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ORIGINAL PAPER

Curettage, phenolization, and cementation in paediatric Ewing's sarcoma with a complete radiological response to neoadjuvant chemotherapy

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Abstract

Purpose Although wide resection is the standard treatment for Ewing's sarcoma (ES), it has complications especially in children. In this study, we compared the oncologic and functional outcomes of wide resection with extended curettage and local adjuvant therapy (phenolization and cementation), as a less extensive surgery for paediatric ES with a complete radiologic response to neoadjuvant chemotherapy.

Methods Children aged ≤ ten years, with ES of non-expendable long-bones and complete radiologic response to neoadjuvant chemotherapy, were included in this case-control study. Twenty-six patients were treated with extended curettage and local adjuvant therapy (case group) and 17 were managed with wide resection (control group). The average follow-up period was 60.1 ± 28.7 months (range 30–168 months). Functional outcome was assessed with the Musculoskeletal Tumor Society (MSTS) scoring system.

Results Three local recurrences (11.5%) and three distant metastases (11.5%) were observed in the case group. Two local recurrences (11.7%) and two metastases (11.7%) were recorded in the control group. The rate of local recurrence was not statistically different between the two study groups ($p = 0.668$). The rate of metastasis was not statistically different between the two study groups as well ($p = 0.668$). The complication rates were 15% in the case group and 53% in the control group ($p = 0.005$). The mean MSTS score was 98.3% and 74% in the case and control group, respectively ($p < 0.001$).

Conclusion The oncologic outcome of extended curettage and local adjuvant therapy in paediatric ES with complete radiological response to neoadjuvant chemotherapy is comparable to wide resection, yet it offers considerably better functional results.

Keywords Ewing's sarcoma · Neoadjuvant chemotherapy · Wide resection · Curettage · Paediatrics

Introduction

Ewing's sarcoma (ES), first described by James Ewing in 1921, is composed of primitive malignant round cells [1, 2]. Although it can affect any age group, approximately 80% of patients are younger than 20 years of age. ES is considered the most common primary malignant bone tumour in children younger than ten years old [3].

The standard management of ES includes neoadjuvant chemotherapy followed by surgical excision, radiotherapy (RT), or a combination of the two and adjuvant chemotherapy. In cases that surgical excision is not feasible due to anatomical limitations, inadequate surgical margin, or high risk of surgical morbidity, RT (without surgery) is the preferred approach [4]. Even so, RT is often overlooked as a primary option mainly due to its potential complications, such as RT-induced malignancies, increased risk of fracture, and its adverse effect on bone growth in children [5, 6].

Wide resection as the standard treatment for ES is an extensive surgery with complications, especially in children. A less-extensive surgical technique would be of considerable value especially in the paediatric group who outlive their disease.

Many investigations have provided convincing evidence on the better prognosis of ES in the paediatric population as compared to the adults [7–10]. In the most recent attempt, the study of Verma et al. who compared the outcome wide resection and/or RT in paediatric vs. adult ES patients revealed that adulthood negatively correlates with overall survival when

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adjusting for potential confounding factors [9]. Obata et al. also conducted a retrospective analysis of 243 patients with ES family of tumors. Local therapy included surgery (excision with different margins) in 35% of patients, surgery combined with RT in 40% of patients, RT alone in 22% of patients, and no local treatment in 3% of patients. Similarly, they found a significantly better overall and event-free survival in patients aged less than 16 years in comparison with patients with the age of 16 or more [8].

Additionally, it is acknowledged that radiologic response to neoadjuvant chemotherapy correlates well with the prognosis of ES, so that a poor radiologic response to neoadjuvant chemotherapy can be strongly associated with a poor prognosis and vice versa [11, 12].

