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Thymoma and thymic carcinomas

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SURGICAL TREATMENT OF THYMIC TUMORS

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Surgery is the mainstay of treatment in the management of thymic tumors, as long as they are completely resected. As a direct consequence, resection should be tailored according to the extent of the disease, which may be preoperatively classified in two different situations: the presence of a small, clinical stage I or II tumor with radiological characteristics of thymoma, and extended tumors suggesting stage III-IV disease and/or thymic carcinoma. These two situations differ in the preoperative, intraoperative and postoperative management.

Preoperative management

It is accepted that in case of isolated mass within the anterior mediastinal space with a radiological aspect suggesting clinical diagnosis of thymoma and without involvement of surrounding organs, a preoperative diagnosis is useless (1). When this strategy is adopted, the risk of performing thymectomy for disease other than thymic tumors (lymphoma, thymic hyperplasia, thymic cyst or other benign disease of the thymus) is in the order of 25% (2), being thymic hyperplasia the most common diagnosis.

Preoperative diagnosis is mandatory in case of unresectable disease, need of neoadjuvant treatment and uncertain differential diagnosis with lymphoma (3). Policies and reporting guidelines for mediastinal mass biopsies has been recently developed by a mixed pathologists and surgeons ITMIG working group (4).

Once completed staging work-up, decision on surgical treatment should be based mainly on two elements: the risk of incomplete resection and the surgical risk for the patient (table 1). Accuracy in the evaluation of both depends on surgeon's experience. In case of resectable disease, surgery is usually the first step of treatment, once that concomitant diseases such as myasthenia gravis have been stabilized. When the risk of incomplete surgery overcomes 30%, a neoadjuvant treatment can be proposed in order to improve R0 resection rate (5,6) in low-

risk patients. Incomplete surgery in high risk patients should be avoided, as debulking procedures are unuseful.

		Surgical risk	
Risk of incomplete resection		Low	High ¹
	Low	Surgery	Surgery
	High ²	Neoadjuvant	Inoperable

Table 1. 1) High surgical risk means an expected postoperative mortality of 10-15%; an higher risk should be considered unacceptable. Every effort should be done to improve conditions which may rise this risk (i.e. MG); 2) higher than 30%.

Intraoperative management

The standard surgical procedure for stage I or II thymic tumor is thymectomy, the removal of the entire thymus gland en bloc with the tumor. Due to the fact that thymic upper poles lye in the neck, for complete thymus removal cervical dissection above the innominate vein should be combined to mediastinal dissection. Additionally, the type of thymectomy may range from complete thymectomy (complete removal of he thymic gland with surrounding fatty tissue, in patients without myasthenia gravis, MG) to extended thymectomy (removal of mediastinal pleura and all the adipose tissue in mediastinal and pericardiophrenic areas), suggested in patients with MG (type C evidence)(7). This attitude is justified by the frequent presence of thymic tissue within mediastinal fat (8), which may be responsible for lack of MG remission or late MG occurrence after surgery.

Standard surgical approach for thymectomy is median sternotomy, allowing both cervical dissection and bilateral pleural exploration in case of tumors extended to the mediastinal

pleura. The development of video-assisted thoracic surgery (VATS)(9,10) and more recently of robotic surgery (11,12) raised the question of utilizing a minimally invasive approach in order to reduce surgical risk (especially in MG patients) and postoperative stay. A minimally invasive resection of thymoma has been recently defined as “any approach as long as no sternotomy (including partial sternotomy) or thoracotomy with rib spreading is involved and in which a complete resection of the tumor is intended”. (type C evidence) (7). Some authors claimed superiority of robotic surgery as compared to VATS (13) or sternotomy (14) in Masaoka stage I thymoma but these retrospective results require further confirmation in controlled trials.

In stage III thymic tumors infiltrating surrounding structures, there is no place for minimally invasive techniques. In this setting, multidisciplinary evaluation is crucial to decide whether a neoadjuvant treatment should precede surgery.

Management of large stage III tumors requires a flexible intraoperative strategy, considering that thymectomy should be performed en-bloc with infiltrated surrounding structures. Sternotomy may be inadequate for surgical exposure and surgical access should be adapted to area of anticipated difficult dissection: sterno-thoracotomy allows proper exposition of lung hylum and superior vena cava in large lateralized tumors meanwhile trans-manubrial approach is required when the origin of the anonymous veins should be exposed. When feasible from a functional point of view, one infiltrated phrenic nerve can be generally sacrificed and diaphragm plication may prevent postoperative eventration (15). Infiltration of the superior vena cava may require tangential resection, patch repair or prosthetic replacement, depending of the extent of the infiltration. The extent of lung resection ranges from atypical resection (tangential infiltration or peripheral lung metastases) to upper lobectomy to pneumonectomy, when the dimension of the tumor preclude proper hilar dissection or transfissural infiltration is present. Pleurectomy may be required when pleural metastases are present. After such combined procedure, postoperative morbidity is usually

proportional to the extent of lung resection (maximal after pleuropneumectomy) and to nerve damage (phrenic, recurrent), particularly when bilateral.

Suspicious lymphnode should be dissected, considering that the risk of nodal metastases in thymoma is around 2% and exceeds 25% in thymic carcinomas and thymic carcinoids (16). For this reason, ITMIG policies suggest to perform a systematic anterior mediastinal node dissection and systematic sampling of appropriate intrathoracic sites (paratracheal, subcarinal, aorto-pulmonary window) in stage III thymoma, adding supraclavicular and lower cervical nodes in case of suspected or known thymic carcinoma (type C evidence)(17).

