Indian Journal of Surgical Oncology (June 2021) 12(2):350–357
https://doi.org/10.1007/s13193-020-01215-2

ORIGINAL ARTICLE

Surgical and Oncological Outcomes in Locally Advanced Thymoma

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Received: 4 July 2020 / Accepted: 8 September 2020 / Published online: 29 September 2020

Abstract

This study aimed at reporting the surgical management of locally advanced thymoma (Masaoka stages III and IVA) and evaluating the factors predicting the survival. This is a retrospective analysis of patients operated for locally advanced thymoma from March 2012 to December 2019 in a thoracic surgery center in India. An analysis of all perioperative variables including complications was carried out. The influence of various predictors on survival was assessed by log-rank test. Out of total 54 patients, 42 (77.8%) had stage III and 12 (22.2%) had stage IVA. Upfront surgery was done in 34 (63%) patients, and induction chemotherapy was given in 20 (37%) patients. Pericardium was the commonest structure resected (79.6%) followed by the lung (51.8%), phrenic nerve (48.1%), major vascular structures (40.7%), parietal pleura (22.2%), diaphragm (9.2%), and right atrial appendage (1.8%). Forty-seven (87%) cases had complete (R0) resection, and the remaining 7 (12.9%) cases had incomplete (R1/R2) resection. There were no perioperative deaths (< 90 days). The median follow-up was 58 months. Overall survival (OS) and disease-free survival (DFS) at 5 years were 77.8% and 75.9%. Higher age (> 60 years), incomplete surgical resection, type B histology, and "> 3" structures resected with tumor were the poor prognostic factors for survival. An aggressive surgical approach, by an experienced team of cardiac and thoracic surgeons, aimed at complete resection is vitally important and can achieve excellent surgical and oncological outcomes even in locally advanced thymomas.

Keywords Locally advanced Thymoma · Masaoka Stage III & IV A · Surgical Outcomes · Survival

Introduction

Thymoma is the commonest anterior mediastinal tumor in adults [1]. It has an indolent behavior and remains localized within the thymus gland. However, few aggressive variants invade the surrounding structures and disseminate to the pleura or pericardium. Modified Masaoka is the most accepted staging method, based on anatomical extent of involvement [2]. Radical resection with negative surgical margins is the key factor influencing the prognosis [3–5]. Extended thymectomy is the recommended procedure which includes the resection of tumor with involved pericardium, lung, phrenic nerve or major vascular structures, the remnant thymus gland, surrounding fatty tissue in the mediastinum and neck, and bilateral pericardial fat pads [6].

Multimodality treatment approach has been recommended for locally advanced thymoma depending on the resectability [7, 8]. Upfront surgical resection is recommended when an R0 resection is considered feasible, based on the extent of disease and the degree of invasion of the tumor into the surrounding structures [9]. Postoperative radiotherapy (PORT) is indicated in all such cases to prevent local recurrence [10]. When complete surgical resection is not considered feasible upfront [11], neo-adjuvant chemotherapy (NACT) is recommended to downstage the tumor, followed by radical surgical resection with PORT/adjuvant chemotherapy [12]. The role of induction radiotherapy (NART) was also evaluated in such situations by few researchers [13, 14]. This study aims at presenting the surgical and oncological outcomes of locally advanced thymoma at our center.

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Material and Methods

Study Population

This retrospective analysis included patients treated for Locally Advanced Thymoma (Masaoka Koga stage III—IVA) from March 2012 to December 2019 at Department of Thoracic Surgery in a tertiary referral center in New Delhi, India.

Pre-operative Evaluation

After detailed history and physical examination, contrast-enhanced computed tomography (CECT) of chest was performed to assess the disease extent. Chest CT angiography was done in patients with suspected involvement of vascular structures. We do not perform PET-CT scan routinely for evaluation of thymoma. Pre-operative computed tomography/ultrasound guided biopsy was done in all cases. Myasthenia gravis (MG) was always ruled out by anti-acetylcholine esterase antibody levels in the blood and a repetitive nerve stimulation test. Neo-adjuvant chemotherapy was advised when complete surgical resection was not considered feasible. Three to four cycles of cyclophosphamide, cisplatin, and doxorubicin were used in standard dosages. Treatment response was assessed by WHO criteria and categorized into complete remission (CR), partial response (PR), or progressive disease.

