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Intuitive evaluation of contemporary management strategies in thymoma — the largest Indian experience

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ABSTRACT

Background: The aim was perusal of the treatment strategies, clinical outcomes and factors impacting these outcomes in thymoma.

Materials and methods: A total of 119 patients diagnosed and treated cases of thymoma, at our hospital, were taken for analysis. Thirty-one patients were excluded due to inadequate medical records. Descriptive statistics were used to report demographic and clinical characteristics. Time period between diagnosis and death was defined as overall survival (OS). Multivariate analysis (MVA), using cox regression modelling, was done by including clinicopathological factors in a bid to identify prognostic factors influencing OS. SPSS version 26 was used for statistical analysis.

Results: The mean age of the patients was 52.17 years and 39 (44.3%), 19 (21.6%), 17 (1.3%) and 13 (4.8%) patients presented with Masaoka stage II, IV, III and I, respectively. Surgery was done in 64 (72.7%) of the patients as a part of the treatment strategy. Radiotherapy was administered to a total of 57 patients with a median dose of 50.4 Gy. Early Masaoka stage at presentation and use of surgery in the treatment plan were statistically significant prognostic factors for a better overall survival on multivariate analysis.

Conclusion: Judicious use of radiotherapy and chemotherapy in locally advanced cases may render them resectable. In a bid to gain good survival rates, aggressive multimodality treatment should be offered to the patients.

Key words: mediastinal tumours; anterior mediastinum; thymoma; Masaoka stage; surgery; chemoradiotherapy

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Introduction

Thymic epithelial tumours (TETs), thymoma, thymic carcinoma and neuroendocrine tumours, though often categorised into orphan tumours, comprise almost 20% of all mediastinal tumours and 50% of anterior mediastinal masses in adult population [1, 2]. Incidence of thymoma is 1.3–3.2 cases per million worldwide, whereas thymic carcinoma is rarer with incidence of 0.2–0.5 per million. Thymomas usually run an indolent course and are usually locally invasive, whereas thymic carcinomas are aggressive and may present with metastatic disease in 7–10% of the patients [3, 4].

Surgery has been the mainstay of treatment, in both early and locally advanced thymomas, with adjuvant radiation and chemotherapy being recommended for invasive thymic malignancies [5]. For unresectable thymic malignancies, chemotherapy and radiotherapy, either in sequential or

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concurrent manner have been given with durable responses reported across literature [6]. The 5-year overall survival rate of around 65% has been documented across literature [7].

Often ignored in oncological research, past decade has seen a reinvigorated interest in thymic malignancies with formation of various collaborative groups like International Thymic Malignancies Interest Group (ITMIG), Japanese Association for Research on the Thymus (JART), the European Society of Thoracic Surgery (ESTS) Thymic Working Group, Chinese Alliance for Research in Thymomas (CHART), and the French Thymic Tumors and Cancer Network (RYTHMIC) which aim to optimize and standardize the care of thymic malignancies [8–11]. Early gains from these collaborations look encouraging, but pending concrete results, the management strategies are predicated on the retrospective series and institutional experiences. Here we report, in a hope to add onto the finite literature, the institutional review of management of thymic malignancies which, to the best of our knowledge, is the largest experience from Indian subcontinent.

Materials and methods

We retrospectively identified 119 consecutive patients diagnosed with thymomas from our institutional database between 1st January 2011 and 31st December 2017, out of whom 88 patients were taken up for this analysis. A nuanced review of the patient records was done to retrieve age, sex, performance status (PS), presence of paraneoplastic syndrome (mainly myasthenia gravis and pure red cell aplasia), Masaoka stage, histology, tumour size, extent of surgical resection, radiation (technique, total dose, dose per fraction, and number of fractions), CCT (regimen, number of cycles), recurrence, progression, and death. Detailed review of the operative notes was done to gauge the gross tumour extension into adjoining structures, and completeness of resection. An assessment of the histopathology reports was done for all patients and the tumours were classified into five World Health Organization (WHO) histopathological classification subtypes [12]. Staging was based on the surgical and pathological criteria as per Masaoka-Koga staging system [13]. The 5-year overall survival was the primary endpoint of our study.

Statistical analysis

Descriptive statistics were reported using percentages and frequencies for categorical variables and median values with interquartile ranges for the continuous variables. Time period between date of diagnosis and date of death was defined to be the overall survival (OS) and death due to any cause was presumed to be due to the disease. Patient related and clinicopathological factors, taken up for univariate analysis (UVA), were analyzed by Kaplan-Meier method for their impact on the OS. Stratified log-rank method (Mantel-Cox), with a p-value < 0.05 set as significant, was used to compare between two factors. For multivariate analysis (MVA), factors showing a trend towards significance (p-value < 0.1) with respect to their impact on OS in UVA were taken. Cox proportional hazards regression modelling method was used for MVA. Relation between two categorical variables was explored using Chi square test. For all statistical analysis purposes, SPSS version 26 was used.