An important clinical implication of this evidence in cases with good prognosis (paediatric ES with strong radiologic response to neoadjuvant chemotherapy) could be the reduction of surgical morbidity to improve quality of life after treatment, using a less-extensive surgical approach. Accordingly, we set out to perform such an approach using extended curettage and local adjuvant therapy (phenolization and cementation) in paediatric ES with complete radiologic response to neoadjuvant chemotherapy and compared its oncologic and functional outcomes to the conventional method of wide resection.

Patients and methods

From 1995 to 2014, 290 patients with ES were treated at our centre. Eligible patients for extended curettage were recruited. We thoroughly described the advantages and disadvantages of the two available surgical techniques of long-bone ES (wide resection and extended curettage) to the surrogate decision-makers of eligible patients and ask them to choose one. In this regard, a superior lifetime function along with a potentially smaller rate of tumour control was pointed as the characteristics of new approach versus inferior function along with a potentially higher rate of tumour control as the features of the conventional approach.

Our inclusion criteria were ES of long-bone, an age of less than ten years, follow-up of at least 24 months, complete response to neoadjuvant chemotherapy in MRI, and written consent from the patients' parents to perform extended curettage. Patients with extra-skeletal ES, expendable-bone ES, Askin tumor, incomplete response to chemotherapy, axial skeletal ES, bone marrow involvement, and metastatic tumour were excluded from the study. Extra-skeletal ES, expendable-bone ES, Askin tumour, and incomplete response to chemotherapy were managed with wide resection. Axial skeletal ES, bone marrow involvement, and metastatic tumor were treated by RT. Patients with the follow-up of less than two years were excluded from the study as well.

During the study period, a total of 43 patients with ES were qualified to include in this case-control study, from whom 26 underwent extended curettage with local adjuvant therapy (case group) and 17 were managed with wide resection (control group). The control group consisted of patients who denied the recommended protocol.

The mean age of the patients was 6.5 ± 2.9 years. The mean follow-up period of the patients was 60 ± 31 months (range 30–168 months). The femur was the most frequent site of involvement (13 cases and 7 controls) followed by tibia (6 cases and 4 controls), humerus (5 cases and 3 controls), and radius (2 cases and 3 controls). The clinical and demographic characteristics of the two study groups are listed in Table 1.

Data collection included pathologic and demographic characteristics, as well as the surgical, oncologic, and functional outcomes of the patients. Core needle biopsy was performed for all the patients except two, in whom the samples were not representative and open incisional biopsy was performed as well. ES was diagnosed with the identification of the small blue round cells and positive CD99 in the immunohistological analysis. Subspecialized pathologists reviewed all cases in-house.

Table 1 The clinical and demographic characteristics of the patients of the two study groups

Variable	Mean ± SD or number (%)		*p* value
	Curettage (*n* = 26)	Wide resection (*n* = 17)	
Age (years)	6.78 ± 2.7	6.1 ± 3	0.506
Gender			
• Female	15 (57.7)	9 (53)	
• Male	11 (42.3)	8 (47)	0.454
Follow-up (month)	60.8 ± 35	56.2 ± 28	0.358
Recurrence	3 (11.5)	2 (11.8)	0.668
Metastasis	3 (11.5)	2 (11.8)	0.668
Death	2 (7.7)	1 (5.9)	0.712
Necrosis (%)	95 ± 7.2	94 ± 7	0.515

Treatment protocols

After four courses of neoadjuvant chemotherapy including vincristine, ifosfamide, doxorubicin, and etoposide (VIDE protocol) [13], the radiologic effect of neoadjuvant chemotherapy was evaluated using MRI with 3-dimensional measurements (RECIST guideline) [14]. The tumour size was assessed both before and after the neoadjuvant chemotherapy, and the response was classified into four categories: complete response (100% volume reduction), partial response (30 to 100% volume reduction), stable disease (30 to − 20% volume reduction), and progressive disease (less than − 20% volume reduction) [15]. Patients with complete radiologic response to neoadjuvant chemotherapy were assigned into the case or control group.

