Intraoperative radiotherapy in the local control of chest wall Ewing sarcoma

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ABSTRACT

Introduction. Ewing sarcoma is a rare malignant tumor with an incidence of 3 cases per 1 million inhabitants annually. Cross-disciplinary management is key to improve survival rates. The role played by intraoperative radiotherapy in terms of treatment is still to be defined.

Materials and methods. A retrospective study of pediatric patients (up to 16 years of age) with chest wall Ewing sarcoma undergoing tumor resection surgery, intraoperative radiotherapy, and chest wall reconstruction in our institution from 2011 to 2024 was carried out. Variables such as age at surgery, sex, neoadjuvant treatment, resection type, characteristics of intraoperative radiotherapy, reconstruction type, complications, local control rate, relapses, survival, and reconstruction's functional result were collected.

Results. 8 patients were included. Mean age at diagnosis was 12.5 years. Full tumor mass removal with free margins (R0) was achieved in 100% of the cases. Reconstructive techniques with flexible patches, titanium plates, and muscle flaps were used. None of the flaps was lost. Overall survival was 87.5%, with a mean follow-up period of 6 years. 3- and 5-year overall survival rates were 100% and 80%, respectively. Local control of the disease was achieved in 100% of the cases.

Conclusions. This paper discusses the role of intraoperative radiotherapy as a good treatment alternative to achieve the local control of Ewing sarcoma associated with large surgical resections.

KEY WORDS: Sarcoma, Ewing; Radiotherapy, adjuvant; Reconstructive surgical procedures; Thoracic surgical procedures; Surgical oncology.

LA RADIOTERAPIA INTRAOPERATORIA EN EL CONTROL LOCAL DEL SARCOMA DE EWING TORÁCICO

RESUMEN

Introducción. El sarcoma de Ewing es un tumor maligno poco frecuente con una incidencia de 3 casos por millón de habitantes al año. En la mejora de la supervivencia es clave el manejo multimodal. El papel que ocupa la radioterapia intraoperatoria en su tratamiento está aún por definir.

Material y métodos. Se diseña un estudio retrospectivo incluyendo pacientes pediátricos (hasta 16 años) con sarcoma de Ewing de pared torácica sometidos a cirugía de resección tumoral, radioterapia intraoperatoria y reconstrucción costal en nuestro centro entre 2011 y 2024. Se registraron variables como edad en el momento de la cirugía, sexo, tratamiento neoadyuvante, tipo de resección, características de la radioterapia intraoperatoria, tipo de reconstrucción, complicaciones, tasa de control local, recaídas, supervivencia y resultado funcional de la reconstrucción.

Resultados. Se incluyeron 8 pacientes. La edad media al diagnóstico fue 12,5 años. Se logró la extirpación completa de la masa tumoral con márgenes libres (R0) en el 100%. Se utilizaron técnicas reconstructivas con parches flexibles, placas de titanio y colgajos musculares. No se ha registrado ninguna pérdida de colgajo. La supervivencia global fue del 87,5% con un tiempo de seguimiento medio de 6 años. La supervivencia global de la serie a 3 y 5 años fue del 100% y 80%. Se logró el control local de la enfermedad en el 100% de los casos.

Conclusiones. Este artículo expone el papel de la radioterapia intraoperatoria como una buena alternativa de tratamiento para el lograr el control local del sarcoma de Ewing asociado a resecciones quirúrgicas amplias.

PALABRAS CLAVE: Sarcoma de Ewing; Radioterapia intraoperatoria; Reconstrucción torácica; Oncología quirúrgica.

INTRODUCTION

Malignant chest wall tumors are rare in children and adolescents, representing 1.8% of all pediatric tumors[1,2]. Sarcoma is the most frequent chest wall tumor. It is of bone or cartilaginous origin in 55% of the cases, whereas soft tissue sarcoma accounts for the remaining 45%. Predom-

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inant subtypes in the pediatric population are Ewing sarcoma followed by rhabdomyosarcoma[2]. These tumors are generally chemo- and radiosensitive. In the last decades, survival rates have improved thanks to the implementation of a cross-disciplinary treatment combining surgical resection and/or radiotherapy with chemotherapy[3].