Surgical Technique

All patients who underwent resection were operated by either a robotic-assisted thoracoscopic surgery (RATS) or a mid-sternotomy or sterno-thoracotomy decided on individual case basis. The institutional decision process regarding the surgical approach is summarized in Image 1. The tumor mobilization was always performed by "No-touch technique" with en bloc removal of all invaded structures. We strictly followed the norm "when in doubt, take it out," wherein, no attempt was ever made to separate the structures adherent to the tumor, but resected en bloc with the tumor. Painstaking efforts were made in all the cases to resect all visible tumor as far as possible and achieve R0 resection. RATS resection was attempted with a very low threshold for conversion in case the oncological goal of R0 resection was doubtful.

- Pericardial involvement—The tumor was resected en bloc with the pericardium keeping a margin of over 2 cm from the periphery of the tumor. The pericardial defect was always closed with vicryl mesh.

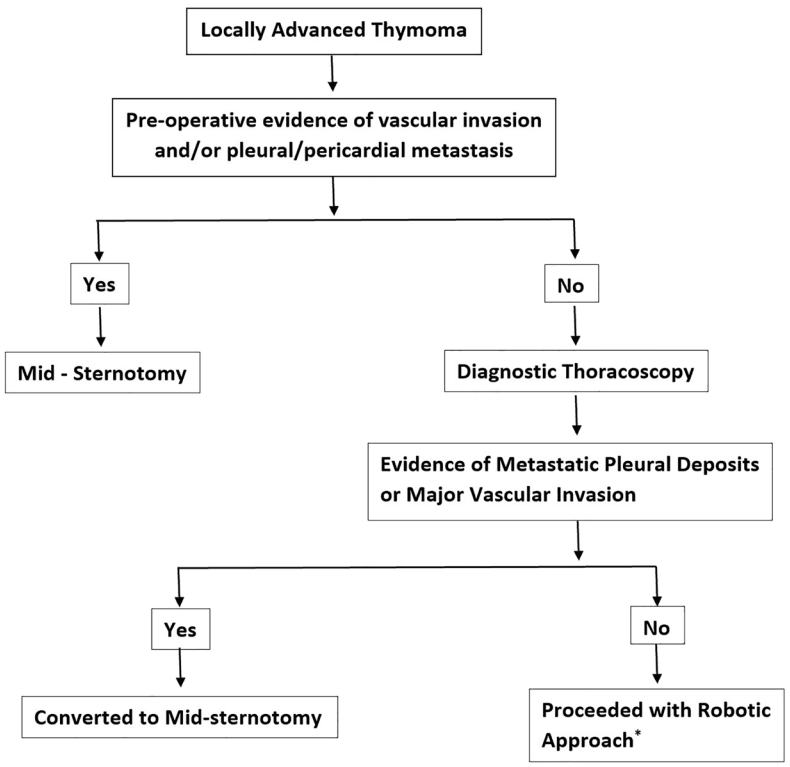

Image 1 Institutional protocol showing operative decision-making

- Lung involvement—An in-continuity wedge resection, lobectomy, or pneumonectomy was performed depending on the extent of lung involvement and patient's fitness.
- Phrenic nerve involvement—Phrenic nerve was resected in continuity with the tumor and the pericardium only when the involvement was unilateral, and trying to save the nerve would have meant R1 resection instead of a clear R0 resection. After phrenic nerve resection, ipsilateral diaphragm was always plicated. In bilateral phrenic nerve involvement, both the nerves were preserved, the tumor was shaved off the nerve surface, and titanium clips were placed close to the residual tumor (not on the nerve) to guide the radiotherapist to especially target the area during adjuvant radiotherapy.
- Brachiocephalic vein (BCV) involvement—If either of the BCV was involved, the same was resected in continuity, without any reconstruction, as the opposite patent BCV takes over the venous drainage.
- Superior vena cava (SVC) involvement—If the extent of resection was < one-third of total circumference, the defect was repaired primarily. In > one-third of circumferential resection and > 2 cm of longitudinal resection, a straight or Y-shaped polytetrafluoroethylene (PTFA) graft was used for reconstruction.
- Right atrial involvement—In cases where the tumor was infiltrating the right atrial appendage, resection was done in continuity and primary closure was done.
- Ascending aorta involvement—In cases where tumor was infiltrating the aorta, it was carefully shaved off from the aorta, leaving as little tumor tissue on aorta as possible and titanium clips were applied on the aortic adventitia around the residual tumor to guide the postoperative radiotherapy.
- Pleural deposits—Complete parietal pleurectomy was performed, and in patients with deposits over visceral pleura, a wedge resection, lobectomy, or pleuro-pneumonectomy was performed depending upon extent of lung involvement, to achieve R0 resection.
- Diaphragmatic deposits—In cases of tumor deposits over the diaphragm, full thickness resection of the same with 1 cm circumferential margin was performed and the resultant defect in the diaphragm was closed primarily.

Postoperative Care

