) Staging Classifications.[1,5,7] Overall Survival and Survival in Completely Resected Tumors[1,3,5,7]

Masaoka Staging		GETT Classification		Complete Resection	Overall Survival	
Stage	Description	Stage	Description		5-yr	10-yr
I	Macroscopically completely encapsulated	IA	Encapsulated tumor, totally resected	95–100%	90–100%	85–95%
IIA	Macroscopic invasion into surrounding fatty tissue, mediastinal fat, or both	IB	Macroscopically encapsulated tumor, totally resected, peroperative suspicion of mediastinal adhesion or potential capsular invasion	85–100%	75–90%	70–85%
IIB	Microscopic invasion into the capsule	II	Invasive tumor, totally resected			
III	Macroscopic invasion in neighboring organs, such as pericardium, great vessels, or lung	IIIA	Invasive tumor, sub-totally resected	65–80%	50–70%	25–60%
		IIIB	Invasive tumor, biopsy			
IVA	Pleural and pericardial dissemination	IVA	Supraclavicular metastasis or distant pleural droplets	30–50%	30–40%	0–15%
IVB	Lymphogeneous or haematogeneous metastasis	IVB	Distant metastasis			

Cooperation between surgeons and pathologists is mandatory to establish the accurate staging of thymomas. Indeed, the pathologic definition of invasive tumors may vary, referring either to (1) capsular invasion, as proposed in the original report of Masaoka et al.[8], but which is difficult to assess unless the capsule is completely breached, or (2) invasion beyond the capsule in the mediastinal fat, corresponding to microscopic invasion, which may also be hard to distinguish from persistent thymic remnants, especially in B1–B2 lymphocytes-rich subtypes. Moreover, peroperative clinical findings of invasiveness, especially tight adherence to surrounding structures and pleural adhesion, are not correlated with microscopic invasion.[4]

Overall, invasive thymomas belong to Masaoka stage II to IV tumors and account for 35 to 45% of cases. Mostly, invasion consists of direct local and regional spread within the lung, the pleura, and the pericardium (some patterns rather considered as "droplet" local spread), thus classified as stage III, than true hematogenous or lymphogeneous dissemination. Rare droplet lesions may even occur within the peritoneum, by direct spread through the diaphragmatic orifices. The WHO classification is highly correlated to stage, as 80 to 90% of A to B1 thymomas are stage I-II tumors, whereas 50 to 60% of B2, and 60 to 80% of B3 and C tumors are stage III–IV, a unique feature which may explain the prognostic value of the pathologic classification (Table 1).[3,4]

General Therapeutic Principles

Surgery

Surgery is the cornerstone of the management of thymic tumors, being most useful for the initial histopathological diagnosis and staging, and in most cases providing the first-line therapeutic modality. For resectable anterior mediastinal tumors compatible with thymoma, immediate surgical resection is advocated; in this way, the capsule is left intact and spoiling avoided. In cases of unresectable tumors or suspicion of lymphoma, fine-needle aspiration or surgical biopsies are recommended.[18]

As a standard, the surgical management of thymoma requires the wide opening of the mediastinum and both pleural cavities, which is classically achieved by median sternotomy.[7,16] In the surgical literature, at least 10 different approaches to the thymus have been described and these are summarized in Table 3.[19–22] Unfortunately, there are no randomized studies showing one technique to be superior over another. Voluminous tumors for which parenchymal lung resection is anticipated, may be operated through an anterior bilateral thoracotomy and transverse sternotomy, a

TABLE 3. Surgical Approaches to the Thymus

1. Transcervical only
2. Transsternal
Full median sternotomy
Partial sternotomy (manubriotomy)
3. VATS (video-assisted thoracic surgery)
Unilateral (right or left)
Bilateral (right + left + subxiphoid)
Robotic techniques (right or left)
4. Combined
Transcervical + sternal retractor
Transcervical + partial sternotomy
VATS + cervical incision
Bilateral anterior thoracotomy + transverse sternotomy (clam shell)

