Long term survival and prognostic factors for Thymoma and Thymic carcinoma. Results from a tertiary care center

Binay Thakur[1], Sun Zhenqing[2], Sagar Khatiwada[1], Manoj Tiwari[1], Shachee Bhattarai[1], Shashank Shrestha[1], Ashish Kharel[1], Mahesh Mani Adhikari[1], Asha Thapa[3]

[1]Department of Surgical Oncology. BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal.
[2]Thoracic Department of the Affiliated Hospital of Hebei University, China
[3]Bharatpur Hospital Nursing College, Nepal.

Abstract:

Background: Thymomas and thymic carcinoma are rare tumors though thymoma is the most common anterior mediastinal neoplasm. We aimed to determine the long-term survival after thymectomy and also to identify the poor prognostic factors of survival.
Methods: A retrospective analysis of tumors with the final diagnosis of thymoma or thymic carcinoma (n = 42) was done. Upfront surgery or a multimodality approach was used depending upon Masaoka-Koga stage. Statistical analysis was done using SPSS 26.0
Results: Median survival was 144, 97, 123, 45, 19 and 20 months in Masaoka-Koga stages 1, 2a, 2b, 3, 4a and 4b, respectively ($p < 0.001$). Median survival and five-year overall survival (OS) were 86 months and 60%, respectively. Median OS was 125, 25 and 24 months for R0, R1 and R2 resections, respectively ($p < 0.001$). Median OS was 123 months in no-tumor spillage group vs 24 months in tumor spillage group ($p < 0.001$).
Conclusion: Masaoka-Koga stage, resection status and intraoperative tumor spillage are the most important predictors of long-term survival.

Key words: Thymoma, classification, surgical resection.

Introduction:

Thymoma and Thymic carcinoma arise from thymic epithelium and are rare tumors. However, Thymoma is most common cause of anterior mediastinal mass in adults.[1] It accounts for 20% of all mediastinal neoplasms and 50% of all anterior mediastinal masses in adults.[2] The current 2021 WHO classification is worldwide accepted and thymomas are classified into types A, AB, B1, B2, B3 and C. Type C indicates thymic carcinoma.[3] Although thymomas can spread locally, they are much less invasive than thymic carcinoma.[4] Complete surgical resection is the preferred treatment. Invasive disease

Correspondence
Dr Binay Thakur . Dept. of Surgical Oncology (Thoracic Unit), BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal. Email: binaythakur@hotmail.com. Phone: +977-9855055931

warrants additional therapies (chemotherapy and radiation therapy).[5,6]

Out of the various staging systems, Masaoka-Koga system is generally used by surgeons for its simplicity.[7,8] Thymomas have excellent 5-OS rates of approximately 90%.[9] However, 5-OS for thymic carcinomas are approximately 55% (stages I-II: 91%; stages III-IV: 31%).[10,11] R0 resection is the most important prognostic factor.[9] Only few reports have been published regarding thymic tumors in Nepal. However, there are no published results of survival for thymic malignancies in Nepal. In the present study, we analyzed the treatment modality, long term outcome and prognostic factors of thymoma and thymic carcinoma.

Methodology:

A retrospective review of the patients with a final diagnosis of thymoma or thymic carcinoma was included in the study. This study was conducted at Thoracic Unit of BP Koirala Memorial Cancer Hospital (BPKMCH) during 2000-2019. Ethical approval was taken from Institutional Review Committee of BPKMCH. Individual consent was waived because of retrospective nature of the study.

Patients: patients who had anterior mediastinal mass at thymic bed in CT chest and who had normal tumor markers e.g. AFP and B-HCG were assumed to have thymic tumors. Patients with resectable tumors underwent upfront surgery. Those who had locally advanced disease (unresectable/ invasion into major intrathoracic organs) underwent tru-cut biopsy for confirmation of thymic neoplasms and were considered for preoperative treatment (chemotherapy/ chemoradiation therapy). Patients with stages III-IV or R1/ R2 resection were advised and considered for post-operative RT/ chemoradiation. Only those patients who had histopathological confirmation of thymoma or thymic carcinoma were included in the study. Patients who were lost to follow up were excluded from the study.