All patients were shifted to ICU for overnight observation. Early ambulation, oral nutrition, and aggressive chest physiotherapy were initiated from the first postoperative day. Effective pain relief was achieved by epidural analgesia supplemented by intravenous medications. The chest drains were removed when there was no air leak; the drainage was not purulent/hemorrhagic and was less than 100 ml in 24 h. The duration of chest tube, hospital stay, and other complications were monitored and recorded.

Adjuvant Radiotherapy

Indications for adjuvant radiotherapy included all microscopic positive and incomplete (R1/R2) resections (irrespective of type of histology), patients with pleural metastasis, and all B2/B3 tumors (irrespective of status of resection). These were the indications in 41 patients who received adjuvant radiotherapy.

Follow-up

First follow-up was done at 1 month from discharge. Further follow-up protocol included CECT chest every 6 months for 2 years and then annually for next 10 years.

Statistical Analysis

Statistical analysis was carried out using Stata 14.0 software (StataCorp LLC, TX, USA). Continuous variables were presented as mean with standard error (SE). Categorical variables were expressed as frequencies with percentages. Student's T test was used to compare the normally distributed continuous variables, whereas Mann-Whitney U test was used to compare non-normal distribution continuous variables. Chi-squared test or Fisher's exact test was used to compare nominal categorical data. Survival was assessed by the Kaplan-Meier method. Overall survival (OS) was calculated from the date of surgery to the date of death due to any cause. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence or death due to any cause. OS was calculated on the entire study population, whereas DFS was evaluated in patients who had undergone only complete resection. Differences between survival rates were assessed by using log-rank test. For all statistical tests, a p value less than 0.05 was taken as "clinically significant."

Results

Demographic Characteristics

Out of 54 patients with locally advanced thymoma, 42 (77.8%) had stage III disease and 12 (22.2%) had stage IVA disease. There were 38 males (70.5%) and 16 females (29.5%), with a mean age of 51.3 years (range, 18–74 years). Twenty-six patients (48%) had myasthenia gravis (MG) associated with thymoma. Based on the pre-operative imaging, 34 (63%) patients underwent upfront surgery, whereas 20 (37%)

patients were given NACT. All 20 patients, who were given NACT, tolerated the procedure well. All had partial response and had 100% conversion rate from initial unresectable stage to resectable stage (Table 1).

Perioperative Variables

Twenty-eight (51.8%) patients underwent surgery through median sternotomy approach, whereas sterno-thoracotomy and robotic-assisted thymectomy were used in 16 (29.5%) and 10 patients (18.5%), respectively. There were no conversions in robotic group. Mean tumor diameter was 8.8 cm. Complete radical resection (R0) could be achieved in 47 (87%) cases, 2 cases (3.7%) had R1 resection, and the remaining 5 (9.2%) cases had R2 resections. Out of the five R2 resections, 2 patients had 1 × 1 cm area of tumor infiltration into ascending aorta, which was shaved off, leaving minimal disease on the wall, and 3 patients had tumor involving both the phrenic nerves; hence, nerve resection was not done and the tumor was carefully shaved off both the nerves and titanium clips placed nearby to aid in targeted radiotherapy. Two patients had microscopically positive pericardial margin. None of our patients had involvement of main pulmonary artery.