VATS, video-assisted thoracic surgery.

so-called "clamshell" incision. Regarding the need for a complete exploration of the thorax to achieve accurate margins and complete staging, cervicotomy only, as described in older reports to reduce the risk of anesthesia in patients with associated myasthenia gravis, is no longer indicated. Similarly, videothoracoscopy is contraindicated in large tumors to avoid any peroperative spread of tumor cells within the pleura. However, with the advent of robotic techniques providing superb three-dimensional visualization and highly flexible robotic arms, thymomas up to 4 cm may be resected safely. In a recent prospective single-center series of 106 consecutive robotic-assisted thymectomies, there was no mortality, and morbidity was only 2%.[23] In a retrospective comparative analysis, operative time was higher with the robotic approach, but hospital stay was shorter and neurologic outcome seemed to be better.[24]

The first step of the operation consists of a careful examination of the mediastinum and pleural cavities, followed by evaluation of macroscopic capsular invasion, peritumoral and pleural adhesions, and involvement of surrounding tissues. Careful exploration of the mediastinal pleura, especially in the costodiaphragmatic sinuses, may detect droplet metastases. These findings, together with the subsequent pathologic examination of the surgical specimen, constitute the basis of the staging system of thymomas, according to the Masaoka, and furthermore the GETT classifications (Table 1).[6,8] Areas of uncertain margins are marked with clips to allow precise delivery of postoperative radiotherapy.

Radiotherapy

Radiotherapy has mainly been reported as an exclusive or adjuvant treatment for thymomas. Evolving trends for locally advanced tumors include multimodal chemoradiation strategies. Current modalities of radiotherapy for thymoma include (1) the use of multifield arrangement conformal radiotherapy and three-dimensional treatment planning; (2) a clinical target volume including the whole thymic space, the tumor and its extensions, and the anterior, superior, and middle mediastinum (with reduction of fields after a total dose of 50–55 Gy). Prophylactic supraclavicular nodes irradiation is no longer recommended, as isolated recurrences in this area are exceptional.[12,13] Some reports indicate the feasibility and efficacy of delivering a 15 Gy prophylactic hemithoracic irradiation, with a reduction of pleural recurrences rates from 100% to 60%, without effect on overall survival[25]; (3) a total dose ranging from 40 to 60 Gy, including a boost on the tumor bed in incompletely or nonresected lesions, as mentioned, surgical clips may be then useful to plan the gross tumor volume-, with a standard-fractionation scheme consisting in daily doses from 1.8 to 2 Gy over a 4 to 6 weeks-period.

Although thymomas have been recognized as highly radiosensitive for years, the benefit of dose escalation on local control has not clearly been established. Arriagada et al.[26] reported similar local control rates with total doses inferior to 48 Gy or superior to 60 Gy. However, in the French series reported by Mornex et al.,[13] local recurrence rate in stage III–IV resected tumors was as high as 80% after adjuvant radiotherapy delivered to median doses of 45 to 50 Gy. This led most investigators to increase radiation doses to 60 to 65 Gy, which was made possible with the availability of conformal radiation planning systems.

The toxicity of radiotherapy for thymic tumors depends on the amount of normal tissues included within the radiation portal, and mainly consists of radiation-induced acute pericarditis and pneumonitis, and late coronary disease and lung fibrosis.[13] No data are yet available regarding the use of new radiation delivery techniques, such as intensity modulated, respiratory gating, and proton-beam radiotherapy, to reduce these late effects.

