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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Surgical treatment of pediatric thoracic Ewing tumors

Pediatrik torasik Ewing tümörlerinin cerrahi tedavisi

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ABSTRACT

Background: This study aims to determine the thoracic surgery techniques, surgical indications, the role and effectiveness of surgical treatment in multimodal treatment applied to pediatric Ewing sarcoma patients.

Methods: Between April 2004 and November 2020, a total of 15 pediatric patients (9 males, 6 females; mean age: 10.1±4.5 years; range, 3 to 18 years) who were diagnosed with primary thoracic Ewing sarcoma and operated were retrospectively analyzed. Tumor-related factors and treatment modalities for Ewing sarcoma originating from the chest wall and mediastinum were examined.

Results: The most common complaint was pain in nine patients. While the tumor originated from the ribs in nine patients, it originated from the soft tissue (n=2), mediastinum (n=2), and extra-thoracic tissue (n=2) in six patients. Complete resection was achieved in 10 patients. While neoadjuvant chemotherapy was applied to eight patients, chemotherapy and radiotherapy was applied to 14 and five patients, respectively. Bone marrow transplantation was performed in one patient. The mean follow-up was 54.2±44.9 months. Recurrence was seen in six patients in a mean duration of 17.8±7.4 months.

Conclusion: The most effective treatment for thoracic Ewing sarcoma is complete resection. Multimodal therapy in the form of surgical resection, chemotherapy and/or radiotherapy provides optimal efficacy and the most favorable survival. The follow-up period should be kept short, since recurrences are common.

Keywords: Ewing sarcoma, local treatment, recurrence, surgery.

ÖZ

Amaç: Bu çalışmada, pediatrik Ewing sarkomu hastalarına uygulanan multimodal tedavide göğüs cerrahisi teknikleri, cerrahi endikasyonlar ve cerrahi tedavinin rolü ve etkinliği belirlendi.

Çalışma planı: Nisan 2004 - Kasım 2020 tarihleri arasında primer torasik Ewing sarkomu tanısı konulan ve cerrahi yapılan toplam 15 çocuk hasta (9 erkek, 6 kız; ort. yaş: 10.1±4.5 yıl; dağılım, 3-18 yıl) retrospektif olarak incelendi. Tümöre bağlı faktörler ve göğüs duvarı ve mediasten kaynaklı Ewing sarkomunun tedavi yöntemleri incelendi.

Bulgular: En sık görülen şikayet dokuz hastada ağrı idi. Dokuz hastada tümör kostalardan köken alırken, altı hastada yumuşak dokudan (n=2), mediastenden (n=2) ve ekstratorasik dokudan (n=2) köken almıştı. On hastada tam rezeksiyon sağlandı. Sekiz hastaya neoadjuvan kemoterapi uygulanırken, 14 ve beş hastaya sırasıyla kemoterapi ve radyoterapi uygulandı. Bir hastaya kemik iliği nakli yapıldı. Ortalama takip süresi 54.2±44.9 ay idi. Altı hastada ortalama 17.8±7.4 ayda nüks görüldü.

Sonuç: Torasik Ewing sarkomunda en etkili tedavi tam rezeksiyondur. Cerrahi rezeksiyon, kemoterapi ve/veya radyoterapi şeklinde multimodal tedavi optimal etkinliği ve en iyi sağkalımı sağlar. Nüksler sıklıkla görülmekte olduğundan, takip süresi kısa tutulmalıdır.

Anahtar sözcükler: Ewing sarkomu, lokal tedavi, nüks, cerrahi.

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Ewing sarcoma (ES) is a rare, aggressive malignant tumor of bone and/or soft tissue. It is a small round blue cell tumor with neuroectodermal differentiation and a wide clinical spectrum. It is most common in the pediatric population and young adolescents. It can be seen in the long bones of the extremities (femur, tibia, fibula, humerus) and pelvis. It is the second most common tumor among pediatric bone malignancies.[1,2] The ratio of occurrence in the thoracic wall is approximately 12%.[3] Micro-metastases are developed at the time of diagnosis in most patients.[4] Although less than 25% of patients have obvious metastases at the time of diagnosis, ES is considered a systemic disease.