Pericardium was the commonest structure resected en bloc with the tumor (79.6%). Lung resection was done in 28 cases (51.8%), which was wedge resection in 21 patients (38.9%), lobectomy in 5 patients (9.2%), and pneumonectomy in 2 patients (3.7%). Both these were pleuro-pneumonectomy in view of the presence of tumor nodules over the visceral pleura. Phrenic nerve resection was required in 26 patients (48.1%), right nerve in 11 patients (20.3%), and left nerve in 15 cases (27.8%). The resection of brachiocephalic vein (right or left) was done in 18 (33.3%) cases, whereas SVC resection and reconstruction were done in 10 cases (18.5%). In 1 case (1.8%) of SVC involvement, tumor was also infiltrating the right atrial appendage, which was also resected en bloc with the tumor. Complete parietal pleurectomy was performed in 12 cases (22.2%) in view of pleural deposits. In 5 of these patients (9.2%) with diaphragmatic deposits, localized diaphragmatic resection was also performed and the resultant defect was closed primarily in all such cases. In two cases (3.7%), tumor was infiltrating the ascending aorta, which was closely shaved off leaving a small amount of tumor tissue left. Titanium clips were placed over the residual tumor, and adjuvant radiotherapy was given in postoperative period, and even after 70 months of surgery, both of these patients are still disease-free. We routinely perform lymph node dissection in every thymectomy. We dissect and label them into superficial/anterior group of lymph nodes (low anterior cervical, perithymic, pre-vascular, para-aortic, and supradiaphragmatic nodes) and deep nodes (internal mammary and paratracheal nodes). However, in none of the tumors, there was lymph node metastasis. Mean operative time was 222 min, and mean blood loss was 298 ml.

Table 1 Demographic details and perioperative outcomes in the study population

	Number of patients
Male (%)	38 (70.5%)
Female (%)	16 (29.5%)
Age in years (mean ± SE)	51.3 ± 2.1
Patient comorbidities	
Yes	20 (37%)
No	34 (63%)
Duration of symptoms in months (mean ± SE)	5.5 ± 1.4
Maximum dimension of the lesion in cm (mean ± SE)	8.8 ± 0.4
Myasthenia gravis	26 (48%)
Pre-operative chemotherapy	20 (37%)
Surgical approach	
Median sternotomy (%)	28 (51.8%)
Sterno-thoracotomy (%)	16 (29.5%)
Robotic (%)	10 (18.5%)
WHO histology	
Type A (%)	4 (7.4%)
Type AB (%)	6 (11.1%)
Type B1 (%)	5 (9.2%)
Type B2 (%)	13 (24%)
Type B3 (%)	26 (48%)
Type of structures resected (in order of frequency)	
Pericardium (%)	43 (79.6%)
Lung (%)	28 (51.8%)
Wedge resection	21 (38.9%)
Lobectomy	5 (9.2%)
Pneumonectomy	2 (3.7%)
Phrenic nerve	26 (48.1%)
Right	11 (20.3%)
Left	15 (27.8%)
Great vessels	22 (40.7%)
Right brachiocephalic vein	5 (9.2%)
Left brachiocephalic vein	18 (33.3%)
SVC	10 (18.5%)
Parietal pleura	12 (22.2%)
Diaphragm	5 (9.2%)
Right atrial appendage	1 (1.8%)
Number of additional structures resected	
1 (%)	5 (9.2%)
2 (%)	12 (22.2%)
3 (%)	12 (22.2%)
4 (%)	11 (20.3%)
5 (%)	9 (16.7%)
6 (%)	3 (5.5%)
7 (%)	2 (3.7%)
Completeness of resection	
R0 (%)	47 (87%)
R1 (%)	2 (3.7%)

Table 1 (continued)

