Original Article

A decisional diagram for the management of thymomas based on a Tunisian multidisciplinary team's experience and a review of the literature

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ABSTRACT

Background: Thymomas are rare tumors with a challenging management. After a review of the literature, we noticed the absence of a simplified decisional diagram. We aimed to present a scheme for the management of these tumors based on the experience of a Tunisian multi-disciplinary team and a review of the literature.

Patients and Methods: We report a retrospective study 100 thymomas diagnosed between 1994 and 2011. We also performed an exhaustive PubMed research using the keywords: Thymoma, prognosis, management. We noticed, that the most famous studies were reported in the 1990s with most of them being a review of the literature.

Results: The proposed decisional diagram is quite similar to the National Comprehensive Cancer Network (NCCN) guidelines with some particularities. These particularities consist in the recommendation of an initial surgical resection even in advances disease (stages IIIb or IVa) and the association of a radiation therapy in R1 or R2 stages I, II, and IIIa thymomas.

Conclusion: This study highlights the necessity of further research performed in the field of thymoma in order to answer the unresolved question. This work seems to be necessary and helpful in daily practice of thoracic surgeons and clinicians.

Key words: Thymoma, Masaoka's classification, thoracoscopic thymomectomy, mediastinal tumor

Introduction

Thymomas are rare epithelial tumors of the thymus that are considered as malignant tumors because of their tendency to metastasize and recur even in early stages. The most relevant prognostic factors of these tumors are represented by the Masaoka stage, the histological World Health Organization classification updated in 2004 and the quality of the resected margins.[1] The term "thymoma" seems to be quite confusing because of the malignant behavior of these tumors and their nonconsensual management. Through a review of the literature, we noticed how challenging their management is, therefore, we present a decisional diagram useful for clinicians and surgeons based on the literature review and the experience of a Tunisian multidisciplinary team.[2,3]

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Patients and Methods

We report a retrospective management of 100 patients who underwent surgical resection or surgical biopsy in the Department of Thoracic Surgery from 1994 to 2011. The patients selected were those hospitalized during

this period with a diagnosis of thymoma. The diagnosis was made in the Department of Pathology of the same hospital. Clinical records, radiologic features, and follow-up information were retrieved and all the slides were reviewed in the Department of Pathology. The staging of the tumors was based on the Masaoka's classification and the histological classification was based on the World Health Organization (WHO) classification updated in 2004. The mortality of the patients was defined as the death during the operation, during the first 30 days after the operation or during the intervention. For the follow-up period, the date of point chosen was the 31 December 2012. The patients were considered loss of view if they were not reviewed after their discharge.

Statistical methods

Statistical analyses were performed using the 18.0 Statistical Package for Social Sciences (SPSS) version (SPSS Inc, Chicago, IL). The Student's *t*-test was used to compare the means. The Kaplan-Meier method was used to estimate the survival and the survival curves were compared using the log-rank test. The differences were considered statistically significant if $P < 0.05$.

We also made a review of the literature. We noticed that the most relevant studies were performed mainly in the 1990s and that the research reported after this period were mainly reviews of the literature with almost the same studies reported.

Results

Fifty men and 50 women underwent a surgical resection in our department between 1994 and 2011. The mean age of the patients was 51.3 years ±7.3 standard deviation (SD). The delay between the onset of the symptoms and the surgical resection varied from 1to 120 months with a mean of 9 months and a median of 4 months. Thoracic symptoms including chest pain, cough, expectoration, or dyspnea were reported in 62 patients. Myasthenia gravis was reported in 26 patients. Chest X-ray performed in all patients showed a mediastinal mass in 89 (89%) patients, a tracheal deviation in 13 cases, a diaphragmatic ascension in six cases and was normal in 11 patients. Computed tomography (CT) performed in all patients showed a mediastinal mass with a mean size of 8.6 cm. Radiologic findings highlighted the diagnosis of thymoma in 51 cases. The infiltration of the pleura or the pericardium was observed in six patients. Extension to the lung was observed in five patients and infiltration of the mediastinal vessels was observed in two patients. In one patient, the CT showed asuprarenal gland infiltration. According to the Masaoka classification, the 100 thymomas were classified into stage I in 25 cases, stage IIa in 26 cases, stage IIb in 21 cases, stage III in 25 cases, stage IVa in two cases, and stage IVb in one case. According to WHO classification, the thymomas were classified into type A in 14 cases, type AB in 24 cases, type B1 in 17 cases, type B2 in 20 cases, type B3 in eight cases, B1/B2 in eight cases, and B2/B3 in nine cases. Table 1 illustrates the major patients' characteristics.

