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Radiotherapy in Ewing's Sarcoma Family Tumor — experience from North-East India

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ABSTRACT

Introduction. The multimodality management of Ewing's Sarcoma Family Tumors (ESFT) consists of neoadjuvant chemotherapy followed by local treatment: surgery, radiotherapy (RT) or a combination of both. The objectives of this study were to analyze disease control and overall survival in patients receiving radiotherapy as local treatment, as part of multimodality management of ESFT at our institute over a period of seven years.

Material and methods. This is a retrospective single institutional study. Hospital records were searched for patients with ESFT who received radiotherapy from January, 2012 to December, 2018. Forty-nine patients were found eligible and evaluated with respect to prognostic factors, treatment-related factors and outcomes. Time to event was measured from the date of diagnosis and survival curves were estimated by Kaplan-Meier method and log-rank test for comparison.

Results. Median follow up for patients was 18 months (range 3–81 months). Local failure/relapse was associated with worse survival. Five-year local control was 79.1% and overall survival 51.2% in the analyzed cohort. Local control did not differ significantly based on prognostic variables or treatment characteristics. Combined surgery and radiotherapy as local treatment along with good response to neoadjuvant chemotherapy were associated with significant improvement in overall survival (p-value < 0.05).

Conclusions. Combined modality local treatment with surgery and radiotherapy along with a favorable response to neoadjuvant chemotherapy are associated with improved survival in ESFT. For unresectable tumors, radiotherapy alone remains the optimum local treatment, albeit with inferior survival outcomes.

Key words: Ewing's Sarcoma, PNET, ESFT, radiotherapy, surgery, chemotherapy

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Introduction

The Ewing's Sarcoma Family of Tumors (ESFT) comprises of a group of primary bone and soft-tissue tumors that include classic Ewing's sarcoma (osseous and extra-osseous), peripheral primitive neuroectodermal tumor (PNET) and Askin tumor of the chest wall. Histologically they are malignant small-round-blue-cell tumors, first described by James Ewing in 1921 [1]. Around 90% of patients have a genetic translocation [t(11;22) or t(21;22)] involving the *EWS* and *FLI1* genes and frequent expression of *c-Myc proto-oncogene* [2].

The incidence of Ewing-family tumors peaks in adolescence, is slightly more common in males, and commonly arises in the extremities [3]. It has a high incidence in the Western population while being rarer in Asia and Africa [4].

Ewing's Sarcoma has a good prognosis nowadays with the advent of newer regimens of systemic therapy in combination with adequate local treatment [5–10]. Definitive local control of the primary tumor is a pre-requisite of cure, and local failures are associated with extremely poor prognosis. Local treatment modalities in Ewing's sarcoma consist of surgery and/or radiotherapy (RT). Because of the radiosensitive nature