	Number of patients
R2 (%)	5 (9.2%)
Masaoka stage	
III (%)	42 (77.8%)
IVA (%)	12 (22.2%)
Perioperative outcomes	
Operative time (mean ± SD) in minutes	222 ± 101
Mean blood loss (mean ± SD) in ml	298 ± 222
Conversions (in robotic group)	Nil
Postop ICD duration (in days) (mean ± SD)	5 ± 3.2
Hospital stay (in days) (mean ± SD)	9.7 ± 2.4
Postoperative complications (%)	19 (35.1%)
Atrial fibrillation	4 (9.2%)
Pleural re-collection	3 (5.5%)
Wound infection	3 (5.5%)
Myasthenic symptoms aggravation	2 (3.7%)
Stroke	2 (3.7%)
Bleeding	2 (3.7%)
Chylous leak	2 (3.7%)
Acute cardiac herniation	1 (1.8%)
Postoperative radiotherapy	41 (76%)
Perioperative mortality (< 90 days)	Nil

Postoperative complications occurred in 35% of patients, which included atrial fibrillation (4 patients), postoperative pleural collection (3 patients), wound infection (3 patients), myasthenic symptom aggravation (2 patients), stroke (2 patients), postoperative bleeding (2 patients), chylous leak (2 patients), and acute cardiac herniation (1 patient). Myasthenic symptom aggravation was managed by neurologists with upgrading of medications. No patient developed myasthenic crisis. Pleural collections were managed with ultrasound guided pig tail catheter insertion. Out of 2 patients with chylous leak, one was managed conservatively with medium-chain triglyceride diet and injection octreotide therapy, whereas another patient required thoracoscopic thoracic duct ligation. Type B3 (48%) thymoma was the commonest histological variant (Table 1).

Survival Analysis

There were no perioperative deaths (< 90 days) in the study population. The median follow-up duration was 58 months. During this follow-up, there were 12 deaths (22.2%). Two patients had recurrence (1 local recurrence and another systemic recurrence). Out of the 12 deaths, 3 were due to myasthenic crisis, whereas dengue shock syndrome, massive intracranial bleed, fungal sepsis, and tumor recurrence were the causes in 1 patient each and in the remaining 5 cases, the cause cannot be ascertained.

Overall survival (OS) and disease-free survival (DFS) at 5 years was 77.8% and 75.9%. On testing the equality of survival functions by log-rank test, type B histology, higher number of additional structures resected with tumor (> 3), age > 60 years, and positive resection margins were poor prognostic factors and the administration of neo-adjuvant chemotherapy was a good predictor for overall survival (Image 2). However, multimodality therapy (NACT or adjuvant RT) did not show any benefit as far as DFS was concerned (Image 3) (Table 2).

Discussion

The evaluation of surgical and oncological outcomes in locally advanced thymoma is challenging due to variability in clinico-pathological behavior of the tumor and heterogeneity in the treatment protocols. Despite advances in chemotherapy and radiotherapy, radical surgical resection remains the cornerstone of management even in locally advanced thymoma [15]. It can provide excellent long-term survival, if complete resection can be achieved at surgery. Unfortunately, sometimes, these resectable patients are deemed unresectable, denied surgery, and sent for chemoradiation alone, leading to poorer outcomes. These locally advanced tumors require specialized skills and a teamwork involving thoracic and cardiac surgeons, experienced anesthetists, neurologists, and medical and radiational oncologists to provide excellent surgical and long-term oncological outcomes.

In ideal situations, pre-operative CT scan should characterize the tumor to identify the patients at risk of an incomplete resection [16]. In reality, the CT findings in locally advanced thymoma in relation to the involvement of surrounding structures (pericardium, lung, major vascular structures) may be exaggerated leading to false labelling of potentially "resectable" tumors as "unresectable." This is due to the inherent technical limitations of the CT scan, where the absence of fat plane between tumor and an underlying structure is interpreted as involvement. In reality, many a time as experienced by us over last two decades, the loss of plane more often than not means a close contact rather than involvement or infiltration.