Treatment modalities

Fourteen patients received a first-line combination chemotherapy regimen consisting of cisplatin, etoposide, and gemcitabine with a mean of four courses (ranged 2-9 courses). These patients had decrease of tumor volume reaching 50% and enabling a surgical resection. A combination of chemotherapy and radiation therapy was performed in two patients. Surgical resection was performed in all patients through a sternotomy in 70 (70%) patients, posterolateral thoracotomy in 19, video-assisted thoracoscopic surgery (VATS) in 10, and mediastinotomy in one. The surgical resection of the tumors was performed in stages I, IIa, or IIb and nine stage III thymomas. Surgical procedure consisted in a total thymectomy including the mediastinal fat in 66% of the patients and a tumorectomy in 34% of the patients. Excision of the adjacent structures was performed in 45% of the patients including the pericardium, the phrenic nerve, the lung, and the tracheocephalic venous trunk. According to the microscopic findings, the surgical resection was classified as R0 in 97/100 patients. One patient presented microscopic invasion of the margins (R1). He presented a stage IIa thymoma and

Table 1: Patients characteristics

Sex	50 male/50 female
Mean age	51.3 (50-59 years)
Symptoms	Thoracic symptoms: 62 patients
	Myasthenia gravis: 26 patients
Radiological findings	Infiltration pleural/ pericardium: 6 patients
	Extension lung: 5 patients
	Extension mediastinal vessels: 2 patients
	Infiltration adrenal gland: 1 patient
Masaoka staging	Stage I: 25 patients
	Stage II: 47 patients
	Stage III: 25 patients
	Stage IV: 3 patients
Microscopic diagnosis	A thymoma: 14 patients
	AB thymoma: 24 patients
	B1 thymoma: 17 patients
	B2 thymoma: 20 patients
	B3 thymoma: 8 patients
	B1/B2 thymoma: 8 patients
	B2/B3 thymoma: 9 patients

died after the operation due to a respiratory deficiency related to a severe myasthenia. The second patient presented a stage III thymoma. The surgical resection consisted of an enlarged thymectomy with resection of the phrenic nerve and the venous tracheocephalic trunk. The resection was incomplete with a gross residual tumor. Radiochemotherapy was given and the patient is still alive. Adjuvant radiotherapy was used in 16 patients; 20% of them underwent a surgical resection: Two patients presented stage I, six stage IIa, four stage IIb, and four stage III. One patient with stage IIa thymoma received second-line chemotherapy. Two patients with stage I Masaoka had a postoperative radiotherapy and chemotherapy. In summary, 48 patients were treated by surgery alone (18 tumorectomies, 30 thymectomies). Twelve patients had first-line followed by a surgical resection and second-line chemotherapy in eight; two patients had a preoperative chemoradiotherapy. Nineteen patients had adjuvant treatment consisting of radiotherapy in 16, chemotherapy in one, and chemoradiotherapy in two.

Follow-up information: Twenty-eight patients died, 15 were lost to follow-up, and 57 patients are still alive. Five patients presented a local recurrence or a metastasis during their follow-up. Two patients presented local recurrences and were initially classified in stage II of Masaoka's classification. The recurrences appeared after 3 years. Three patients with stage II disease presented with pulmonary and pleural recurrences. The mean survival of the patients was 136 months (confidence interval (CI;114-158)). The 1-, 3-, and 5-year survival was estimated to 89, 78, and 67%, respectively. Table 2 illustrates the treatment, stage, and the histologic type of tumors in patients with recurrences.

Discussion

Multivariate analyses revealed that the major prognostic factors of thymomas consist in the Masaoka stage and completeness of surgical resection. The management of thymomas is based on both parameters. According to the National Comprehensive Cancer Network (NCCN) guidelines updated in 2013, surgical resection is recommended in noninvasive thymomas stage I and II and in stages III and IVa in cases of resectable pleural metastases.[1] In stages I, II, and IIIa; postoperative radiation therapy is used in cases of incomplete resection and is still debated in complete resection in stage II thymomas.[1] According to this scheme, many questions remain unresolved. The place of an incomplete resection in invasive thymoma (R1 or R2) is still debated, the place of the radiation therapy in noninvasive tumors is nonconsensual, and the efficacy of a second-line chemotherapy in R1 or R2 tumors has not been clearly established.