Surgical resection and/or radiotherapy (RT) is used for intensive localized treatment and chemotherapy (CT) is used for systemic disease treatment in localized chest wall ES. Application of CT in addition to surgery increases survival from 20 to 60 to 70%.[1,5] However, the most optimal approach to achieve local control is controversial.

In the present study, we aimed to determine the thoracic surgery techniques, surgical indications, the role and effectiveness of surgical treatment in multimodal treatment applied to ES patients in the pediatric population.

PATIENTS AND METHODS

This dual-center descriptive, retrospective study was conducted at Çukurova University Faculty of Medicine Department of Thoracic Surgery and Adana City Training and Research Hospital Department of Pediatric Surgery between April 2004 and November 2020. A total of 15 pediatric patients (9 males, 6 females; mean age: 10.1±4.5 years; range, 3 to 18 years) who were diagnosed with primary thoracic ES at thoracic surgery clinics in regional hospitals were included. A patient with bilateral multiple parenchymal metastases was not included to the study, since no surgical procedure was performed. Medical records of the patients, demographic data, admission symptoms, presence of pre-admission neoadjuvant systemic treatment, radiological findings, surgery details, histopathological results, neoadjuvant-adjuvant treatments, and follow-up results were recorded. The survival time and the follow-up periods of the patients after diagnosis were calculated according to the final outpatient clinic examination records and General Directorate of Civil Registration and Citizenship of Türkiye.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD), while categorical data were expressed in number and frequency.

RESULTS

All patients were evaluated with a multidisciplinary approach in the Pediatric Oncology Council. Only diagnostic surgery was performed in three of our patients (Patient No. 1, 3, 4). Transthoracic Tru-cut biopsies were performed in all other patients (except for Patient No. 11) with diagnostic purposes before surgery. In Patient No. 11, the diagnosis was made by intraoperative frozen-section analysis due to clinical urgency (Table 1).

The most common complaints at the time of admission were pain (n=9), swelling (n=6), dyspnea (n=5), and cough (n=1). Thoracic computed tomography (TCT) was performed in all patients after admission.

The tumor was located on the right side in seven patients and on the left in eight patients. The mean tumor diameter was 11.2±7.7 (range, 3 to 28) cm (Table 1). Neoadjuvant systemic CT was applied before surgical treatment in eight patients. Complete resection was performed in seven of these patients.

Tissues from which primary thoracic ESs originated from were detected intraoperatively. Accordingly, the tumor was originated from the ribs in nine patients, from soft tissue in two patients and from mediastinum in two patients. The primary origin of two patients was extra-thoracic tissues (Patient No. 6, 15). Surgical procedures included isolated thoracic wall resection and reconstruction (n=6), wedge resection of the lung with thoracic wall resection (n=1), diaphragm resection with thoracic wall resection (n=1), diaphragm resection with mass excision, and wedge resection of the lung (n=1), diaphragm resection and pleural decortication with mass excision (n=1), and pericardial resection with mass excision (n=1) (Table 2).

In patients undergoing diagnostic surgery, Patient No. 1 and 3 had soft tissue origin and Patient No. 4 had rib origin. Three of our patients received CT after biopsy, and the tumor regressed after CT in Patient No. 1, but the survival time was unknown due to the lack of follow-up. On the other hand, Patient No. 3 died after 19 months of follow-up and Patient No. 4 was still alive at the end of a 114-month-follow-up.

In a six-year-old female patient (Patient No. 8) presenting with swelling in the right chest wall and dyspnea, a giant mass filling the thorax and