Surgical procedure:

Depending upon the location, size and extent of tumor, the following surgical procedures were performed:

1. Open
    a. Median sternotomy
    b. Right or left thoracotomy
    c. Clamshell thoracosternotomy
2. Video-assisted thoracoscopic surgery (VATS)
    a. Right VATS
    b. Left VATS

During VATS, one 10 mm optical port and two 5 mm working ports were used with CO2 capnothorax of 6-8 mm Hg. At the end, a utility incision was made for retrieval of specimen.

Patients were followed up for a minimum of 5 years. For the first two years, they were evaluated every 4 months and for the next 3 years, they were followed up every 6 months. CT chest was obtained annually.

Statistical analysis:

SPSS version 26.0 was used for statistical analysis. Categorical variables were compared using the Chi square test, and continuous data were analyzed using the Mann–Whitney U test. Survival was estimated using Kaplan–Meier survival

curves and compared using the log-rank test. P<.05 was considered significant.

Results:

Forty-nine patients underwent thymectomy since 2000-2019. Seven patients were lost to follow-up; hence forty-two patients were included in the study. Demographics and clinical findings have been shown in Table 1.

Table 1. Basic parameters.

Parameters	n=42
Male	27 (64%)
Female	15 (36%)
Mean age	44 years
Presentation: Cough Hemoptysis SVC obstruction Myasthenia Gravis Asymptomatic	 29 (69%) 5 (12%) 5 (12%) 2 (5%) 13 (30%)
Mean post-operative stay	8 days
Intra-operative blood loss	160 ml
Intra-operative blood transfusion	0 ml
Operative time	115 min
Mean tumor size	12 cm

Various treatment and surgical approaches have been shown in table 2 and 3, respectively.

In 28 patients (67%), adjacent structures, namely wedge of lung (7%); pericardium and pleura (10%); pericardium, lung, pleura (19%); and pleurae (31%) needed to be divided due to local invasion by the tumor. In two of the above cases (5%), unilateral phrenic nerve needed to be divided. In three patients (7%), multiple lung metastases were detected during surgery (IVb Masaoaka Stage).

Table 2. Treatment approaches.

Approaches	n=42
S*	17 (40.5%)
S-CTRT/ RT†	8 (19%)
CT-S-CTRT/ RT‡	6 (14%)
CT-S§	4 (9.5%)
CTRT-S‖	3 (7%)
CT-S-CT¶	2 (5%)
S-CT**	2 (2%)

* Surgery

† Surgery - chemoradiation/ radiation

‡ preoperative chemotherapy - surgery - chemoradiation/ radiation

§ preoperative chemotherapy - surgery

‖ preoperative chemoradiation - surgery

¶ preoperative chemotherapy - surgery - postop chemotherapy

** surgery - postop chemotherapy

Table 3. Surgical approaches.

Approach	n=42
Median sternotomy	27 (64%)
Thoracotomy Right Left	5 (12%) 4 (9.5) 1 (2.5)
VATS Right Left	8 (19%) 7 (16.5%) 1 (2.5%)
Clamshell	2 (5%)

Intra operative tumor spillage/ rupture happened in 8 (19%) of patients. R0, R1 and R2 resections were achieved in 32 (76%), 2 (5%), and 8 (19%) cases.

Final staging (Masaoka-Koga) and histological subtypes along with median survivals have been shown in tables 4 and 5.

Table 4. Masaoka-Koga staging.

Stage	n	%	Median survival (months)	p
1	8	19	144	< 0.001
2a	2	4.8	97	
2b	9	21.4	123	
3	18	42.9	45	
4a	2	4.8	19	
4b	3	7.1	20	

Table 5. WHO types.

Type	N	%	Median survival (months)	p
A	7	16.7	158	< 0.001
AB	11	26.1	86	
B1	10	24	203	
B2	3	7	29	
B3	4	9.5	28	
C	7	16.7	25	

Median OS for the whole group was 86 months with 5-OS of 60%.

Kaplan-Meier survival curves showing OS, stage vs survival, WHO type vs survival, intra operative tumor spillage vs survival and resection status vs survival have been shown in figures 1,2, 3, 4 and 5, respectively. Median survival for tumor spillage and positive resection margins has been shown in table 6. Median survival was 124, 25 and 24 months for R0, R1 and R2 resection, respectively (p <0.001). Similarly, intra operative tumor spillage had poor median survival of 24 months in comparison to 123 months in no spillage group (p < 0.001).