The case group underwent extended curettage and local adjuvant therapy, which included phenolization and cementation (Figs. 1 and 2). For this procedure, the biopsy tract was excised to the surface of the involved bone through a longitudinal incision. Then an oval large cortical window with rounded ends was made over the entire length of the involved bone. Subsequently, the tumor in the medulla was removed with a curette. The bony margin at the cortical wall was extended a few millimeters with a high-speed 2-mm burr. Local adjuvant therapy including chemical (phenolization) and thermal adjuvant (cementation) was applied afterward. Application of cement also provides an early stability and easier detection of local recurrence.

After three minutes of phenolization (6% concentration) [16] followed by rinsing with a saline solution, the defect was filled with polymethylmethacrylate and a prophylactic surgical stabilization was applied if needed.

Frozen sections of adjacent soft-tissue were intraoperatively sent to pathology and investigated for any residual tumor. We were prepared to change the surgical procedure to wide resection when a positive soft-tissue frozen section was detected. However, this was not the case in any of our patients.

For the control group, we performed wide resection with a wide margin and reconstruction as described previously [17]. Osteoarticular and intercalary allografts were used for the reconstruction of proximally located and diaphyseal tumors, respectively.

After the surgery, all the resected tissues were sent to pathology to assess histopathological response to the neoadjuvant chemotherapy in a semi-quantitative manner, which was performed by grading the extent of necrosis relative to the percentage of the residual viable tumor [18]. Patients received chemotherapy after surgery. In recurrent cases, the chemotherapy regimen was carboplatin-based adjuvant chemotherapy (prior to 2007 [19]) or a