Table 1. Overall characteristics of patients operated for thoracic Ewing sarcoma

No	Age/Sex	Complaint	Localization	Size (cm)
1	10/M	Swelling/pain	Right under the clavicle	-
2	6/F	Swelling	Right lower thoracic wall	-
3	17/F	Swelling	Right paravertebral intramuscular	-
4	16/M	Pain	Left 4^{th}-, 5^{th}, 6^{th}, 7^{th} rib	5
5	6/F	Pain	Left 4^{th} rib anterior	3
6	18/M	Pain	Left 3^{rd}, 4^{th}, 5^{th} rib lateral	10
7	8/M	Pain	Left 4^{th}, 5^{th}, 6^{th}, 7^{th}, 8^{th} rib	5
8	6/F	Dyspnea	Extends from the right wall to the mediastinum, displaces the mediastinum	9.5
9	15/F	Pain	T5-6 right paravertebral rib invasion, posterior vertebral fixation	8
10	11/F	Swelling	Left 7^{th} rib	6
11	3/M	Dyspnea	Left mediastinal mass, completely filling the hemithorax, destroying the ribs, mediastinum was pushed to the right	21
12	10/M	Swelling/pain	Mass at right 9^{th}, 10^{th}, 11^{th} rib	9
13	8/M	Dyspnea	Left anterior mediastinal mass	20
14	9/M	Pain, dyspnea, cough	Mass filling the left hemithorax, invasion to mediastinum and left anterior chest wall	10
15	8/M	Swelling, pain, dyspnea	8 cm lesion on the right proximal tibia, a mass that completely fills the right hemithorax and causes respiratory distress, pushing the mediastinum to the left prominently was found after 18 months	28

mediastinal shift was seen on TCT, and the diagnosis of ES was made by Tru-cut biopsy. Thirteen months after observing severe regression after neoadjuvant CT (Figure 1), partial resection of the fourth, fifth, and sixth ribs, wedge resection of the upper lobe of the right lung and thoracic wall reconstruction were performed. The patient who was followed by the pediatric oncology department was still alive 113 months after the first admission and no recurrence was observed.

In a three-year-old male patient (Patient No. 11) presenting with dyspnea, a mass filling the left hemithorax with a mediastinal shift was detected with a diameter of 21 cm in the largest diameter. Afterwards, left thoracotomy was performed and following the diagnosis with the intraoperative frozen-section analysis, mass excision, diaphragm resection and reconstruction, and wedge resection were applied to the lung invasion area. In this patient, the lesion involving the T3-T7 vertebral bodies was excised incompletely. One month later, the patient was operated again by the neurosurgeon due to spinal cord compression and received postoperative CT. The patient who was followed by the pediatric oncology department underwent bone marrow transplantation at the postoperative fourth month. Unfortunately, the patient died at 22 months after diagnosis.

In an eight-year-old male patient (Patient No. 13) presenting with dyspnea, TCT revealed a mass, with the largest diameter of 20 cm, located in the anterior mediastinum and ES was diagnosed with Tru-cut biopsy. Following the diagnosis, neoadjuvant CT was applied, and total excision and pericardial resection were performed on the mass showing pericardial invasion with anterior thoracotomy. The patient who received postoperative adjuvant CT has been followed for 35 months.

In a nine-year-old male patient (Patient No. 14) admitted with complaints of pain, severe dyspnea and cough, a mass located at the left hemithorax was detected with the largest diameter measuring 10 cm on TCT. Following the release of the mass from the lung and chest wall with left thoracotomy, the mass invaded

Table 2. Treatment methods and results in patients operated for thoracic Ewing sarcoma