Radicality of the resection and stage are the main prognostic factors after surgery for thymic tumors. Additionally, most of decisions on postoperative adjuvant treatment will be taken based on these elements. For these reasons, maximal effort should be done to improve precision of pathologist assessment. Therefore, the specimen should be properly oriented and marked intraoperatively and operative report should precise the state of the resection (R0 versus R2), area of adhesions, surrounding resected areas, whether the pleural and the pericardial space were inspected (17).

Pathological staging, adjuvant treatment and follow-up

After surgical resection, three issues should be addressed: a) proper definition of pathological staging and WHO type, b) the need of adjuvant treatment, c) the type of required follow-up

For pathological staging, several staging systems have been proposed (18-21), being the Masaoka-Koga system (19) the recommended one (type C evidence)(22). Modifications from original Masaoka classification mainly regard staging of partial capsular invasion (stage I in the Masaoka-Koga) and the definition of adhesions or microscopic incomplete pleural/mediastinal infiltration as stage IIb (not mentioned in the Masaoka system).

Masaoka – Koga staging system	
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
IIb	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e. pericardium, great vessels, or lung)
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastasis

In order to define the need of adjuvant treatments, three factors are usually considered in deciding for adjuvant radiotherapy: radicality of the resection, stage and histology. In case of incomplete resection, radiotherapy is usually proposed to reduce the risk of mediastinal progression (23-25). More controversial is the use of radiotherapy after complete resection of stage \geq II thymoma, situation in which radiotherapy have been classically proposed in the past (26-29). This attitude has been reported as being unuseful (30) or even detrimental (31,32) by some authors. More recently, it has been proposed that radically resected thymoma stage I and II WHO types A, AB and B1 do not benefit from postoperative radiotherapy and therefore should not be treated (33,34). Decision on adjuvant radiotherapy in higher stages and/or WHO type B2 B3 and C should be based on multidisciplinary evaluation. Even in thymic carcinoma, which is the most aggressive thymic tumor, the role of postoperative radiotherapy remains unclear due to contrasting results from published data (30,35).

Follow up should take into account that thymomas are indolent tumors that may develop recurrences many years after resection. For that reason, annual CT scan is proposed for the first 5 years after surgical resection of stage I-II thymoma. CT is alternated with chest X-ray for the next five years and annually chest X ray is proposed afterwards. In higher stages, incomplete resection or thymic carcinoma, a CT scan every 6 months for the first 3 years is proposed (type C evidence)(36). An alternative strategy is to maintain annual CT scan for life,

the rationale being the peculiar risk in thymoma patients of developing second tumors (15-20%)(37-39) and very late recurrence (40,41).

Results of surgical treatment and prognostic factors

Interpretation of results of surgical management of thymic tumors should take into account three different elements: a) thymic tumors are a rare disease and large series have been collected over a long period of time, during which many aspects have evolved (staging systems, histotype classification, preoperative work-up and surgical techniques; b) thymoma is an indolent disease, therefore survival should be measured with an adequate follow-up (>10 years, type C evidence)(36); c) overall survival may be not the best measure in order to assess the efficacy of surgical resection of thymoma, as less than 50% of recorded deaths are due to the tumor itself (42).

A recent analysis of published evidence on prognosis in thymic malignancies showed that only 3 prognostic factors resulted as being significant in more than 50% of published studies: stage (stage I and II versus others), radicality (R0 versus others) and histology (thymoma versus thymic carcinoma)(43).

In stage I, 10 year survival ranges from 80% to 100% meanwhile in stage II results are more variable (42%-100%)(27,37, 44-53), probably due to the different rate of radical resection (100% in stage I, 88% in stage II)(3). Stage III 10 year survival is in the order of 50%, meanwhile ten year survival in stage IV is around 30% (50,52,53).

The rate of R0 resection varies with stage, been very high in stage I and II, and significantly reduced in stage III (50%) and IV (25%)(3). In advanced stage, a certain variability in the reported R0 resection rate is observed, probably due to different attitudes toward extended resections in different centers. Nevertheless, when a radical resection is obtained, stage III prognosis dramatically improves, reaching stage I prognosis (53,54). A 10 year survival (50%)

can be achieved even in presence of selected cases of stage IV thymoma radically resected by pleuro-pneumonectomy (55).

Histologic WHO subtypes correlate with invasiveness and complete resection. Type A, AB, B1 and B2 type have an homogeneous rate of invasiveness and of complete resection (28%-44% and 88-100% respectively)(56). Thymic carcinoma has a worse prognosis, with a 5 year survival of 35% (57,58), due to its aggressive biological behaviour, translating into high. Invasiveness risk (91%) and low complete resection rate (58%). Type B3 shows the same behaviour of thymic carcinoma in term of invasiveness and complete resection but an intermediate long term survival. Clinical impact of WHO subtyping is limited by only moderate interobserver and intraobserver agreements and by the fact that, when properly sampled, most than 50% of the tumors shows a mixed pattern (59).

Surgical treatment of recurrence

A certain proportion of patients may experience recurrence after surgical resection. In stage I thymoma, recurrence is a rare event (3%), occurring after a mean time of 10 years. As stage increases, the risk of recurrence increases (11% in stage II and 30% in stage III) and time to recurrence shortens (3 years)(42). Most frequent sites of intrathoracic recurrence are mediastinum, pleural and/or diaphragm and the lung. In many cases, treatment options are limited, because radiotherapy has been already administered in an adjuvant setting after the first resection. In some selected cases, these recurrences may be considered for surgery, as long as a radical resection can be anticipated. When a radical resection is achieved (50%), good results can be obtained in terms of long-term survival (31,60-62).

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