The interpretation of reported data regarding radiotherapy as a single modality for thymomas is difficult, as only small series have been published, most of which included patients with various tumor stages, heterogeneous performance status, and different total radiation doses and techniques. Overall, local control rates following exclusive radiotherapy in nonresectable tumors might not be higher than 45 to 50%.[27,28]

The role of adjuvant radiotherapy in thymic tumors has been debated for years, and has to be discussed both regarding the tumor stage and the completeness of the surgical resection. In reported series of thymomas, radiotherapy was also delivered in a neoadjuvant setting to 10–20% of patients, mostly bearing stage IV primary unresectable tumors, in association with chemotherapy.[29] The precise effect of neoadjuvant radiotherapy is difficult to determine in these heavily treated patients. The feasibility and efficacy of preoperative radiotherapy to a total dose of 18 Gy has also been reported in patients with great vessel invasion or mediastinal compression, to achieve subsequent complete resection.[30]

Chemotherapy

Evidence-based data regarding the role of chemotherapy for thymomas are scarce, mainly due to the small populations studied. The chemosensitivity of thymoma was established in many small studies reporting the efficacy of single-agent chemotherapy regimens in nonresectable tumors (Table 4). The highest responses rates were observed in controlled studies

TABLE 4. Prospectively Evaluated Chemotherapy Regimens in Thymic Tumors

Regimen	Drugs	Doses	Response Rate		Reference
			Overall	Complete	
Single agent					
Cisplatin		50 mg/m²/3 wk	10–62%	10%	31
Ifosfamide		1.5 g/m² × 5 d/3 wk	46–54%	38%	32
Multiple agents					
PE	Cisplatin	60 mg/m²/3 wk	56–60%	31%	33
	Etoposide	120 mg/m² × 3/3 wk			
PAC	Cisplatin	50 mg/m²/3 wk	51%	10%	34
	Adriamycin	50 mg/m²/3 wk			
	Cyclophosphamide	500 mg/m²/3 wk			
ADOC	Adriamycin	40 mg/m²/3 wk	85–92%	40–43%	35
	Cisplatin	50 mg/m²/3 wk			
	Vincristine	700 mg/m²/3 wk			
	Cyclophosphamide	0.6 mg/m²/3 wk			
VIP	Etoposide	75 mg/m² × 4 d/3 wk	32%	0%	36
	Ifosfamide	1.2 g/m² × 4 d/3 wk			
	Cisplatin	20 mg/m² × 4 d/3 wk			

PE, cisplatin and etoposide; PAC, cisplatin, adriamycin, cyclophosphamide; ADOC, adriamycin, cisplatin, vincristine, cyclophosphamide; VIP, etoposide, ifosfamide, cisplatin.

with cisplatin and ifosfamide.[31,32] Noncisplatin containing regimens have been abandoned for many years. Current standard regimens include the following: cisplatin and etoposide[33]; cisplatin, adriamycin, cyclophosphamide (PAC)[34]; adriamycin, cisplatin, vincristine, cyclophosphamide (ADOC)[35]; and etoposide, ifosfamide, cisplatin (VIP)[36] (Table 4). However, these have never been compared with single-agent regimens in a randomized setting. Response rates range between 32 and 92%, including 10 to 43% of complete responses (Table 4). In the 10-year observational study reported by Giaccone et al.,[37] the PAC and the VIP regimens were the most used in an exclusive setting, and overall response rate was 32%. The VIP regimen, even if showing slightly lower responses rates, is significantly less toxic than the PAC regimen.

Nonchemotherapeutic systemic treatments have also been used in nonresectable thymoma. The association of octreotide and prednisone, based on the evidence of growth hormone secretion by thymic epithelial cells, has been reported as an effective treatment in thymomas which show up positive on octreoscan, achieving an objective response rate as high as 30%.[38] Targeted therapies have been disappointing, despite the overexpression of epidermal growth factor and c-Kit[39,40]: reported response rates to gefitinib and imatinib are as low as 1 to 4%, what may be explained by the exceptional presence of activating mutations of the corresponding targeted genes in these tumors.[37,39–42]

Finally, in all these studies, the evaluation of response to chemotherapy rarely takes into account (1) the short-term effect of associated corticoids on the lymphocytic cells, which may be important in AB and B lymphocyte-rich subtypes, without efficiency on the epithelial tumoral component, and (2) the possible rebound thymic hyperplasia after chemotherapy.[43]