No	Surgical procedure	Primary/ metastatic	Neoadjuvant chemotherapy	Chemotherapy	Radiotherapy	Follow-up duration (months)	Recurrence	Second surgery	Mortality
1	Biopsy	Primary	-	+	-	-	-	-	-
2	Chest wall resection and reconstruction	Primary	-	+	-	164	-	-	-
3	Biopsy	Primary	-	+	-	19	-	-	19
4	Biopsy	Primary	-	+	-	114	-	-	-
5	Chest wall resection and reconstruction (with methyl methacrylate)	Primary	-	-	-	34	-	-	34
6	Chest wall resection and reconstruction (with methyl methacrylate)	Metastatic	+	+	-	51	Thoracic wall metastasis at 17th month postoperatively after orthopedic surgery for ES at the left tibia	-	51
7	Chest wall resection and reconstruction (with methyl methacrylate)	Primary	+	+	+	17	Recurrence at the operation site after 16 months	Reconstruction with Dacron mesh	-
8	Right anterior 4-5-6 rib resection + wedge resection of the lung, reconstruction with methyl methacrylate and prolene mesh	Primary	+	+	-	113	-	-	-
9	5th, 6th rib excision	Primary	+	+	+	86	-	-	-
10	Left 7-8th rib excision, reconstruction with titanium bars + dual mesh	Primary	+	+	-	31	Recurrence in T12 vertebral corpus at 24 months	-	31
11	Mass excision + diaphragmatic resection, due to lung invasion in the fissure subtotal wedge resection was performed. Due to posteriorly paravertebral localized tumor between T3-T7 total excision could not be performed, marked with clips, neurosurgery applied fixator 1 month later	Primary	-	+	-	22	-	-	22
12	9th, 10th, and 11th rib and diaphragm resection + reconstruction with titanium plate at 2 ribs + dual mesh	Primary	+	+	+	40	Recurrence in the left knee after 26 months	-	-
13	Mass excision with left anterior thoracotomy + pericardium excision	Primary	+	+	-	35	-	-	-
14	Left phrenic nerve invasion, innominate vein invasion, total removal cannot be achieved, plication to the diaphragm	Primary	+	+	+	9	Aggressive growth in mass after 5 months	-	9
15	Right thoracotomy, mass excision, pleural decortication and diaphragmatic resection and reconstruction	Metastatic	-	+	+	25	The patient refers to thoracic surgery 19 months after orthopedic surgery		25

ES: Ewing sarcoma.

the left innominate vein and left phrenic nerve, and it was revealed that total resection was not possible, and surgical margins were marked after incomplete resection. The patient received postoperative CT and RT. Aggressive growth was observed in the mass at the fifth month of follow-up. Unfortunately, the patient died at the ninth month.

A giant mass filling the right hemithorax and pushing the mediastinum to the left was detected in an eight-year-old male patient (Patient No. 15) who was referred to our clinic with pain, swelling and severe dyspnea 19 months after the right tibial resection operation and during CT/RT (Figure 2). During right thoracotomy, the mass was found to involve the mediastinum and diaphragm. Total mass excision, diaphragmatic resection-reconstruction and parietal decortication were performed. In addition, CT and RT were applied to the patient with postoperative orbital wall and intracranial metastases. Unfortunately, the patient died at 25 months of follow-up.

An 18-year-old male patient (Patient No. 6) was referred to our clinic with left thoracic wall recurrence at 17 months while he was receiving CT after resection of the mass at left tibia. Thoracic wall resection and reconstruction was performed by left thoracotomy. The patient who received postoperative CT again died at 51 months after the initial diagnosis.

Except for patients undergoing diagnostic surgery, complete chest wall resection and reconstruction was performed in the remaining six patients due to primary ES at the thorax wall and all patients received postoperative CT.

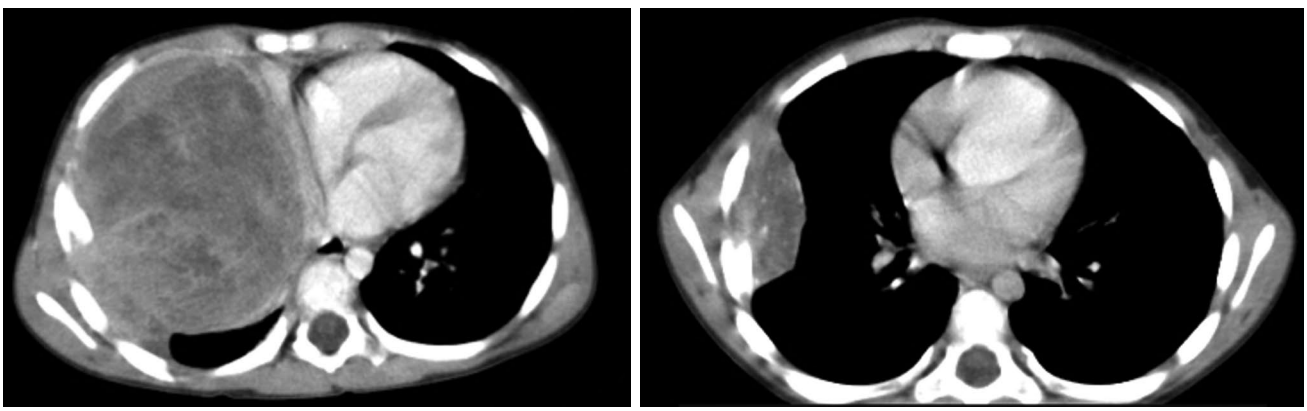

Figure 1. Thoracic computed tomography images before and after neoadjuvant chemotherapy in Patient No. 8.