Today, radiotherapy is aimed at achieving the local control of the disease. Around half of the patients with these tumors receive radiotherapy treatment[1,4], generally in the form of postoperative external radiotherapy (40-55 Gy dose). Radiotherapy treatment indications include tumors that cannot be fully resected or with diseased margins following surgery, tumors that can be resected following neoadjuvant treatment in which the structures initially involved are not fully removed, progression in spite of chemotherapy treatment or poor histological response following induction treatment, tumor with spine involvement, pleural involvement in costal tumors, and in some institutions, a tumor size > 8 cm or 200 cc in areas with poor access[5]. In the last years, efforts have been made to develop therapeutic alternatives that help maintain radiotherapy's effect on local control while reducing side-effects[3]. Intraoperative radiotherapy, administered in the surgical bed during tumor resection, allows the radiation dose employed in the tissue involved (around 10 Gy) to be located, thus maintaining the effect of local recurrence prevention[6,7], and also protecting surrounding healthy tissues. There is also concern regarding the negative effect of radiotherapy on the healing process of reconstructive surgery[8], which could be lower in the case of intraoperative radiotherapy, since covering tissues are not involved.

The objective of this study was to analyze the results of intraoperative radiotherapy in pediatric patients with chest wall Ewing sarcoma, and to assess the various reconstructive techniques available.

MATERIALS AND METHODS

A retrospective study of all pediatric patients (≤ 16 years of age) diagnosed with chest wall Ewing sarcoma who underwent removal surgery, chest wall reconstruction, and intraoperative radiotherapy was carried out. All patients treated in our institution from June 2011 to June 2024 were included. Epidemiological, treatment, progression, and follow-up variables were gathered. Data was collected in tables, and the IBM SPSS Statistics software, version 26 (IBM Corporation®), was used for statistical analysis.

The Euro Ewing 1999 and subsequently Euro Ewing 2012 (International Randomized Controlled Trial for the Treatment of Newly Diagnosed Ewing Sarcoma Family of Tumors)[9] protocols were employed in the management of these patients.

Intraoperative radiotherapy was used in patients with indication of adjuvant radiotherapy undergoing surgical resection. During surgery, the costal arches involved and the immediately superior and inferior ones, as well as the surrounding infiltrated tissues, were resected. The surgical goal was to achieve tumor-free margins. Once the tumor had been resected and before chest wall reconstruction, intraoperative radiotherapy was administered using a linear accelerator at doses ranging from 7.5 to 15 Gy. Dosage was calculated according to tumor volume, surgical bed, and external radiotherapy dosing.

Radiotherapy was applied directly on the surgical bed, while protecting the surrounding structures. Beveled applicators (0-45°), with a diameter ranging from 5 to 15 cm according to the area and location of the tissue to be radiated, were used.

The reconstructive technique was chosen on a case-by-case basis, depending on the area involved, the costal arches and structures resected, the defect's size, and the patient. The objectives of chest wall reconstruction were to establish a structural and anatomical support, to maintain respiratory function, to preserve the adequate mobility of the trunk and the limbs, to adapt to the child's growth, to favor the administration of adjuvant therapies, and whenever possible, to achieve a good cosmetic result. Three different types of reconstructive techniques were employed –expanded polytetrafluoroethylene (Gore-Tex®) patch covering, plate and absorbable screw reconstruction, and titanium plate reconstruction. In most cases, titanium plates were used combined with 2 mm thick Gore-Tex® patches adjusted to the defect's size. Preformed titanium plates were chosen during surgery, prioritizing the most adequate size. They were shaped and adjusted to the rib borders through anchors and screws. Latissimus dorsi and pectoralis major muscle flaps were employed to cover the reconstructed area. The flaps were obtained in cooperation with the Pediatric Plastic Surgery Department.

RESULTS

8 patients, 62.5% of whom were male and 37.5% female, were included in the study. Mean age at diagnosis was 12.5 years (SD= 2.5). 5 left and 3 right tumors were recorded. 62.5% of the patients had only one costal arch involved. Mean costal arches resected were 2.88 (SD= 0.64). The preoperative characteristics of these patients –age at diagnosis, sex, structures involved, preoperative treatment, age at surgery, and tumor size at diagnosis and following neoadjuvant treatment– are featured in Table 1.

Patient 2 had a history of sacrococcygeal dysgerminoma treated with chemotherapy, surgical resection, and intraoperative radiotherapy prior to Ewing sarcoma.