Current Therapeutic Recommendations in Thymic Tumors

Masaoka-Stage I Thymomas

The treatment of Masaoka stage I thymoma consists of upfront surgery, although its role has never been proven in a randomized study. Peroperatively, resectability is carefully evaluated. Extended thymectomy is indicated in every case including the thymic gland and complete resection of all perithymic fat.[15] Capsular invasion may be subtle and not visible by the surgeon, so the tumor should not be shelled out but rather resected with all surrounding tissues. In the absence of capsular invasion at pathologic examination (stage IA tumors in the GETT classification), no adjuvant treatment is recommended.[44] However, the major challenge is to ensure the absence of microscopic invasion, which may require a clarification of the pathologic definition of capsular invasion. Completely resected stage I thymomas carry a 0.9%-overall recurrence risk and a 5-year survival of 100% after surgery as single treatment modality.[44] Adjuvant radiotherapy in these cases will not provide any additional survival benefit.[45,46] In all cases, mandatory follow-up should be longer than 10 years, as late recurrences are described up to 15 years after initial resection.[7]

In medically inoperable patients, exclusive radiotherapy may improve local control, although overall survival may not be influenced.

Recommendation: for stage I thymoma, surgery is recommended with the aim to obtain a microscopically complete resection (level of evidence 1C).

Masaoka–Stage II–III Resectable Thymomas

The treatment of Masaoka stage II–III resectable thymomas also consists of upfront surgery. After tumor

stage, complete resection which is obtained in 50 to 70% of cases, is the most constant and significant prognostic factor for progression-free and overall survival in thymomas (Table 1).[5,7,9–12,14–16] As most thymic lesions are initially operated, some European authors have criticized the Masaoka staging system, which, contrary to the GETT classification, does not take into account the completion of upfront surgical resection. The GETT classification may thus better reflect the aggressiveness of thymomas: for example, Masaoka-stage III tumors undergoing complete resection may achieve similar survival rates to stage I tumors, with a 5-year progression-free survival up to 95%.[12] These tumors are thus "up-classified" as stage II in the GETT system.

In completely resected Masaoka stage II and III (GETT stage II) thymomas, adjuvant radiotherapy reduces local recurrence rates from 28–36% to 0–5%, and from 53% to 28%, respectively.[13,45,47] This benefit may exist especially in tumors showing capsular invasion (Masaoka stage IIB and III). In incompletely resected tumors, Curran et al.[47] reported that postoperative radiotherapy also increased mediastinal recurrence-free survival from 0 to 79%. These results were better than the 47% recurrence-free survival of patients having received complete resection without adjuvant radiotherapy, suggesting that postoperative radiotherapy could even catch up an incomplete resection.[47] However, postoperative radiation has never been reported to increase overall local control rate and survival.[10,16,45] Overall, if postoperative radiation to total doses above 50 to 55 Gy achieves relapse rates within the radiation field as low as 15 to 20%, radiotherapy fails to control recurrent pleural dissemination, what may reflect the normal tumor dissemination pattern before or during surgery.[10,12] Some authors reported the use of hemithoracic prophylactic radiation, while others suggested that delivering radiation in a neoadjuvant setting may decrease the rate of pleural recurrences.[10,48]

In case of incomplete resection (GETT stage IIIA tumors), postoperative radiotherapy is systematically recommended to a total dose of 60 to 65 Gy including the boost on areas of macroscopic invasion (marked with surgical clips).

Recommendation: for resectable Masaoka stage II–III thymomas, surgery is recommended (level of evidence 1C). The role of postoperative radiotherapy remains controversial but is clearly recommended for incompletely resected tumors (level of evidence 2C).