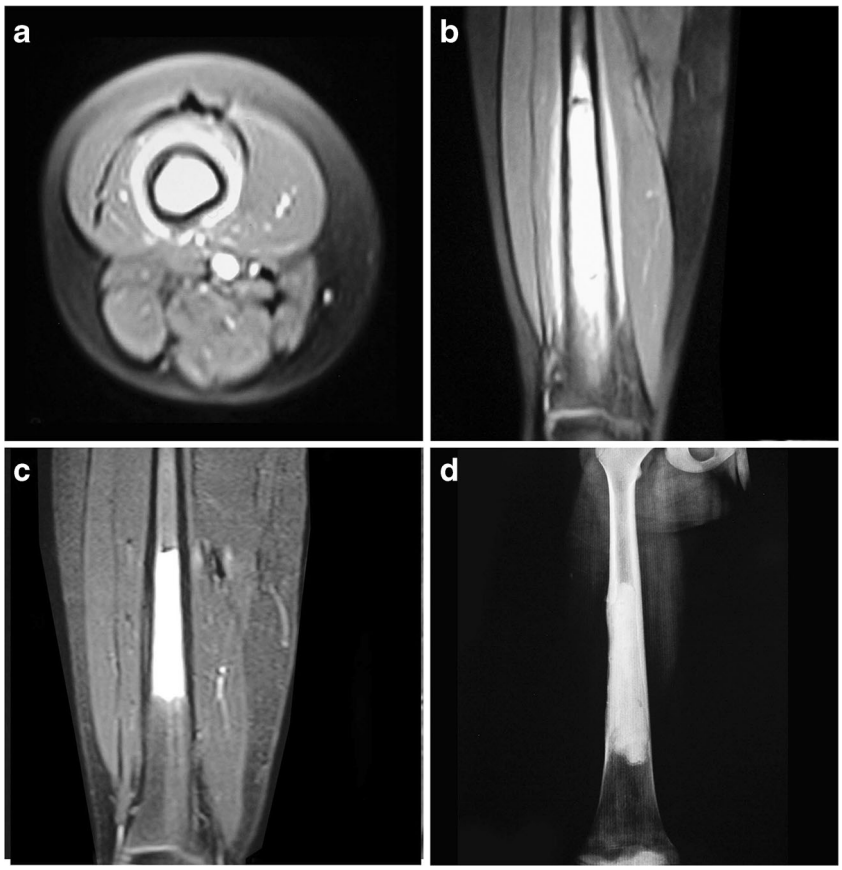

Fig. 1 A 10-year-old girl with Ewing's sarcoma of the right femoral shaft; **a** Axial T2-weighted fat suppressed MRI showing soft tissue component of tumor before neoadjuvant chemotherapy; **b** Coronal T2-weighted fat suppressed MRI showing medullary extension and extra-medullary involvement of affected bone; **c** Coronal T2-weighted fat suppressed MRI showing the complete disappearance of soft tissue component after neoadjuvant chemotherapy; **d** Antero-posterior radiograph of the femur, 3 years after extended curettage and cementation

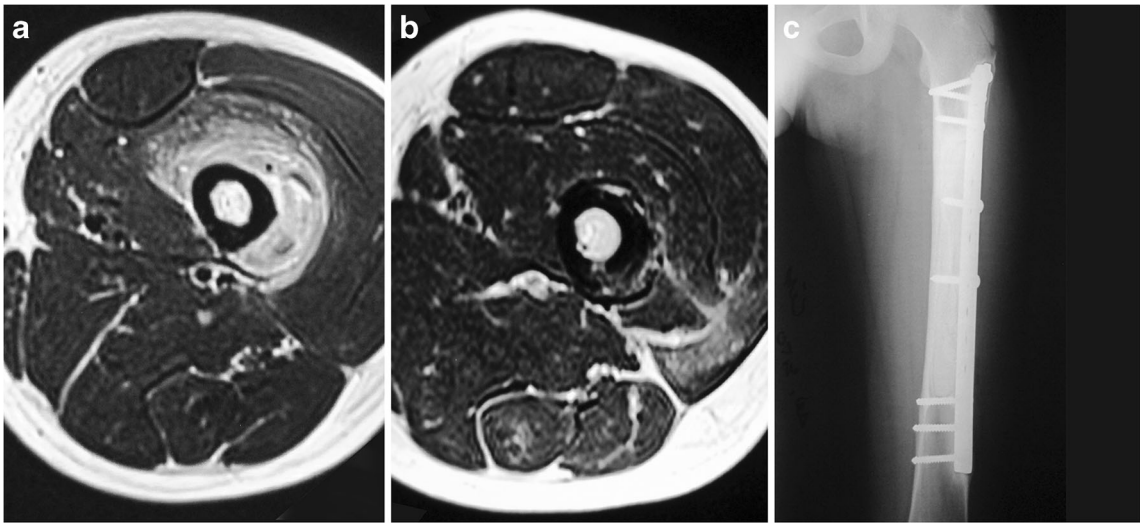

Fig. 2 A 9-year-old girl with Ewing's sarcoma of the left femoral shaft; **a** Axial T2-weighted MRI showing the soft tissue component before neo-adjuvant chemotherapy; **b** Axial T2-weighted MRI showing the complete shrinkage of soft tissue component after neoadjuvant chemotherapy; **c** Antero-posterior radiograph of the femur 4 years after extended curettage and cementation with fixation

combination of temozolomide and irinotecan as second-line chemotherapy (after 2007 [20, 21]). The therapeutic approaches for relapsed cases are outlined in Table 2.

Post-operative protocol and follow-up

In the case group with upper limb involvement, the limb was immobilized using a sling for two weeks after surgery. No immobilization was performed, however, for the lower limb involvement. The patients were allowed to bear weight as soon as tolerated. In the control group with upper limb involvement, the shoulder was immobilized in sling and swathe, and motion exercises were administered four weeks after the surgery. For the lower limb, patients were asked to have non-weight bearing ambulation until radiological union. Post-operative follow-ups were every three months for the first two years and every six months afterward. During each visit, clinical and radiological evaluations of the patients were performed. Post-operative adjuvant RT was not administered. At the last follow-up, the functional outcome was assessed using the Musculoskeletal Tumor Society (MSTS) scoring system, assessed with the help of the patients' family.