We present a diagram in Figure 1 based on our experience and a review of the literature. In this diagram, we emphasize surgical resection as a mainstay in the treatment of thymomas. Stage I tumors are localized, encapsulated without invasion of the capsule. The utility of surgical resection of these tumors has been proved in many studies. In fact, Masaoka reported, in 96 stage I thymomas, a 5-year survival of 96% and a 10-year survival of 66.7% after surgical resection.[2] Detterbeck and Parsons reviewed 10 studies on 2,000 patients and reported a 5-survival without recurrences of 92% and a 10-year survival of 88% in stage I tumors.[3] Stage II tumors are defined by the microscopic or gross infiltration of the capsule. The treatment of these tumors when localized is based on a surgical resection followed by a postoperative radiotherapy. In 2008, Gupta and coworkers reported that there was no significant statistical difference between stage I and II tumors based on the review of 21 studies including 2,451 thymomas classified into stage I in 1,419 cases and stage II in 102 cases.[4] In 2011, Detterbeck and colleagues reviewed all the studies reported between 1980 and 2010, they concluded that stages I and II were noninvasive and were correlated to a better survival and less recurrences than the other stages. Stage III tumors are characterized by the microscopic and macroscopic infiltration of the pleura, the pericardium, the lung, the nerves, or the large mediastinal

Table 2: Recurrences and metastases according to the initial treatment, stage, and the histologic type

Complications	Initial treatment	Stage	Histotype
Local recurrence	First-line chemotherapy –Surgery-second-line chemotherapy	IIa	B3
Local recurrence	Surgery resection	IIb	B1
Pleural recurrence	Surgery and postoperative radiotherapy	IIa	B3
Pulmonary metastasis	Tumorectomy	IIb	B2/B3
Pulmonary metastasis	Surgery and postoperative radiotherapy	IIa	B2/B3

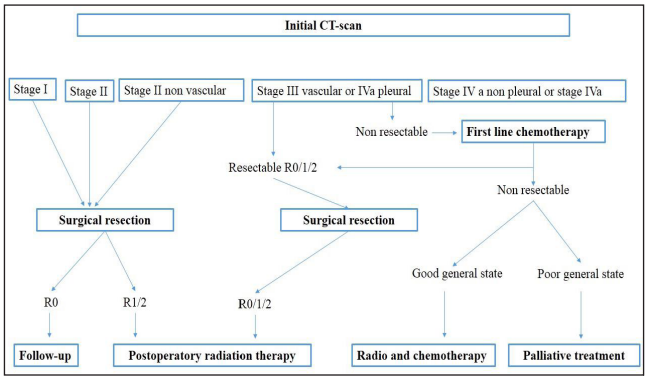

Figure 1: Decisional diagram proposed by our multi-disciplinary team

vessels. Masaoka and coworkers established that in the group of stage III tumors, those with a local infiltration of the pleura, the pericardium or the lung reached a 10-year survival of 97% and a 20-year survival of 75 vs 70% and 29% in case of infiltration of the large mediastinal vessels with a significant statistical difference ($P = 0.003$).[5] This finding induced the use of first-line chemotherapy in the latter in order to reduce the infiltration of the large vessels.[6,7] Stage IVa is characterized by the presence of neoplastic nodules that are independent from the thymoma. Complete surgical resection of these tumors is challenging.[3] This stage is characterized by recurrences reaching 46% and a survival of no more than 10 years in 47% of the cases.[8-12] The treatment of this stage has been based on a palliative chemotherapy because of the indolence of the tumors, but the patients presenting this stage are in their majority young with a good general state. This fact encourages many authors to try a multimodal therapy. Wright and coworkers, treated five patients with stage IVa thymomas with a neoadjuvant chemotherapy followed by a thymectomy with pleuropneumonectomy and an adjuvant therapy.[13] The 5- and 10-year survivals reached 75 and 50%, respectively. Ishikawa and colleagues tried a multimodal treatment in four patients and reported a better survival in comparison with patients treated with palliative chemotherapy alone (75 versus 16% after a 5-year follow-up period).[14] Stage IVb is characterized by distant metastases. This stage has been reported to have a worse prognosis in comparison to the stage IVa, but the studies in the literature remain rare.[11,12] The role of an incomplete surgical resection in advanced thymomas remains debated. Maggi and coworkers and Nakahara and colleagues reported the utility of an incomplete resection in comparison with surgical biopsy alone with a 10-year survival of 39 versus 33%,[2,10-12,15-17] with a significant statistical difference.[10,11] Table 3 illustrates these results in the literature. Kondo and Monden reported a 5-year survival of 93% in patients with complete resection, 64.4% in patients with incomplete resection and 35.6% in patients with biopsy alone[12] with a significant statistical difference between incomplete resection and biopsy alone ($P = 0.002$). In this study, they recommended surgical resection even if a complete resection is impossible. The only study which compared the survival between R1 and R2 group was conducted by Jackson and coworkers and concluded a lower recurrence rate in R1 group (71 versus 36%).[18] In our study, the surgical resection was incomplete in two patients. The patient with R1 resection died because of a complication of myasthenia gravis and the patient with R2 resection received a multimodal therapy and presented no complications. Based on these findings, we recommend surgical resection even if the tumors are advanced. The residual tumor should be as minimal as possible. We noticed in the literature that the authors did not indicate the proportion of the residual tumor. Besides, there is no consensus regarding the adjuvant treatment due to the heterogeneity of the studies reported concerning the stage and the histotypes. In stages III and IVa, there is a consensus about the necessity of the radiation therapy. Its major aim is the prevention of local recurrences. Whereas, it seems nonconsensual in stages II and III. Ten studies demonstrated the inefficiency of postoperative radiation therapy in cases with R0 resection.[8,9,19-24] Besides, Ruffini and coworkers reported more recurrences in irradiated patients.[22] The results of a postoperative radiation therapy following a complete surgical resection are represented in Table 4. In case of incomplete resection, second-line chemotherapy decreases the recurrences. Two studies have proved this fact about invasive thymoma treated by incomplete surgical resection followed by a radiation therapy, but these studies included few patients with a