Masaoka-Stage III–IVA Marginally Resectable Thymomas

Surgical procedures for invasive stage III–IVA thymic tumors include some specific crucial issues: (1) extensive en bloc resection of the tumor, cervical and mediastinal fat, and all invaded local structures. If no fat plane exists between the tumor and the pericardium, frozen tissue examination with clear indication of suspicious margins is mandatory to ensure complete resection; otherwise, en bloc resection of the underlying pericardium may be necessary. Major vascular resections have been reported to be feasible, including the removal and prosthetic reconstruction of the superior vena cava, innominate veins, aortic arch, anterior wall of the pulmonary artery, and even the cardiac right cavities[49–51]; (2) the maximal preservation of phrenic nerves, especially in patients with associated myasthenia gravis to avoid respiratory insufficiency. Unilateral resection of the involved phrenic nerve is optional (5% of cases), and may be balanced by the positioning of surgical clips to plan a subsequent adjuvant radiation boost. However, phrenic nerve resection may be inevitable, especially in cases requiring pericardial resection[7]; (3) the possible need for lung parenchymal resection, reported in almost 10% of cases, which consists in most cases of limited resection rather than traditional lobectomy or pneumonectomy.[14] However, pleuropneumonectomy has been successfully performed in selected patients with stage IVA lesions[52]; and finally, (4) the peroperative control of doubtful resection margins using fresh-frozen tissue examinations, a meticulous ink-labeling of surgical specimens, and the application of surgical clips to guide subsequent postoperative radiotherapy. In recent series, overall reported morbidity and mortality rates range from 10% to 15%, and 1% to 3%, respectively.[5,7] In case of resectable pleural droplets metastases, surgical resection is controversial but may be performed, possibly after induction chemotherapy.[53–55]

The role for incomplete ("debulking") surgery in patients with stage III–IVA thymomas has been debated for many years, mainly following small, retrospective and heterogeneous series which showed survival rates of only 5 to 10%. Improvement in surgical techniques allows more extensive resection, in particular as part of multimodality treatment. Furthermore, an eventual incomplete resection significantly reduces local recurrences in comparison to a simple tumor biopsy: in the French series of Mornex et al. local control rates were 46% versus 16%, respectively.[11,13]

Adjuvant chemotherapy has been reported to favorably influence survival in patients with Masaoka stage III–IV thymomas.[13,16] However, chemotherapy has never been directly compared with radiotherapy in an adjuvant setting, but has mostly been applied sequentially, before or after radiotherapy. Main regimens were cisplatin-based, including cisplatin, epirubicine, etoposide (CEE) and PAC.[13,56] In incompletely resected tumors, response rates were higher when chemotherapy was administered before radiotherapy, than after radiotherapy (60–62% versus 40–55%, respectively). In sequential association with chemotherapy, radiotherapy was delivered to total doses ranging from 30 to 70 Gy.

Recommendation: for Masaoka-stage III–IVA marginally resectable thymomas, surgery and postoperative radiotherapy are recommended (level of evidence 1C). Perioperative chemotherapy may be delivered in cases of incomplete resection (level of evidence 2C).

Masaoka-Stage III–IVA Initially Unresectable Thymomas

Chemotherapy is the initial treatment of Masaoka-stage III–IVA unresectable thymomas. The main objective is to reduce the tumor volume either to allow subsequent surgery with higher chances of achieving negative margins, or to deliver radiotherapy sparing more nontumoral tissue. In a neoadjuvant setting, most protocols used the VIP regimen.[34]

Response rates of 50% are higher than in an exclusive setting.[37] Other regimens used in a neoadjuvant setting are the CEE and the PAC-methylprednisolone associations, with response rates up to 92%.[57–59]

Several recent, but only small series including no more than 7 to 22 patients, reported the feasibility of extensive resection after response to neoadjuvant chemotherapy with CEE, ADOC, or PAC regimens and followed by postoperative radiotherapy to total doses from 30 to 60 Gy, and by adjuvant chemotherapy in some cases.[54–56,58–62] The high response rates to neoadjuvant chemotherapy, ranging from 77 to 100%, associated with survival rates ranging from 77 to 95%, may question, when compared with the results of similar strategy in locally advanced non-small cell lung cancer. However, local control was achieved in more than 80% of cases in these series.