Table 1. Preoperative characteristics of study patients.

N	*Age at diagnosis (years)*	*Sex*	*Involvement*	*Preoperative treatment*	*Age at surgery (months)*	*Tumor size at diagnosis (cm)*	*Tumor size before surgery (cm)*
1	14	F	Posterior arch of the 9th rib (left). Left pleural effusion	CTP + RTP (48.6 Gy) Decompression laminectomy D7-8-9	178	14x12x12	9.8x2.8x5.2
2	10	F	Posterior arch, 9-10th ribs (right)	CTP + RTP (48 Gy) + autologous bone marrow transplantation	127	9.7x6.8x10.8	4.2x2.1x4.1
3	14	M	Posterior arch, 6th rib (left). Subscapular. Contralateral pulmonary metastasis	CTP + RTP (36 Gy) + contralateral pulmonary metastasectomy	177	15x15x20	3.6x1.6x1.8
4	8	F	Anterior arch, 6th rib (left)	CTP	120	8.4x4.6x5.7	1.5x3.6x2.3
5	12	F	Mid and anterior arch, 3rd rib (right)	CTP	152	12x10x10	4x2.5x3.8
6	13	M	Posterior arch, 7th rib (left)	CTP	166	17.7x12.7x12.7	9.7x4.2x10.7
7	13	M	Posterior third of the 1st rib (left)	CTP + RTP	163	5.2x3.5x6.8	2x2.7x2.1
8	16	M	Posterior arch, 10th rib (right)	CTP	207	6.1x9.1x8.5	4.5x6.2x7.6

CTP: chemotherapy; RTP: radiotherapy.

All the patients experienced tumor size reduction following neoadjuvant chemotherapy. The chemotherapy regimen was based on combinations of vincristine, Adriamycin, cyclophosphamide, ifosfamide, doxorubicin, and etoposide. Following induction, all the patients underwent surgical treatment, with full tumor mass removal with free margins (R0) being achieved in 100% of the cases. In 62.5% of the patients, the structures adjacent to the costal arches (soft parts, pleura, and/or pulmonary parenchyma) were involved, and in 3 patients (37.5%), pulmonary wedge resection was also necessary.

After removal, intraoperative radiotherapy was applied, with a mean dose of 10 Gy (SD= 2.67).

Chest wall reconstruction required the use of prosthetic material in all patients. An absorbable plate was employed in 1 case, whereas flexible Gore-Tex® meshes were used in 7 patients. In 5 patients, costal titanium plates were also placed. Regarding muscle flap covering, the latissimus dorsi was used in 5 patients, and the pectoralis major was employed in 1 patient.

Surgical details –structures resected, obtention of free margins, reconstructive technique used–, characteristics of intraoperative radiotherapy, and postoperative progression are featured in Table 2.

No local recurrence cases were recorded in the series. There was 1 recurrence in a patient with history of contralateral pulmonary metastases (Patient 4). This patient had a relapse with multiple contralateral pulmonary nodules 11 months following primary tumor removal associated with intraoperative radiotherapy. The patient died after 51 months of follow-up as a result of disseminated metastatic disease.

25% of the patients (2 cases) had postoperative complications –a pleural effusion that was difficult to manage and required pleurodesis, and a case of complicated Herpes Zoster with pneumonia.

50% of the patients were treated with adjuvant radiotherapy following intraoperative radiotherapy treatment.

62.5% of the patients had uneven chest with scoliosis, which led to surgical repair in 4 cases. Regarding postoperative musculoskeletal disorders, 1 case of breast asymmetry and 1 case of osteoporotic vertebral fractures between T10 and L4 causing an 18-degree mild scoliosis but not requiring surgical repair were recorded.

No complications associated with prosthetic material infection were noted, but one costal titanium plate had to be removed in Patient 4 as a result of plate extrusion 6 years following surgery. Prosthesis removal was uneventful. All muscle flaps were viable in the long-term.

Overall survival was 87.5%, with a mean follow-up of 72 ± 51.4 months (6 years). Mean sample survival was 140.6 ± 20 months (11.7 years), and mean time to recurrence was 141.28 ± 20 months (Figs. 1 and 2).

Overall 3- and 5-year survival were 100% and 80%, respectively.