Results

Patient characteristics have been summarized in Table 1. Out of the total of 119 patients registered at our department between 1st January 2011 and 31st December 2017, 88 patients were included in this analysis. The mean age of the patients in the study cohort was 52.17 years (range 2–81 years). Seventy-four patients (84%) were males and 14 patients (16 %) were females. Most of the patients (68%) were of Eastern Cooperative Oncology Group performance status (ECOG PS) 1. The mean duration of symptoms was 2 months. Twenty-one patients had paraneoplastic syndrome (PNS), at the time of presentation, out of whom 16 patients had Myaesthenia gravis (MG) and 5 patients had pure red cell aplasia. Cough was the most common presenting symptom (27.2%) followed by chest pain in 16 patients (26%). Two patients had presented with Superior vena cava obstruction (SVCO). Median volume of the primary tumour was 336 cc and ranged from 26.25 cc to 3509 cc. Masaoka stage II was the most common stage at presentation found in 39 patients (44.3%) followed by stage IV in 19 patients (21.6%), stage III in 17 patients (19.3 %) and stage I in 13 patients (14.8%). Type B2 was the most common histopathological subtype seen in 38 patients (43.2%). Other sub-

Table 1. Clinicopathological characteristics of the entire study cohort

Total number of patients	88	
Age (Range) (in years)	Mean	53.08 (16–81)
Sex	Male	74 (84.1%)
	Female	14 (15.9%)
ECOG PS	1	60 (68.2%)
	2	28 (31.8%)
PNS	Present	21 (23.9%)
	Absent	67 (76.1%)
Myasthenia gravis	16	
Pure red cell aplasia	5	
Median volume of tumour	336 (cc)	
Range	26.25–35.09 (cc)	
Masaoka stage	I	13 (14.8%)
	II	39 (44%)
	III	17 (19.3%)
	IV	19 (21.6%)
WHO histopathology subtype	A	7 (7.9%)
	AB	7 (7.9%)
	B1	14 (16%)
	B2	38 (43.2%)
	B3	22 (25%)

ECOG PS — Eastern Cooperative Oncology Group Performance Score; PNS — paraneoplastic syndrome; WHO — World Health Organisation

types were B3, B1, AB and A seen in 22 (25%), 14 (16%), 7 (7.9%), and 7 (7.9%) patients, respectively, as shown in Table 1.

A total of 64 (72.7%) patients underwent surgery in their management of thymoma and 24 (27.3%) patients did not undergo surgery in any form. Amongst the 64 patients who underwent surgery, 52 (81.2%) patients had R0 resection, 10 (15.6%) patients had R1 resection and the remaining 2 (3.2%) had R2 resection. Of these 64 patients, adjuvant radiotherapy was given in 34, adjuvant chemotherapy in 2, a combination of both adjuvant radiotherapy and chemotherapy in 10 patients, whereas 18 patients received no adjuvant treatment. Amongst the 24 patients in whom surgery was not done, 6 were treated with both radiotherapy and chemotherapy, radical radiotherapy alone was given in 7 patients and chemotherapy alone was given in 11 patients.