Statistical analysis

The descriptive evaluation of the variables, such as central tendency and variability, were performed using the mean and standard deviations (SD), respectively. The Kaplan-Meier estimator was used to measure the overall and event-free survival of the patients. The log-rank test was used to compare the survival rate of the two study groups. SPSS for Windows, version 16, was used for all statistical analyses. Type I error significance level used was 5% ($\alpha = 0.05$).

Results

In long-term follow-up, three local recurrences (11.5%) were observed in the case group. Two of these recurrences occurred in the soft tissue, while the other one recurred in the bone. The mean time for the development of local recurrence was 21 months. In addition, three metastases (11.5%) were observed in this group of patients. The mean time to the occurrence of metastasis was 22 months. The metastasis led to the death in two patients.

In the control group, two local recurrences (11.8%) were recorded. Both of these tumors recurred in the soft tissue. The mean time to the development of local recurrence was 24 months. Two metastases were observed in this group of patients (11.8%), which led to the death of one patient. The mean time to metastasis was 24 months.

The rate of local recurrence was not significantly different between the case and control group (three vs. two cases, $p = 0.668$). The rate of metastasis was not significantly different between the case and control group as well (three vs. two cases, $p = 0.668$). Moreover, the death rate was not statistically different between the case and control group (two vs. one case, $p = 0.712$).

The two and five year overall survivals of the patients were 100% and 92% in both groups, respectively. Accordingly, the two and five year overall survivals of the patients were not significantly different in the two study groups (log-rank test, $p = 0.991$) (Fig. 3a). The two and five year event-free survivals

Table 2 Management and outcome of the relapsed Ewing sarcomas

Event	Group	Involved bone	Month	Management of relapse	Follow-up after event (months)	Patient status
Local recurrence	Case	Diaphyseal tibia	21th	Segmental resection and intercalary allograft and chemotherapy	18	Alive without disease
Local recurrence	Case	Distal tibia	18th	Amputation and chemotherapy	18	Alive without disease
Local recurrence and lung metastasis	Case	Diaphyseal humerus	24th	Local radiotherapy and chemotherapy	6	Dead
Widespread metastasis	Case	Diaphyseal femur	24th	Aggressive chemotherapy	6	Dead
Metastasis in the fifth rib	Case	Proximal humerus	18th	Excision of the rib and chemotherapy	18	Alive without disease
Lung metastasis	Control	Proximal humerus	30th	Chemotherapy	6	Dead
Local recurrence	Control	Diaphyseal femur	24th	Tumor resection and local radiotherapy and chemotherapy	24	Alive without disease
Local recurrence	Control	Proximal femur	24th	Tumor resection and local radiotherapy and chemotherapy	36	Alive without disease
Lung metastasis	Control	Diaphyseal tibia	18th	Chemotherapy	18	Alive with disease

of the case group were both 81%. The two and five year event-free survival of the control group were 82% and 78%, respectively. Event-free survival was not significantly different between the case and control group as well (log-rank test, $p = 0.631$) (Fig. 3b).

The mean MSTS score of the patients was 98.3% (90–100%) in the case group. The mean MSTS score of the control group was 74% (60–90%). This difference was statistically significant ($p < 0.001$).

The percentage of histologic necrosis was not significantly different between the two study groups ($p = 0.515$) (Table 1).

In total, a 100% histologic necrosis was observed in 27 out of 43 patients. Four oncologic events occurred in this group, which found to be distant metastasis in all cases. Less than 100% histologic necrosis was reported in the remaining 16 patients. Six oncologic events including five local recurrences and one metastasis occurred in this group.