Table 2. Characteristics of intraoperative radiotherapy, and postoperative progression

No	*Structures resected*	*Free margins*	*Reconstructive technique*	*Characteristics of intraoperative radiotherapy*	*Postoperative adjuvant therapy*	*Local recurrence*	*Metastatic recurrence*
1	Costal arches 8-9 + transverse processes	Yes	Absorbable plate and screws	7.5 Gy/10 cm/30°	CTP	No	No
2	Costal arches 9-10-11 + transverse processes	Yes	ePTFE patch	12.5 Gy/7 cm/30°	CTP	No	No
3	Rib 6, costal arches 5-7 with costotransverse joint preservation	Yes	Titanium plate + ePTFE patch + latissimus dorsi muscle flap	15 Gy/7 cm/15°	CTP	No	Yes
4	Costal arches 5-6-7 and pulmonary parenchyma involved	Yes	Titanium plate + ePTFE patch + latissimus dorsi muscle flap	10 Gy	CTP + RTP (45 Gy)	No	No
5	Costal arches 2-3-4 and pulmonary parenchyma involved	Yes	Titanium plate + latissimus dorsi muscle flap	10 Gy/10 cm/0°	CTP + RTP (45 Gy) + autologous bone marrow transplantation	No	No
6	Costal arches 6-7-8 + transverse processes + costal arch 9 and pulmonary parenchyma involved	Yes	Titanium plate + ePTFE patch + latissimus dorsi muscle flap	10 Gy/10 cm/15°	CTP + RTP (50.2 Gy)	No	No
7	Costal arches 1-2 and adjacent soft tissues	Yes	Titanium plate + ePTFE patch + pectoralis major muscle flap	7.5 Gy/3 cm/15°	CTP	No	No
8	Costal arches 9-10-11 + transverse processes + pulmonary parenchyma involved + adjacent soft tissues	Yes	ePTFE patch + latissimus dorsi muscle flap	7.5 Gy	CTP + RTP (45 Gy)	No	No

CTP: chemotherapy; RTP: radiotherapy; ePTFE: expanded polytetrafluoroethylene.

DISCUSSION

The 5-year survival of patients with Ewing sarcoma has improved in the last years, with a 70% rate achieved in the first decades of the 21st century vs. < 50% in the last decades of the 20th [3,10].

This improvement has been made possible thanks to cross-disciplinary management and to the standardization of induction and consolidation chemotherapy regimens based on randomized clinical trials, with surgical resections allowing for removal with free margins (R0) [4,9,11]. Radiotherapy has been regarded as a key tool for the local control of the disease[12]. The surgical advances made in chest wall reconstructive techniques and the creation of reconstruction materials adapted to pediatric patients have allowed for wide resections with free margins[2,4,13].

Local and distant recurrence are known to play a role in the overall mortality of patients with Ewing sarcoma[12].

However, the best approach to achieve local control of the disease is little standardized and remains an issue of discussion[2,4].

5-year survival in localized disease cases is currently 60-70%[4]. Our results revealed a mean 6-year overall survival of 87.5%, and of 100% in localized disease cases, which could reflect the role of intraoperative radiotherapy in terms of preventing local recurrence. This promising data should be interpreted with caution given the retrospective nature of the study, with no control group and a small sample size.

Conte et al.[14] reported 10 cases of Ewing sarcoma receiving intraoperative radiotherapy, with a 2-year local progression or recurrence rate of 10%, and a 5-year rate of 20%. In their series, they included multiple tumor loca-

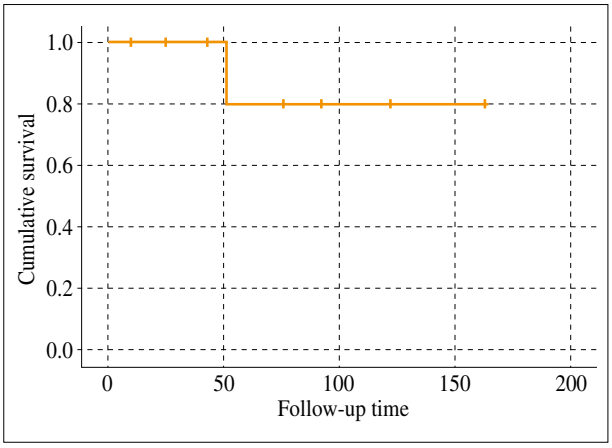

Figure 1. Overall survival Kaplan-Meier curve.