Table 6. Positive margin and intra operative tumor spillage.

Parameter	Median survival (months)	p
Resection status		<.001
R0	125	
R1	25	
R2	24	
Tumor spillage		<.001
No	123	
Yes	24	

Fig. 1. Kaplan - Meier curve. Overall survival.

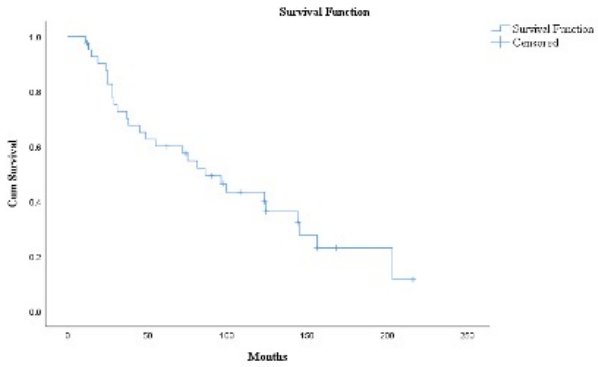


Fig. 2. Kaplan - Meier curve. Stage vs survival.

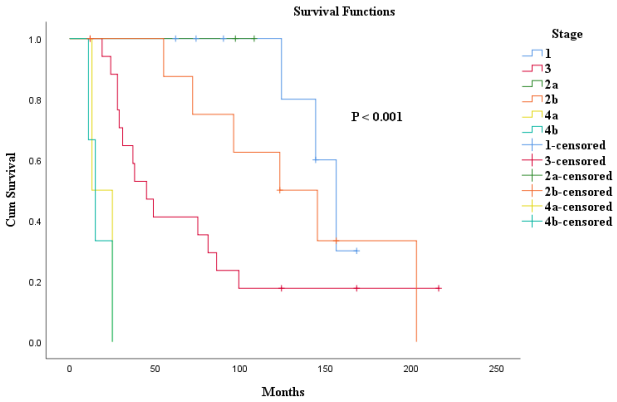


Fig. 3. WHO type and survival.

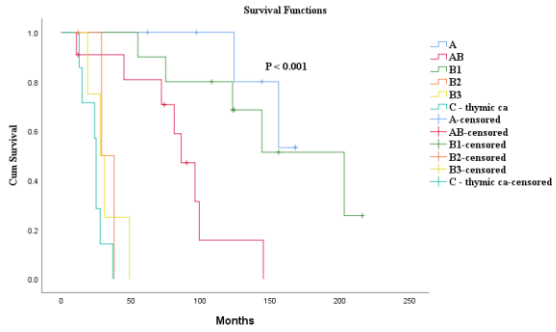


Fig. 4. Intra operative tumor spillage vs survival.

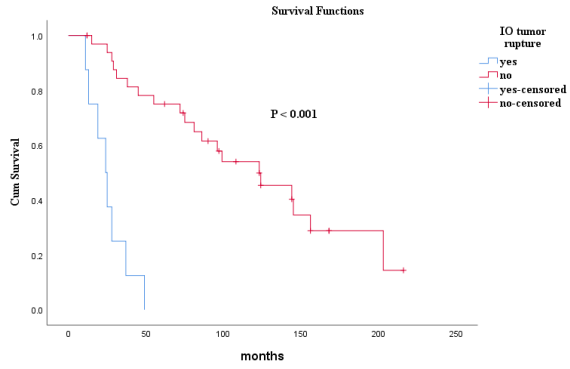
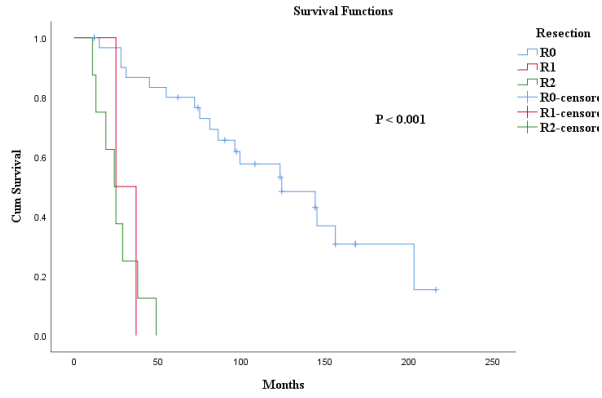


Fig. 5. Resection status vs survival.