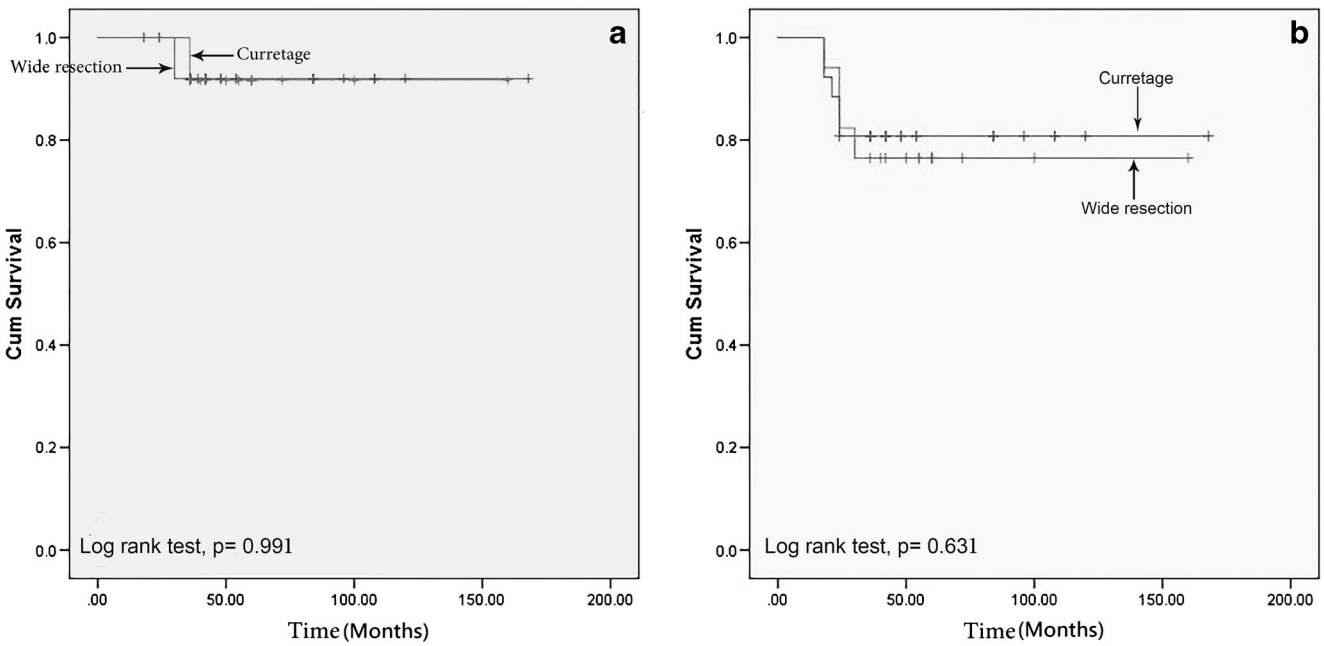

Fig. 3 Log-rank test; **a** Comparison of survival to death between the two study groups; **b** Comparison of survival to any oncologic event between the two study groups

In the case group, complications occurred in 15% of the patients (four out of 26 patients). In this respect, post-operative varus deformity was seen in two patients. In one of them, the varus deformity was spontaneously corrected after 2 years. However, the deformity remained unresolved in the other patient up until the last follow-up. Pathologic fractures occurred in two patients, which were managed with open reduction and internal fixation. No further complications were recorded in this group of patients.

In the control group, complications occurred in 53% of cases (nine out of 17 patients). Two deep infections were observed (one tibia and one femur), which were managed with debridement and antibiotic therapy. Four nonunion and three allograft fractures occurred which were managed by autogenous bone graft and reinsertion of a new allograft, respectively.

The difference of complication rates between the two study groups was statistically significant ($p = 0.005$).

Discussion

Age and radiologic response to neoadjuvant chemotherapy are frequently reported as the prognostic factors of ES, so that childhood and a significant decrease in the size of the tumour after chemotherapy could predict a favourable outcome [7–12]. These results highlight that a single therapeutic approach should not be used for all cases of ES and features such as age and radiologic response to neoadjuvant chemotherapy could be employed in planning treatment individually. We used these features to plan curettage and local adjuvant therapy instead of wide resection of ES in a selected group of patients. Our rationale with extended curettage was to prevent compromising the limb functions, yet providing a tumour control comparable to wide resection.