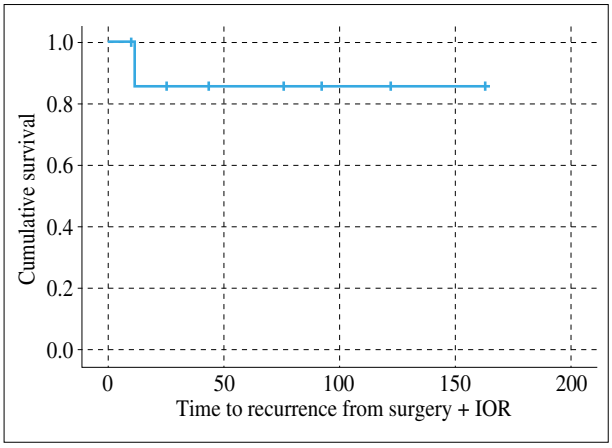

Figure 2. Recurrence-free survival Kaplan-Meier curve.

tions, and radiotherapy was indicated in the first surgery in only 5 patients. In the remaining 5, it was indicated as a treatment of recurrences. This may have had an impact on survival rate, which was lower (2-year rate of 60%), and on the local control of the disease, which was poorer than in our study. In addition, indication differences should be considered –in our series, intraoperative radiotherapy was indicated associated with the first surgery (when adjuvant radiotherapy had been indicated), and patients in whom indication took place following recurrence were not included.

The series published by Bedetti et al. showed the results achieved with radiotherapy treatment associated or non-associated with surgery, but intraoperative radiotherapy was not used. In their study, 3-year local recurrence-free survival was 95%, and 5-year survival was 89% in the group receiving radiotherapy after surgery[4]. In spite of the good results, which highlight the important role played by radiotherapy in the local control of the disease, radiotherapy treatment was not demonstrated to improve overall survival. Additionally, when comparing treatment with surgery ± adjuvant radiotherapy or definitive radiotherapy, the differences were not statistically significant.

Given the complexity of conducting randomized clinical trials in pediatric patients, along with the low incidence of Ewing sarcoma and the absence of certain treatment options in some medical institutions, the benefits of therapies such as proton therapy or intraoperative radiotherapy are difficult to analyze.

In the series published by Indelicato et al., the use of proton therapy translated into an increase in survival rate of up to 81.6% (mean follow-up of 4 years) and a 5-year local control rate of 97.2%[10]. These results are similar in terms of survival rate to those from our series with intraoperative radiotherapy.

Regarding chest wall reconstruction, successful reconstruction was achieved in all cases from our series. The availability of different chest plate sizes was key to provide rigid support and organ protection.

Today, there is no scientific evidence advocating the use of a given patch over the others[2,15]. Gore-Tex® patches entailed no complications in our series, which means they could be an adequate option when combined with muscle flaps.

67% of the patients undergoing surgery developed a certain degree of scoliosis after reconstruction. This proportion was greater than in other papers (43% in the series published by Scalabre et al.). Factors potentially favoring the development of scoliosis include resecting a large number of costal arches, resecting posterior arches, and conducting surgery in a stage of rapid growth or at an early age[16,17]. In our series, this was the most frequent complication. However, it should be noted that the increase in survival rates implies a higher incidence of long-term growth-related complications, such as scoliosis[3,15], which may have been reflected in our data.

The treatment of chest wall Ewing sarcoma requires a cross-disciplinary surgical approach consisting of oncological surgeons trained in thoracic surgery, surgeons trained in complex thoracic reconstruction, and pediatric plastic surgeons with experience in designing muscle covering flaps[2,18]. Today, this publication, along with other papers and scientific series, demonstrates that the increase in the survival rate of patients with Ewing sarcoma is directly related to a cross-disciplinary approach[4], based on the local control of the disease through highly complex, individualized surgeries, as well as individually targeted radiotherapy schemes. In our experience, and as part of the cross-disciplinary approach applied in our institution, the combination of wide resection surgery and intraoperative radiotherapy has allowed for a high survival rate, especially in patients with localized disease.

This paper demonstrates the role of intraoperative radiotherapy as a treatment option for the local control

of chest wall Ewing sarcoma, with good results in our patient series.

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