In the earlier published series, pericardium was reported to be the commonest structure resected en bloc with the tumor followed by brachiocephalic veins (i.e., 8.9–24.8%) [17]. The rate of radical resection in Masaoka stages III and IVA is highly variable in the published studies. In a multicenter trial in Masaoka stage III patients, macroscopically complete surgical resection (R0) was achieved in 81.6% patients, R1 resection in 10.4% of patients, and R2 resection in 8% patients [7]. The results of R0, R1, and R2 resections in our study were similar to the published literature.

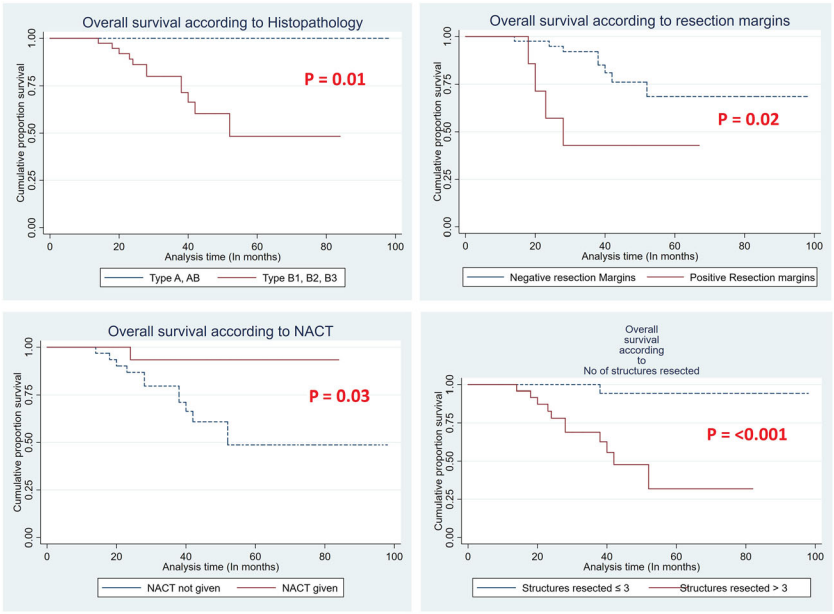

Image 2 Kaplan-Meier graphs: analysis of overall survival (OS)

All patients with suspected vessel involvement were posted with cardiopulmonary bypass on standby in the operation theater. We were able to resect and reconstruct all the cases of SVC and atrial involvement without requirement of cardiopulmonary bypass, except in only one patient. The aggressive approach and readiness to put the patient on CPB, if necessary, allowed us to completely resect the tumor with great vessel involvement in all but 2 cases. In these 2 cases, tumor was infiltrating the aortic wall and all except a thin sliver of tumor tissue was left behind leading to R2 resection. All these patients received adjuvant radiotherapy guided by the clips placed intraoperatively. The value of "completeness of resection" as a prognostic factor affecting the overall survival (OS) was reconfirmed in our analysis too. Many previous studies also reported incomplete resection to be a predictor of poor prognosis [18–22].

Out of 54 locally advanced tumors in our series, 20 received tri-modality therapy (NACT+ surgery + adjuvant RT), 21 patients received bimodality therapy (surgery + adjuvant RT), and 13 patients received only surgery. We give 3–4 cycles of chemotherapy (combination of cisplatin, adriamycin, and cyclophosphamide) before the surgery in upfront unresectable tumors. After 3–4 cycles, we repeat the CT chest to re-assess the tumor and take up the patient for surgery. After surgical resection, all these patients were given adjuvant