For thymomas definitely judged to be unresectable, chemoradiation is administered. Chemotherapy and radiotherapy in this setting have always been administered sequentially to avoid the accumulation of treatment toxicities, especially the high risk of radiosensitization with anthracyclins. Exclusive chemoradiation combining PAC chemotherapy with standard radiation to a total dose of 54 Gy provided an overall response rate of 70%, and a 5-year survival of 53%, comparing favorably with the results of incomplete resection.[53]

Recommendation: for Masaoka-stage III–IVA initially unresectable thymomas, multimodal therapy includes upfront chemotherapy, followed by surgery or radiotherapy, depending on whether sufficient downstaging is achieved (level of evidence 2C).

Masaoka-Stage IVB Thymomas

Chemotherapy only is the treatment of choice for stage IVB thymomas; the PAC and ADOC chemotherapy regimens may be the most efficient to achieve significant response rates.[37] Subsequent surgery of residual masses and radiotherapy may be feasible in case of major response to first-line treatment.[53–55]

Recommendation: for Masaoka-stage IVB thymomas, chemotherapy is recommended (level of evidence 1C).

Treatment of Associated Auto-Immune Manifestations

Associated parathymic manifestations occur in association with thymoma in 50 to 70% of cases. The most frequent parathymic disease is myasthenia gravis, present in 30 to 50% of cases.[63] Identified in old series as a negative prognostic factor increasing perioperative mortality rates, myasthenia gravis is presently regarded as a favorable factor influencing outcome, as it may lead to an earlier disclosure of the tumor. In 10 to 15% of cases myasthenia gravis precedes the diagnosis of thymoma and with current anesthesiologic techniques, the risk of thymectomy has been reduced.[63,64] Thymectomy, but also chemoradiation, has been reported to improve symptoms of myasthenia gravis in 50 to 60% of cases, with achievement of complete remission in 8 to 30% of cases.[63–65] Recurrence of myasthenia may rarely herald recurrence of the tumor, but may also be associated with any other transient medical stress.

Although more than 25 additional parathymic manifestations have been described, few data exist regarding their evolution after thymectomy: only hypogammaglobulinemia (10% of thymomas), pure red cell aplasia (5–10% of thymomas), and stiff-person syndrome have been reported to improve with the treatment of the thymic tumor.[66,67] Especially, pure red cell aplasia, rather than hypogammaglobulinemia, may hamper the completion of the therapeutic strategy. This especially refers to chemotherapy due to increased hematological toxicity.

Local and Locoregional Recurrences of Thymoma

Late recurrences occurring more than 5 or 10 years after resection are not uncommon in thymoma. If local control mainly depends on the completeness of initial surgery, pleural "droplets" recurrences are rather related to local spread than to hematogenous metastases. In cases of recurrent thymoma, surgery, when feasible, remains then the major therapeutic option.[68] Complete reresection, obtained in as many as 68% of local recurrences,[14] obtains a similar outcome than for those patients without tumor recurrence after initial resection, with 5-year survival rates ranging from 65% to 80%.[14,50,69] Adjuvant radiation is also feasible.[28,69]

In nonresectable local recurrences, exclusive radiotherapy has been reported as an efficient treatment, especially on pleural recurrences, even if irradiation had previously been delivered. High response rates with 5-year survival rates as high as 80% were obtained in small retrospective series.[28]

Future Directions

The management of thymic tumors is a paradigm of cooperation between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the therapeutic strategy and evaluating the prognosis. As a consequence of their rarity, collaborative studies are warranted to evaluate and improve current therapeutic standards, taking into account recent improvements in techniques, such as robotic surgery, radiotherapy, and supportive treatment. Furthermore, along with the large variety of questions relative to the therapeutic strategy, thymic tumors represent a model of therapeutic implementation and achievement in oncology, showing how the advent of new results induces new questions, as well as diversifies further clinical research directions.

ACKNOWLEDGMENTS

Supported by fellowship awards from the French College of Professors in Respiratory Medicine/Astra-Zeneca, and the French Lilly Institute (to N.G.). The authors thank J. Chmielecki for linguistic review of the manuscript.

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