Table 3: Comparison of survival between incomplete surgical resection and surgical biopsy alone

Authors	*N*	P (R1, R2/biopsy)
Kondo and Monden[12]	260	<0,03
Maggi *et al.*[10]	241	0,001
Nakahara *et al.*[11]	141	<0,01
Mornex *et al.*[18]	90	<0,02
Régnard *et al.*[9]	83	NS
Blumberg *et al.*[8]	118	NS

NS = Non statistically significant

Table 4: Results of the postoperatory radiation therapy (RT) in stage II and III thymoma with complete surgical resection

Authors	*N*		Recurrence rate (%)		Local recurrence rate (%)	
			With RT	Without RT	With RT	Without RT
Monden *et al.*	127	II	8	29		
		III	29	40		
Curran *et al.*	117	II			0	33
		III			0	66,7
Quintanilla-Martinez *et al.*	116	II	23	8		
		III	13	13		
Blumberg *et al.*	118	II				
		III	48	52		
Régnard *et al.*	307	II + III	30 (10 years)	45 (10 years)		
			41 (15 years)	45 (15 years)		
Haniuda *et al.*	89	II	18	23	3,6	17
		III	25	25		
Ruffini *et al.*	310	II	31	4		
		III	64	16		
Kondo and Monden	1093	II	4,7	4,1	0	1,6
		III	23	26	5	3
Mangi *et al.*	155	II	0	2,9		
		III	32	29		

bias of selection.[10,25] In fact, the patients presented with advanced disease.[3,10,25] A third study conducted by Monden and coworkers and including R0, R1, and R2 thymomas reported a lower recurrence rate if an adjuvant therapy was added to the treatment (24 versus 40% on 40 patients).[17] This study included 13 patients with stage IV thymoma and reported a recurrence rate of 44% in case of associating the radiation therapy versus 75% in case of surgical resection alone, but the stages IVa and IVb have not been proposed and the complete character of the resection has not been proved.[17] Arakawa and colleagues reported a study about 15 patients with stage III and IV thymomas treated by an initial surgical resection followed by a radiation therapy. Only two patients (13%) presented recurrences.[26] Few studies tried an initial radiation therapy obtaining a surgical resection in 59 and 75% of the cases.[27,28] Otherwise, the survival of the patients is not better than in case of surgical resection alone reaching 44-48%.

Chemotherapy is indicated in stages III and IV thymomas. In our study, first-line chemotherapy according to the PAVEP protocol was used and a regression of more than 50% was obtained in 86% of the patients. This result may be considered as biased because only patients with limited disease were included. Many studies have proven the improvement of the survival of the patients with a multimodal therapy in stages III and IV.[26,27]

Conclusion

Based on a review of the literature and our experience on the management of 100 thymomas, we present a decisional diagram which is quite similar to the NCCN guidelines with some particularities. These particularities include an initial surgical resection even in advanced disease (stages IIIb or IVa) and the addition of adjuvant radiotherapy in stages I, II, and IIIa thymomas with R1 or R2 resection.

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