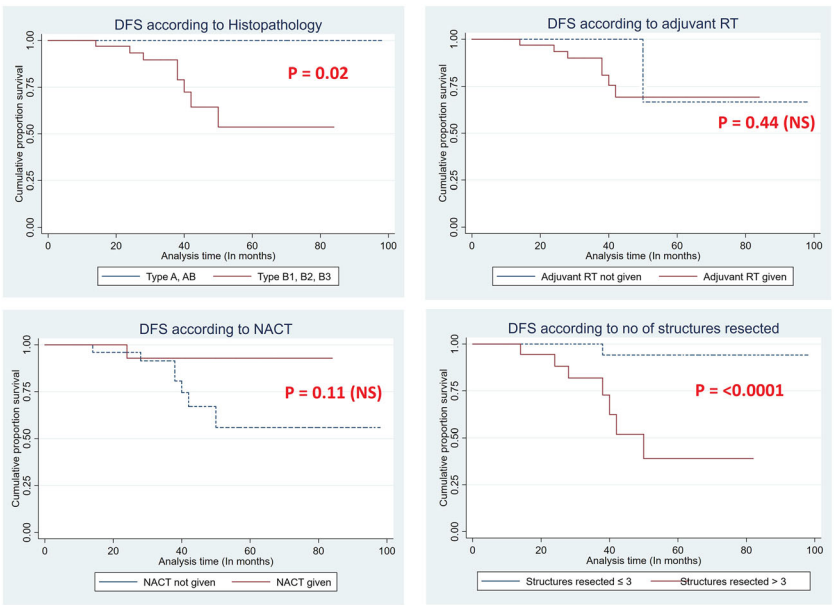

Image 3 Kaplan-Meier graphs: analysis of disease-free survival (DFS)

Table 2 Log-rank test analysis of variables affecting survival

Variables	Characteristics	Overall survival (OS)		Disease-free survival (DFS)	
		No. of patients	*p* value	No. of patients	*p* value
Sex	Male	38	0.65	36	0.66
	Female	16		11	
Age	< 60 years	38	*0.0007*	35	*0.004*
	≥ 60 Years	16		12	
Comorbidities	Yes	20	0.58	16	0.51
	No	34		31	
Myasthenia gravis	Present	26	0.77	21	0.69
	Absent	28		26	
Number of additional structures resected	≤ 3	29	*0.0004*	28	*0.002*
	> 3	25		19	
Incomplete resection	Yes	7	*0.02*	-	-
	No	47			
Neo-adjuvant chemotherapy	Yes	20	*0.03*	19	0.11
	No	34		28	
Histopathology	A, AB	10	*0.01*	10	*0.02*
	B1, B2, B3	44		38	
Adjuvant radiotherapy	Yes	41	0.41	37	0.44
	No	13		10	

The P values which were significant (<0.05) were italicized.

radiotherapy, based on the criteria mentioned earlier. The dose of adjuvant radiotherapy was between 45 and 50 Gy for R0 resections, 54 Gy for R1 resections, and up to 56–60 Gy for R2 resections. The role of neo-adjuvant chemotherapy and adjuvant radiotherapy in locally advanced thymoma was evaluated by many studies, and they found definite survival benefit with this multimodal management [23–26]. Similar to these results, our study also revealed NACT as a favorable prognostic factor for OS; however, adjuvant radiotherapy failed to reveal significant survival benefit. This may be due to shorter follow-up duration where the actual benefit of adjuvant radiotherapy did not start to show-up.

In our study, type B histology and higher (> 3) number of structures resected were found to be poor prognosticator for OS and DFS. This can be explained by the more aggressive nature of the tumor. Similar observation was reported by Cardillo et al. in a study of 61 locally advanced thymomas [27]. We also evaluated "age" as a prognostic factor and found that age > 60 years was an adverse prognostic factor. Similar observations were reported earlier that along with tumor characteristics, patients age and surgical factors may also play a significant role in the prognosis of these patients [28].

Retrospective nature was the major limitation of this study which can cause selection and treatment bias. Another drawback has shorter follow-up time. Due to the indolent nature of the thymoma, at least 10 years of follow-up is required to evaluate any therapeutic option appropriately. So, multicentric prospective studies with longer follow-up are recommended for further assessment of factors predicting survival in this rare clinical entity.

Conclusion

In conclusion, this study found age > 60 years, incomplete surgical resection, type B WHO histology, and greater number (> 3) of additional structures resected with tumor to be poor prognostic factors for survival in locally advanced thymoma. Neo-adjuvant induction chemotherapy should be utilized in patients considered unresectable upfront. In addition, the need for an aggressive surgical approach aimed at complete resection by an experienced team at a high-volume center cannot be overemphasized for improved surgical oncological outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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