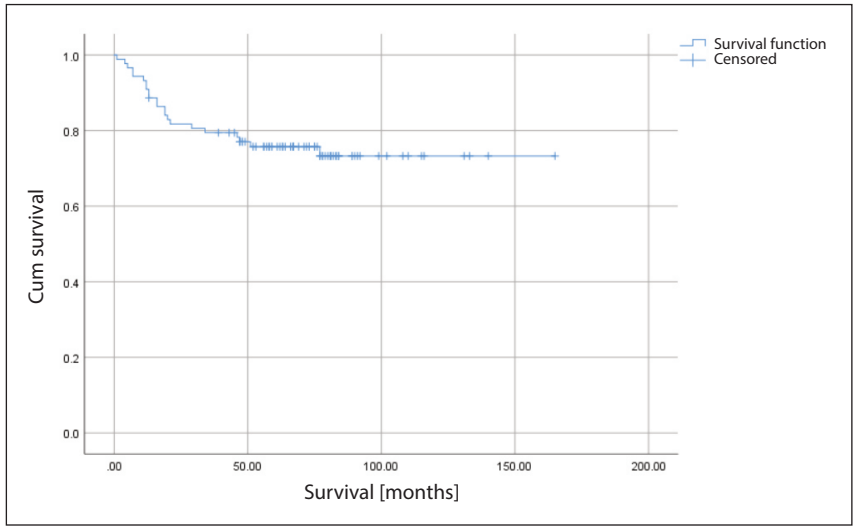
In total, 57 patients received radiotherapy in one of the forms of treatment, either as a single modality or in combination with chemotherapy or surgery. Median radiation dose delivered was 50.4 Gy, with the range of dose being 40–60 Gy. Radiation was delivered daily with a fractionation schedule of 1.8–2.0 Gy per day five days a week. For definitive RT, Clinical target volume (CTV) was generated after giving a cranio-caudal margin of 1.5 cm and radial margin of 0.6cm to the Gross tumour volume (GTV) as seen on the diagnostic and planning scan. For adjuvant RT, CTV was generated after giving 1.5cm cranio- caudal and 0.6cm radial margin to the reconstructed GTV (preop GTV drawn on the planning scan after image registration). CTV was extended to include the post operative changes and clips if the margins given did not include them sufficiently. CTV was cropped from the lungs and heart if there was no invasion of the organs. Planning target volume (PTV) was generated by giving 0.6cm isotropic margin to the CTV. Radiation delivery in all the patients was done through conformal techniques (Intensity modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3DCRT). Out of the total 57 patients who received RT in their treatment course, 41 patients were treated with IMRT and 16 patients were treated with the 3DCRT technique.

Chemotherapy was given to a total of 29 patients. Chemotherapy alone was given to a total of 11 patients which were all metastatic at initial presentation, 12 patients received it in adjuvant setting and in 6 patients it was given in a definitive setting along with radiotherapy. CAP [cyclophosphamide 500 mg/m^2 intravenous (*i.v.*) day 1], doxorubicin (50 mg/m^2 *i.v.* day 1), and Cisplatin (50 mg/m^2 *i.v.* day 1) was the most common chemotherapy regime used. Chemotherapy was administered on a 3-weekly basis and the median number of cycles administered was 4. Treatment details of the study cohort are summarised in Table 2.

Of all the patients who underwent radiotherapy, no grade 3 toxicity was seen amongst them. Most of the patients had grade 2 esophagitis and grade 1–2 pneumonitis and were able to complete the treatment as per the institutional protocol. Haematological toxicities were not available consistently across the electronic records and, therefore, are not reported here. Five-year OS of the patients was 75.7% and median OS was not yet reached in the study cohort, as shown in Figure 1. Out of the total 22 patients that died, 13 patients died from local progression, 5 patients died of local recurrence and 4 patients succumbed to distant metastasis. Out of the 4 patients that died due to metastatic disease,

Table 2. Details of the treatment offered in the study cohort

Surgery	Y/N R0 R1 R2	64/24 52 10 2
Radiotherapy (RT)	Y/N Dose (Median) Dose (Range)	57/31 50.4 Gy 40–60 Gy
Chemotherapy (CT)	Y/N	29/59
Treatment approach		
Surgery alone	18 (20.5%)	
RT alone	7 (7.9%)	
CT alone	11 (12.5%)	
Surgery + RT	34 (38.6)	
Surgery + CT	2 (2.3%)	
Surgery + RT+ CT	10 (11.4%)	
CT + RT	6 (6.8%)	



Mean				Median			
Estimated	S.E*	95% CI		Estimated	S.E	95% CI	
		Lower bound	Upper bound			Lower bound	Upper bound
127.534	6.943	113.925	141.144	–	–	–	–

Figure 1. The Kaplan-Meier survival curve for the entire study cohort with the 5-year overall survival and median overall survival (not reached due to inadequate number of events) along with confidence intervals mentioned towards the bottom of the figure. *S.E — standard error; CI — confidence interval

2 had peritoneal metastasis, 1 had liver metastasis and one had adrenal metastasis.

On univariate analysis ECOG PS ($p = 0.02$), tumour volume ($p < 0.01$), Masaoka stage ($p < 0.01$), surgery done or not ($p < 0.01$), R0 resection margins ($p < 0.01$), giving radiotherapy during treatment ($p = 0.02$) and offering combined treatment modality instead of a single modality ($p < 0.01$), were the factors that were seen to have significant impact on the overall survival. All

these factors which were significant on UVA along with clinically relevant factors were then used for a MVA to see their impact on the overall survival. MVA showed that stage at presentation and use of surgery in the treatment plan remained statistically significant in Table 3.