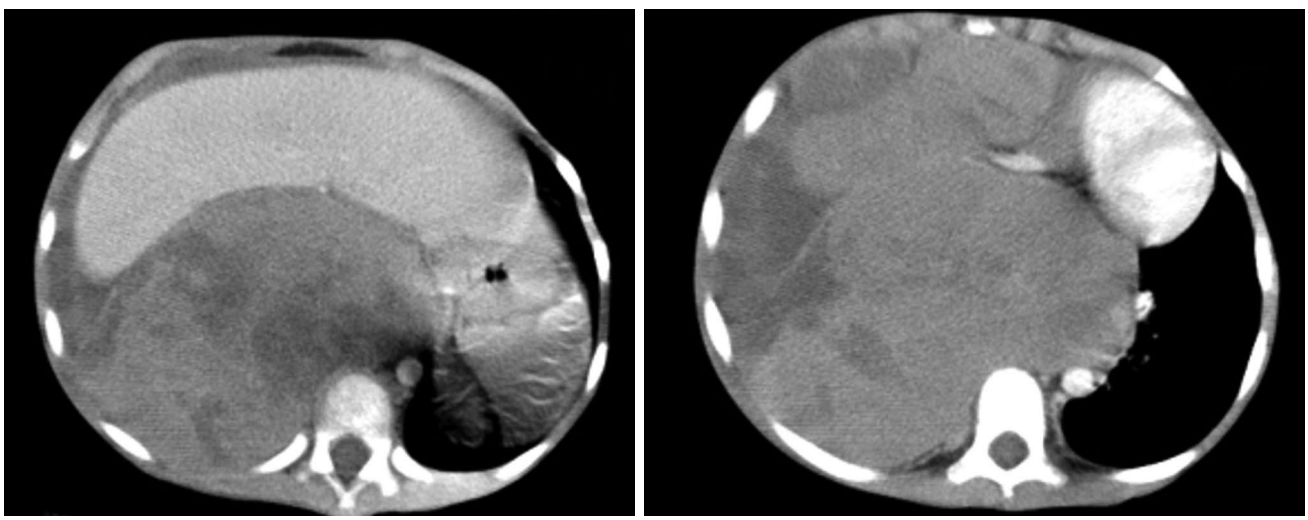

Figure 2. Thorax computed tomography images of a progressive mass before and after preoperative neoadjuvant chemotherapy in Patient No. 15.

Five of our patients received RT in the postoperative period: one patient received RT, as the tumor was too close to the surgical margin and four patients received RT due to recurrence. Recurrence was detected at a mean duration of 17.8±7.4 (range, 5 to 26) months after surgery. Chest wall re-resection and reconstruction were performed in one of the patients with recurrence (Patient No. 7) by re-thoracotomy at the postoperative 16th month.

The mean follow-up was 54.2±44.9 (range, 9 to 164) months. The overall mortality rate in the postoperative period was 46%. Time to mortality times was as follows: at 19, 34, 51, 31, 22, 9, and 25 months for Patient No. 3, 5, 6, 10, 11, 14, 15, respectively).

DISCUSSION

In this study, we found that the surgical treatment was an important part of multimodal treatment in local control of the disease and increasing long-term survival rates, and surgical treatment provided symptomatic relief, particularly in large-sized ES, even if total excision could not be achieved.

In our study, male pediatric cases were in the majority, consistent with the literature (9/6).[3] Of note, ES is the third most common primary malignant neoplasia in children after osteosarcoma and rhabdomyosarcoma. It is usually observed in children and young adults in the first or second decade of life.[6] In our study, the mean age of our patient group was 10.1±4.5 years.