Since ES is usually a diaphyseal tumour far from the growth plate [22], RT does not adversely affect the growth plate in such cases. However, extended curettage provides the opportunity for histologic evaluation of the chemotherapy effect intra-operatively by frozen section and post-operatively by permanent section, which could be considered as the advantage of this approach. Moreover, extended curettage does not cause other RT-associated complications including RT-induced malignancies and increased risk of fracture [5, 6].

Extension of margin manually by high-speed burring, chemically by phenolization, and thermally by cementation is another reason for the selection of this treatment.

The rates of local recurrence and metastasis following the wide resection of ES vary among studies (range 10–15% for local recurrence and 38.8–45% for metastasis) [23–25]. In this study, the rate of local recurrence and metastasis was 11.8% following the wide resection of the tumour and 11.5% after the extended curettage and local adjuvant therapy. It could be concluded that the oncological outcomes of the two surgical strategies are comparable in paediatric ES population with complete radiological response to neoadjuvant chemotherapy.

Unfavourable functional results have been frequently reported following the wide resection of ES. Do Kim et al. reported an MSTS score of 53% following the wide resection of ES [25]. Another study by Bacci et al. assessed the functional outcome of 38 patients with ES of the femur treated with wide resection including rotationplasty in three cases [26]. With this extensive approach, the excellent functional result was seen in only one patient, while good and poor results were observed in 32 and five patients, respectively. This study again highlights the significant morbidity subsequent to wide resection surgical techniques.

In this study, the mean MSTS score of the patients was 98.3% in the case group and 74% in the control group. In line with the results of earlier investigations, the inferior functional outcome was seen in the resection group.

From a biological point of view, the tumour cannot recur after intralesional surgery of ES with 100% necrosis. No local recurrence was seen in 27 patients of our study who showed 100% necrosis in the histologic examinations. The necrosis percentage obtained from histologic examinations was less than 100% in 16 cases. Local recurrence occurred in five of these patients.

Our results were in accordance with the study by Albergo et al. which showed significantly better rates of event-free survival in patients with 100% necrosis after chemotherapy compared to those with any viable tumour cells in the surgical specimens [27]. In other words, in children with complete radiological response to chemotherapy and 100% histologic necrosis (27 out of 43 patients of this study), there was a very good chance of tumour control with curettage. Similar results were reported in the study of Kadhim et al. Based on their report, ES lesions with nearly complete histological response to chemotherapy survived with no evidence of tumour, while those who had lower necrosis rate indicated reduced event-free survival [28].

Thus, development of a more definitive approach for pre-operative identification of patients with 100% histologic necrosis could considerably optimize the current method and help the stratification of patients who may most benefit from this approach. Modern imaging modalities such as serial positron emission tomography (PET) scan, although challenging in children, can be helpful in this regard [29].

In cases with less than 100% necrosis in the histologic evaluation, the surgeon might employ additional therapy such as adjuvant RT to reduce the risk of local recurrence.

In terms of the limitations of this study, we had a small number of cases compared in a retrospective design. Moreover, the choice of treatment strategy was non-randomized. Thus, prospective randomized studies with a larger sample size are needed to be performed in the future.

Altogether, extended curettage and local adjuvant therapy, as a less-extensive surgical approach, could be used in the management of pediatric ES with a complete radiological response to neoadjuvant chemotherapy, giving rise to an acceptable oncologic outcome and a considerably superior functional outcome in comparison with wide resection. The results are more favourable in patients with 100% necrosis compared to those with < 100% necrosis in the post-operative histological examination. Thus, this approach could be further personalized in future investigations in order to determine which patient will most benefit from this technique and which patient will need additional therapeutic intervention such as adjuvant RT.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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