Thymic tumours in children – single institution experience

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Abstract

Background Thymomas are very rare neoplasms in children and they represent less than 1% of mediastinal tumours in a paediatric population. The aim of our study was to assess the long term treatment results of children with thymic tumours. Material and methods A total number of 8 children (4 boys and 4 girls) with thymic tumours were identified. Median age at diagnosis was 7 years. In 7 of them thymoma was diagnosed, in 1 thymic carcinoma. In 5 of them WHO type was assessed – in two of them B1 type was found, in one B2, in one AB and in one C. In all but one surgery was the first-line treatment, but 6 patients had only partial resection. One patient started treatment with chemotherapy and four others received chemotherapy after the surgery. Radiotherapy was applied in 6 patients with median total dose of 37.5Gy. Results Follow-up ranged from 8.5 to 273.5 months with median of 6.1 years. During that time 4 patients died – 1 due to progression of the disease, in 3 others reason of death was unknown. In all evaluated patients complete regression was observed (100% local control). Two-, 5- and 10-years OS and PFS were 85% and 72%, 51% and 54%, 51% and 54%, respectively. Conclusions Combined treatment could provide satisfactory results in thymoma patients. There is need for further larger studies which can help establish optimal management strategies.

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Abbreviations:

CTH	chemotherapy
CTV	clinical target volume
CR	complete regression
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group

CTH	chemotherapy
OS	overall survival
PR	partial regression
PFS	progression free survival
PTV	planned target volume
RTH	radiotherapy

Abstract

Background

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Material and methods

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Results

Follow-up ranged from 8.5 to 273.5 months with median of 6.1 years. During that time 4 patients died – 1 due to progression of the disease, in 3 others reason of death was unknown. In all evaluated patients complete regression was observed (100% local control). Two-, 5- and 10-years OS and PFS were 85% and 72%, 51% and 54%, 51% and 54%, respectively.

Conclusions

Combined treatment could provide satisfactory results in thymoma patients. There is need for further larger studies which can help establish optimal management strategies.

Introduction

Thymomas are very rare neoplasms in children and they represent less than 1% of mediastinal tumours in a paediatric population [1]. Majority of literature presents single case studies with only few national or international reports and one SEER analysis performed in 2013 [2-9]. As in adults, thymic tumours in children may be asymptomatic or present with compressive or respiratory symptoms. Classification (WHO) and staging system (Masaoka-Koga) are the same as in adult tumours but there are only few studies on the treatment of thymic neoplasms in paediatric population [4,6-12] (Table 1 and 2). Treatment for these tumours often requires a combination of modalities, including chemotherapy (CTH), radiotherapy (RTH) and surgery, based on tumour histology and extent of disease [4]. Due to the rarity of thymic tumours in children it is impossible to conduct prospective clinical trials. For this reason retrospective studies like this represent the only way to collect experience.

The aim of our study was to assess the long term treatment results of pediatric patients with thymic tumours in a single institution during the period of 35 years.

Methods

A retrospective study of patients with thymic tumours treated in our Institution between 1985 and 2019 was performed. All consecutive patients with thymic tumours younger than 18 years old were included into the study.

The following parameters were included in the analysis: date of diagnosis, primary tumour characteristics, given curative treatment, performance status, systemic therapy, RTH characteristics - total dose, irradiated volume, early and late toxicity, local response, date and reason of death. Missing dates of deaths were obtained from the Polish National Cancer Registry.

The criteria for diagnosing thymoma or thymic carcinoma used were as established by the WHO classification [10] (Table 1). Tumours were staged according to the commonly-used Masaoka-Koga staging system [11,12] (Table 2). Eastern Cooperative Oncology Group (ECOG) scale was used to classify patients' performance status. EORTC/RTOG toxicity criteria were used to assess treatment morbidity [13]. Tumour response was classified, as follows: complete regression (CR) was defined as complete disappearance of all clinical and radiological evidence of the disease, partial regression (PR) as a decrease of tumour size in clinical or radiologic evaluation and progression as increase in lesion size or occurrence of new lesions.