Typically, ES presents to the clinic with pain and swelling around the tumor.[7] Although the most common complaints in our study were pain and swelling, dyspnea was also present at the time of admission in five patients.

The most common localizations of ES are flat bones or lower extremity long bones (pelvis, axial skeleton, and femur). Extra-skeletal ES localization ranges from 1/5,000,000 to 1/10,000,000.[7] While the tumor was originated from the skeletal system in nine patients (60%), the primary origin was outside the skeletal system in 40% of our patients in our study.

The size of ES is usually large at presentation (ranging from 1 to 40 cm) and is usually detected over 10 cm in diameter.[6] In our study, the mean diameter of tumors originating outside the skeletal system was 15.5±8.8 (range, 5 to 28) cm, while the mean diameter of tumors originating from the skeletal system was 6.8±2.6 (range, 3 to 10) cm.

Prognosis is related to age, presence of metastases, tumor diameter, tumor origin, response to CT, and tumor localization.[8,9] Five-year disease-free survival reaches 60 to 75% in patients with non-metastatic ES/peripheral neuroectodermal tumor.[10] The mean follow-up in our study was 54.2±44.9 (range, 9 to 164) months. While 54% of the patients in our study were alive, we had only three patients whose follow-up duration reached five years due to the insufficient number of patients.

One of the important factors determining local recurrence in ES is complete resection of the tumor. To achieve complete resection, the response to neoadjuvant CT is important in terms of tumor size regression. Complete surgery was performed in seven of our eight patients who received neoadjuvant systemic CT. The correlation between response to CT and survival was determined by Picci et al.[11] In a study of Lin et al.,[9] the percentage of necrosis in resected tumors of patients undergoing neoadjuvant CT was a significant predictor of local recurrence.

The local recurrence rate in patients with poor response has been shown to be 50% at five years.[9] However, the histological response to CT alone is insufficient to predict local recurrence. Necrosis rates of the central part of the tumor and the stage of the tumor (presence of metastasis) are considered other important factors in predicting local recurrence.[9] In our study, local recurrence could be seen in high rates of necrosis (68 to 99%) after CT/RT. Patient No. 7 with the lowest necrosis rate (27%) had local recurrence. However, we could not elucidate the role of necrosis rate for the development of local recurrences in this study.

In previous studies, positive surgical margins have been shown to be important for local recurrence;[12,13] however, in current studies,[9] the correlation of local recurrence with surgical margins was found to be low, and only 5% of the patients who developed local recurrence had a positive surgical margin on the inked side, as defined in the traditional sense. An important consideration regarding margins is that soft tissue tumor mass often regresses after preoperative CT. A previously involved muscle may appear normal on an magnetic resonance imaging (MRI) scan after CT, but may have disease at microscopic level. If this tissue is not resected, it can potentially be a source of local recurrence. This should not be interpreted as evidence that broad boundaries are unimportant. Probably, it demonstrates our inability to judge true margins accurately and quantitatively. Thus, while reaching wide negative margins is important, this alone does not provide a strong prediction for local recurrence and may not be helpful in guiding subsequent therapy.[13,14]

Neoadjuvant CT was applied to eight of 15 patients in our study and the survival rates of these eight patients were better than the other patients. The mean follow-up of these eight patients was 47.8±35.2 (range, 9 to 113) months.

The main limitations of this study are its retrospective nature, the small number of patients in the patient group, not being suitable for a statistical analysis, and the inability to prove the benefit of total resection. This study was not suitable for further statistical analysis due to the small sample size. Further studies with larger patient groups are needed to confirm the results and to provide new perspectives.

In conclusion, Ewing sarcoma is a disease that often progresses with local recurrences or metastases. Combination of surgery with clean surgical margins, chemotherapy and/or radiotherapy and bone marrow transplantation, when necessary, with a multimodal treatment approach are the main considerations that need to be done to prevent recurrences and achieve long-term survival.

Ethics Committee Approval: The study protocol was approved by the Adana City Training and Research Hospital Ethics Committee (date: 02.12.2021, no: 1661). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the patients and/or parents of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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