Discussion:

In a thorough search of literature, we could find only results focusing on pattern of management of thymoma in Nepal. There is one case report of successful surgical removal of large thymic tumor[12] and one retrospective study of clinicopathological profile of thymoma in 51 patients during 2009-2015.[13] In the later study, Acharya et al had shown the mean age was found to be 47 years, most common presentation was shortness of breath (37%), myasthenia gravis (MG) in 29.4%, most common Masaoka stage was stage III (57%), WHO type B was most common (39%) and 41% of patients underwent surgery.

In general, one third of patients is asymptomatic. Common presentations are chest pain, neck swelling or SVC obstruction.[14] Roughly 30-50% patients have MG.[15] An association with autoimmune disease and hematological disorders have also been found. In one of the largest series of thymomas ever reported (n = 1470), Weissferdt et al found myasthenia gravis (17%), autoimmune disorders (3.8%) and other neoplasia (6.8%).[16]

Complete surgical excision or radical thymectomy is the mainstay of treatment for stages I and II.[6] In cases of pericardial or pulmonary invasion, the respective structures need to be excised for the curative intent.[17] In cases of locally advanced disease, chemotherapy both in neoadjuvant and adjuvant setting has a reasonable response rate of 30-60%.[6] In general, cisplatin-based regimens are safe and effective. Postoperative radiation therapy (PORT) is indicated in stages III-IV. PORT reduces the recurrence rate by 20-50% in stages III-IV.[18] For resected stage I-II thymomas, 10-OS rate is approximately 90% and 70%, respectively.[19] Thymic carcinoma is more aggressive tumor that often metastasizes to regional nodes and extra thoracic sites. Hence, it has worse prognosis than

thymoma.[20,21] PORT with or without chemotherapy is recommended after surgery.[22] In a metanalysis of retrospective multicentric review of 2451 patients with Masaoka Stages I-II, completeness of surgery was found to be the most important prognostic factor.[5]

To our best of knowledge, our study is the first to show the results of long-term survival for thymic neoplasms from Nepal. In our study, most of the surgical candidates were symptomatic (70%) with cough being the most common symptom (69%). A significant proportion of patient (59%) received multimodality approach and only 41% received exclusively surgery only. Due to larger size of tumor (mean size 12 cm) and locally advanced stage III in most of the cases (43%), a minimally invasive VATS thymectomy could be performed only in 19% cases. Globally as well, VATS thymectomy is not routinely recommended because only a few long-term results are available.[23] However, if oncological goals can be met with VATS, the results are not inferior.[24] A systematic review of 1061 patients with thymomas showed 5-OS after VATS (VATS: 83-100%; open: 80-93%) and 10 year recurrence free survival (VATS: 89-100% vs Open: 80-93%) were similar to open thymectomy.[25]

In our study, the most common WHO type was AB (26%) followed by B1 (24%). Excellent surgical results have been shown after surgical excision of thymomas. Zhao et al showed 5-OS of 92.8% in 544 patients (proportion of Stage I-II = 73%, stage III-IV = 26.9%).[9] In our study, the 5-OS of 60% for the whole group was in acceptable range. The inferior results of survival may be explained due to higher proportion of tumor with stages III-IV (55%). The best median survival was achieved in Masaoka stage I (144 months) and WHO type B1 (203 months) and A (158 months). Masaoka-Koga Stage I had 5-OS of 100%. Two important prognostic factors determining the survival were R+ resection and intra operative tumor spillage. Zhao et al showed median OS of 144 months and 117 months in complete and incomplete excision of tumors. Median survival was 124, 25 and 24 months for R0, R1 and R2 resection, respectively ($p < 0.001$).[9] In our study as well, intra operative tumor spillage had poor median survival of 24 months in comparison to 123 months in no-spillage group ($p < 0.001$).

The limitations of our study are its retrospective nature, small number of total patients (n=42) and a single institutional result.

Conclusion:

Our study is first of its kind in Nepal showing the long-term survival after thymectomy and multimodal approach. The overall survival results are acceptable. Three important prognostic factors were found to be Masaoka-Koga stage, positive resection margins and intra operative tumor spillage.

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