Median follow-up was estimated by Kaplan-Meier analysis with the reversed meaning of the status indicator. Overall survival (OS) was calculated from the date of disease diagnosis to the date of last follow-up or death. Progression free survival (PFS) was calculated from the date of diagnosis to the date of local/distant progression or death. The Kaplan-Meier method was used to estimate survival. Statistical analyses were performed using Statistica 12.0.

A total number of 8 children (4 boys and 4 girls) with thymic tumours were identified. Median age at diagnosis was 7 years (range 1 to 18). In all the cases, the diagnosis was based on diagnostic imaging and pathologic examination of the tumour tissue samples obtained during the surgery. In 4 cases, tumour was found on a computed tomography (CT) of the chest and in 4 cases (treated in the earlier years of a study) on the chest X-ray. Mean tumour dimensions were 82 x 62 x 93 mm and the tumours ranged from 50 to 135 mm in the greatest dimension. In 3 patients tumour showed contrast enhancement, in 4 cases tumour was constricting nearby organs and in 1 case infiltration of surrounding tissues was described. In one patient lung metastases were diagnosed simultaneously with primary tumour.

All patients had histopathologic confirmation of thymic neoplasm – in 7 of them thymoma was diagnosed, in 1 thymic carcinoma. In 5 of them WHO type was assessed – in two of them B1 type was found, in one B2, in one AB and in one C. Tumours were staged according to the commonly-used Masaoka-Koga staging system in 5 cases – stage II in one, stage III in three and stage IV in one.

ECOG scale was used to classify patients' performance status and all but one patient were in a good performance status at the time of the diagnosis (ECOG 0-1). Symptoms of the disease were present in 5 of them and lasted for 1 to 24 months – weakness in 3 of them, dyspnea in 1, cough in 2, weight loss in 2 and fever in 2. Other symptoms presented individually were: doubled vision, oedema of the neck and face and palpable neck tumour. In one patient diagnostic was introduced due to the lung infection. None of them presented with myasthenia.

All the patients were treated with radical intention. The characteristics of the treatment used in particular patients are presented in Table 3. In all but one surgery was the first-line treatment, however only in two cases a complete removal of the tumour was performed and other patients had partial resection. One patient started treatment with CTH and four others received CTH after the surgery. In one patient CTH was combined with RTH. Systemic treatment applied was: ADOC (doxorubicin 40mg/m^2 + cisplatin 50mg/m^2 + vincristine 0.6mg/m^2 + cyclophosfamid 700mg/m^2) – in 3 patients; cisplatin + adriamicin + bleomycin + encorton in 2 patients, VIP (etoposide 75mg/m^2 + cisplatin 20mg/m^2 + ifosfamide 1.2g/m^2) in 1 patient and PACE (cisplatin 50mg/m^2 + doxorubicin 50mg/m^2 + cyclophosfamid 500mg/m^2) in 1 patient. In 2 of them ADOC was followed by VIP and in one by cisplatin + adriamicin + bleomycin + encorton. Usually six cycles of CTH was applied.

RTH was applied to median total dose of 37.5 Gy. Radiotherapy characteristics is presented in Table 4. In all patients conformal technique (two or three fields' technique) was used. Irradiated volume (CTV, clinical target volume) included mediastinum in 4 patients combined with boost on lung metastasis in stage IV patient and with tumour bed boost and chest lymph nodes irradiation in 1 patient, tumour in 1 patient and

tumour bed in 1 patient. Planned target volumes (PTVs) were created by adding additional margins to CTV in order to correct for inaccuracies in the delivery system (set-up margins) or interfraction and intrafraction of organ motions.

Results

Follow-up ranged from 8.5 to 273.5 months with median of 6.1 years. During that time 4 patients died – 1 due to progression of the disease, in 3 others reason of death was unknown but during the last visit no evidence of thymoma was present. All others are still alive and free of the disease. After the treatment, the size of the tumour was assessed based on a comparative radiologic analysis - images taken before and after the treatment were compared for all but one cases. In all evaluated patients complete regression was observed and no local progression was found in any of the patients (100% local control). Patient with progression of the disease (lung metastases) received RTH as salvage treatment and lived for 21 more months. Two patients had mild acute radiation reactions – one leucopenia and one pneumonia. All patients received planned dose and no treatment interruptions was noted. After the treatment, CT imaging revealed radiological fibrosis of the irradiated lung volume in 1 patient, however, without clinical symptoms. During the follow-up one patient (one year old at the time of thymoma diagnosis) was diagnosed with lymphoma 22 years after the treatment which eventually was the reason of death.