Table 3. Results of the univariate and multivariate analysis

Survival and prognostic factors			
	5-year survival (%)	UVA P value	MVA P value
Sex			
Male	65	0.732	0.528
Female	70 (p = 0.729)		
Performance score			
1	84.4	0.002	0.548
2	57.1 (p < 0.01)		
Tumour volume			
< 523 cc	77	< 0.01	0.456
> 523 cc	53 (p < 0.01)		
Myaesthenia gravis			
Present	100	0.217	0.955
Absent	68 (p = 0.014)		
Masaoka stage			
I	100		
II	92.2	< 0.01	**0.036**
III	87.4		
IV	12 (p < 0.001)		
WHO pathological type			
A	100		
AB	100	0.563	0.135
B1	64.3		
B2	75.8		
B3	68.3 (p = 0.226)		
Surgery			
Yes	95.3	< 0.01	**0.026**
No	31 (p < 0.001)		
Surgical margins			
R0	98.1		
R1	90	< 0.01	0.378
R2	50 (p < 0.01)		
Radiotherapy			
Yes	85.3	0.02	0.311
No	58.1 (p < 0.001)		
Chemotherapy			
Yes	40	< 0.01	0.961
No	90 (p < 0.01)		
Treatment modality			
Surgery alone	94.4		
Surgery + RT	97	< 0.01	0.516
CT+RT	50		
Surgery +RT+CT	83		
RT alone	50 (p < 0.001)		

UVA: Univariate Analysis; MVA: Multivariate Analysis

Discussion

Thymomas are a rare group of neoplasms constituting around 0.5% of all cancers [1, 2] Thymomas predominantly spread out by local extension and metastasis, if present, is usually confined to the thoracic cavity [3, 4]. In the present study, out of the total of 88 patients, 19 had presented with metastasis and all the metastases were intrathoracic.

Surgery serves the dual purpose of establishing the diagnosis accurately and has a profound therapeutic value. It is prudent that during surgery an extensive exploration around the surgical bed should be undertaken to complete a R0 resection though R2 resection/debulking in large tumors; that has also been shown to have a positive impact on treatment outcomes in a few series [14]. Placing surgical clips around the edges of the surgical bed helps a great deal to delineate the target volume during radiotherapy planning where adjuvant treatment is being contemplated. In the present study, 64 out of total 88 patients underwent surgery at various points in time of their management. Amongst all the patients who underwent surgery, R0, R1 and R2 resection was done in 52 (81.2%), 10 (15.6%) and 2(3.2%) of the patients. The patients who underwent surgery had a 5-year OS of 93% as compared to 21% (p-value < 0.01) for the patients who did not undergo surgery, highlighting that surgery has a significant impact on the overall survival in thymoma patients.

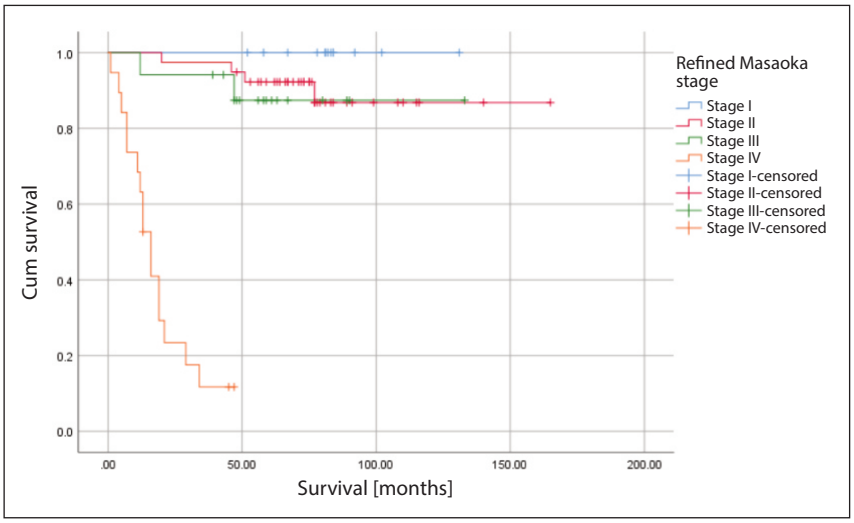
In a patient diagnosed with thymoma, radiotherapy can be offered in preoperative, postoperative and palliative settings. Preoperatively, it is offered to patients who are deemed unresectable or borderline resectable upfront, to make the lesion resectable afterwards. Postoperatively, radiotherapy is given in patients who have undergone R1, R2 resection or in patients with complete resection of the tumour but who had an advanced stage (IIB-IV) at presentation [15]. In our study a total of 57 patients received RT, 44 in the adjuvant setting and 13 patients with the intent being radical (7 upfront and 6 after neoadjuvant chemotherapy).