Two-, 5- and 10-years OS and PFS were 85% and 72%, 51% and 54%, 51% and 54%, respectively (Figure 1). None of analyzed factors had statistically significant impact on OS or PFS.

Discussion

Thymic neoplasms are very rare tumours in pediatric patients. Present literature concerning thymic tumours is mostly comprised of single case reports with only few larger series [2-9]. Diagnosis, as in adults, is made after biopsy or tumour resection, but could be difficult due to the rarity of this tumour in pediatric population. Differential diagnosis of mediastinal mass usually reveals lymphoma or neurogenic tumours [4]. Patients presents with nonspecific symptoms of airway obstruction which was also observed in our study although not all of the patients had disease signs [1-9]. None of children presented with myasthenia gravis, but the coexistence of it with thymoma in children is less frequent with incidence of 7 to 15% [2,3,14,15]. WHO histopathological classification and Masaoka-Koga staging systems are the basis for treatment choice in adults as well as in children [10-12].

Fonseca AL. et al. in her report described the results of thymic tumours in children and found that this tumours presents more often in male but our group shows no sex predominance [15]. The largest study of Stachowicz-Stencel of 36 thymoma and thymic carcinoma patients showed male predominance – 21 male vs 15 female patients, also Rod J. in his literature analysis found male predominance in pediatric thymoma population [2,3]. Median age of patient described in our study is younger than reported in literature (median 12 years old) [2,3].

Surgery, possibly with R0 resection, remains the gold standard for treating all thymic neoplasms. CTH and RTH are used in patients with large or inoperable tumours, in the presence of metastases or after non-radical resections [1-3,5-9] (Table 5). Thymic carcinoma carries more poor prognosis and chemoradiotherapy is often offered after resection [2,3,6]. RT doses used in other studies usually are within the range of 40 to 54 Gy, which corresponds to the total doses used in majority of our patients [1-9]. Very young age could be the reason for implementing doses below 40 Gy in our group. A report from the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) written by Stachowicz-Stencel T. et al described results of 16 patients with thymoma and 20 with thymic carcinoma [2]. Only one child with thymoma received RTH and at the end of median follow-up of 5 years only 2 patients (12.5%) died due to the disease. Cisplatin was the most commonly used systemic agent, but only 4 patients received CTH. What is important, radical surgery (R0) was achieved in 11 of them and was the only treatment in those patients. Thymic carcinoma patients in majority had only biopsy (80%), received CTH (70%) and RTH (60%) with total dose of 38 to 54 Gy which could translate into such poor results of 5-year OS of only 21% [2]. The same observation could be made based on Ramon y Cajal S et al. study with median survival of patients with thymic carcinoma of

only 8 months [8]. Also Rod et al. in the report from French Society of Pediatric Oncology observed poor results in patients with thymic carcinoma [3]. The patient with thymic carcinoma included in our analysis had radical surgery and received postoperative RTH to 44 Gy which resulted in 74-month free of disease follow-up.

The limitations of our study are like in all studies on rare tumours - a retrospective study covering a long time period with different treatment modalities. Although, due to the rarity of this tumour in pediatric population, studies like ours are the only way to collect the experience in this topic.

Combined treatment, including surgery, chemotherapy and radiotherapy could provide satisfactory results in thymoma patients. There is need for further larger multi-national or institutional analysis with long-term follow-up which can help to provide more information for optimal management strategies and outcome.

Conflict of interest : The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions : Conceptualization, A.N., L.M.; methodology, A.N.; software, A.N.; formal analysis, A.N.; investigation, A.N.; resources, A.N.; data curation, A.N.; writing—original draft preparation, A.N.; writing—review and editing, A.N., L.M..; visualization, A.N.; supervision, L.M. All authors have read and agreed to the published version of the manuscript.

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16.

Legend: FIGURE 1. Overall and progression free survival

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