Radiation induced toxicities mainly depend on the portals used: the larger the portals, the more toxicity is anticipated. With increased use of newer conformal techniques, the radiotherapy volumes have been significantly reduced, thereby bringing down the toxicities. [16] We used intensity modulated radiotherapy (IMRT) or minimum three-dimensional conformal radiotherapy (3DCRT) for treatment planning of our patients and did not encounter any grade 3 odynophagia or pneumonitis.

Chemotherapy has traditionally been used in locally advanced, unresectable or metastatic cases of thymoma in anticipation of downstaging the tumour and making it resectable. [17] Neoadjuvant chemotherapy, in select cases, may help to bring down the size of the tumour so that it can be safely incorporated into radiation portals [18]. The most commonly used chemotherapeutic drugs have been cyclophosphamide, adriamycin, cisplatin, etoposide, taxanes and 5-fluorouracil. The regimens which are currently in wide use are: cyclophosphamide, adriamycin and cisplatin (CAP), etoposide and cisplatin (PE), etoposide, ifosfamide and cisplatin (VIP). Response rates with these drug regimens have generally been good ranging from 30% to 90% [17]. In our study cohort, chemotherapy was utilized in adjuvant (n = 12), definitive setting with radiotherapy (n = 6) and neoadjuvant (n = 11). In the adjuvant setting, two patients were given chemotherapy alone and 10 patients received adjuvant chemotherapy along with radiotherapy after surgical excision. Chemotherapy, when given as part of multimodality treatment strategy in post op setting, was scheduled after completion of radiotherapy.

Concurrent chemoradiotherapy is a viable option in unresectable thymic malignancies and has been shown to induce a durable and complete response in such cases [19]. Six patients in our study group underwent definitive chemoradiotherapy. Among the patients who underwent definitive chemoradiotherapy, three patients were unresectable stage IV and the other three were stage III, of whom one was deemed inoperable and the other two denied surgery. All three patients who had stage IV disease at presentation were dead at the time of reporting of this analysis and the patients with stage III were still alive without disease. Thus, definitive chemoradiotherapy with the latest conformal techniques offers a potentially curable option for unresectable/inoperable thymomas.

Early Masaoka stage at presentation and use of surgery in the treatment plan were the prognostic factors which were statistically significant for a better overall survival as in Figure 2. Patients who



Stage	5 year OS (%)	Log Rank (Mantel Cox)		
		Chi Square	dF	p-value
I	100	88.936	3	**< 0.001**
II	92.2			
III	87.4			
IV	12			

Figure 2. The Kaplan Meier survival curve analysis of the different stages at presentation in the study cohort. The details of the 5-year overall survival (OS) and the relevant Log Rank (Mantel Cox) test details have been summarised in the table below the curve

underwent surgery at some point of their management did significantly better than the others who did not have surgery ($p < 0.001$). Fifteen out of the total 24 patients who did not undergo surgery were diagnosed of stage IVb thymoma, 12 out of these 15received chemotherapy alone and 3 patients who were started on chemotherapy were later deemed amenable for radical radiotherapy. These results were in line with previous studies where these two factors were significant for better overall survival [3, 20, 21].

Thymomas express a distinctive genomic footprint, as among the adult human cancers they have the lowest mutational burden; a distinctive point mutation in the GTF2I gene in WHO type A and AB thymomas; almost characteristic KMT2A-MAML2 translocations in type B2 and B3 thymomas; a YAP1-MAML2 translocation in almost all metaplastic thymomas; and exclusive miRNA profiles in relation to GTF2I mutational status and WHO histotypes [22]. While morphological features continue to be the criteria for diagnosing thymomas, challenging diagnostic situations can be solved on the basis of mutational analyses. Amidst these molecular advancements, biomarkers predictive of response to chemotherapy or targeted drugs remain elusive [23]. Though thymomas elicit a strong expression of PDL1, in spite of this, use of Immune check point inhibitors (ICIs) in management of these malignancies is limited due to heightened risk of immune mediated toxicities caused by unparalleled propensity of thymomas towards autoimmunity [24].

Major strides in molecular field of thymic malignancies are yet to get translated into clinically meaningful outcomes and until then the treatment strategies continue to be driven by the body of evidence generated from retrospective studies and large institutional experiences.

Conclusion

Early stage at presentation and use of surgery in management strategies of thymoma are two sig-

nificant prognostic factors navigating outcomes in a meaningful direction. Sagacious use of radiotherapy and chemotherapy in locally advanced cases may render them resectable. In a bid to gain good survival rates, aggressive multimodality treatment should be offered to the patients.

Ethical permission

Ethical approval was not necessary for preparation of this article.

Conflicts of interest

None declared.

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