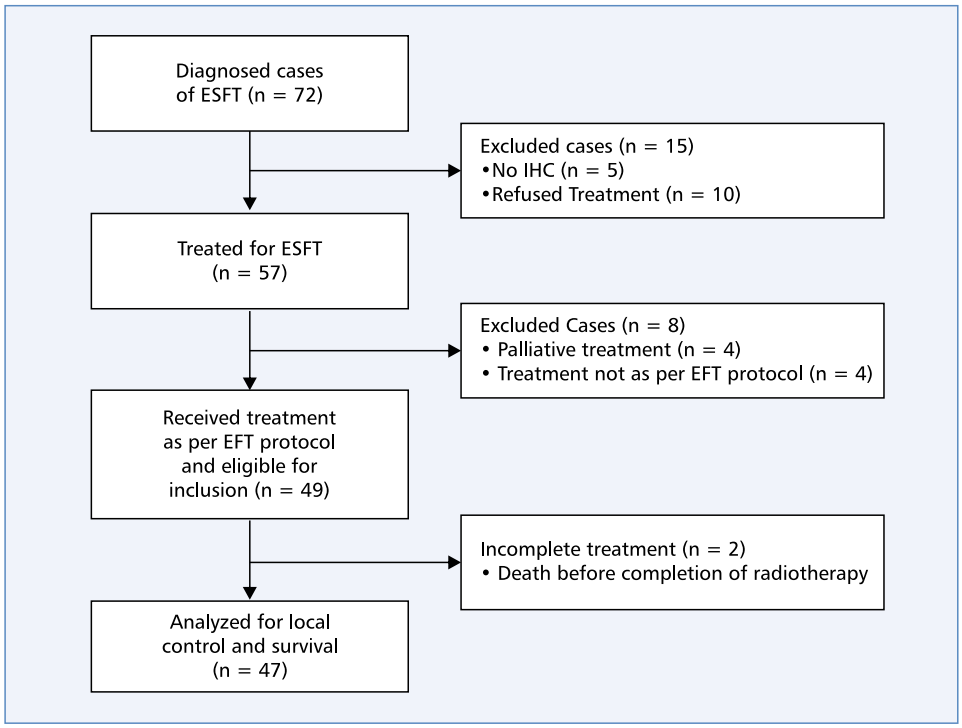

Figure 1. Schematic chart showing patient evaluation and analysis for the study

of this tumor, radiotherapy had been the local treatment of choice for many years. However, with better systemic control of disease, advances in orthopedic surgery and chances of second malignancy post irradiation, the use of radiotherapy in ESFT is gradually declining [11]. However, for lesions located in the axial skeleton or where surgery is not feasible, RT remains the sole option for local therapy.

In this single-institution retrospective study from North East India, we investigate the role of radiotherapy as local treatment in the multimodality management of ESFT patients. The objectives were to analyze disease control and overall survival in patients of this group of tumors receiving radiotherapy at our institute over the study period.

Material and methods

From the period of January, 2012 to December, 2018, patients registered with diagnosis of Ewing's Family Tumor in the hospital were assessed. All data were obtained from patients' case files and Hospital-Based Cancer Registry records and all the analyzed data for this study are included in this published article. The study was approved by the Institutional Ethics Committee and because this was a retrospective study, the requirement of patients' consent was waived.

Patients

Patients diagnosed as osseous or extra-osseous Ewing's Sarcoma, peripheral Primitive Neuro-Ectodermal Tumor (PNET) and Askin's tumor of the chest wall with Immunohistochemistry confirmation (CD 99, FLI-1 positive) were considered for evaluation in this study. Those without IHC confirmation of tumors and who declined or defaulted treatment were excluded. Also, patients who did not receive radiotherapy as part of their local treatment were omitted from assessment in this study. A summary of cases evaluated and analyzed is shown in Figure 1.

Taking into consideration the above criteria, 49 patients were found eligible for retrospective review during the study period. Patient demographics, tumor characteristics and treatment details for them were noted.

Treatment and follow-up

The intent of treatment received was as per the decision of the Multidisciplinary Joint Tumor Board of the institute and all patients received treatment as per Ewing's Family Tumor (EFT) protocol. Neoadjuvant Chemotherapy included two courses of Vincristine, Ifosfamide and Etoposide (VIE) 3 weekly followed by two courses of Vincristine, Adriamycin and Cyclophosphamide (VAC) 2 weekly. Local therapy in the form of surgery or radiotherapy or both, depending on the

location and resectability of the primary tumor, had to be offered between weeks 9 and 12 of treatment. Resectable tumors underwent surgery as the primary local treatment followed by adjuvant radiotherapy based on histopathology and margin status. Borderline resectable cases after induction chemotherapy underwent pre-operative radiotherapy followed by surgery, whereas tumors which were found inoperable received radical radiotherapy alone as local treatment. Radiotherapy doses were 45 Gy pre-operatively, 50–54 Gy post-operatively and 50–60 Gy in radical setting (at 180–200 cGy per fraction). Maintenance therapy after local treatment consisted of 3 weekly chemotherapy with 4 cycles of VAC, 2 cycles of VIE and 6 cycles of VCD – Actinomycin D replacing Doxorubicin after a cumulative dose of 360 mg/m^2. Vincristine was given weekly throughout the chemotherapy schedule and also along with radiotherapy [12].

Treatment records of patients were evaluated for details of chemotherapy, surgery and radiotherapy received by them. Follow up details of local examination and imaging of primary site as well as metastasis was also noted. Response to induction chemotherapy was assessed from the surgical specimen in resected cases and by imaging in unresected cases.

Outcome analysis

Response to treatment was classified as per the revised Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 [13]. A good response to induction chemotherapy was classified as > 90% necrosis in resected specimen in patients who underwent surgery and a complete or partial response in the tumor site for unresectable cases.

Tumors with complete or partial response or stable disease at the primary site without appearance of new metastatic lesions were considered locally controlled. Disease progression was defined as clinical or radiographic increase in the size of primary or metastatic tumor or appearance of new metastatic lesion. Overall survival (OS) was defined as the time interval from diagnosis till death.

Statistical analysis

SPSS version 19 (IBM Company Copyright 1989, 2010 SPSS, Inc.) was used for statistical analysis. Chi-square test was used to evaluate treatment and prognostic factors for local control. Survival and local control rates were calculated using Kaplan-Meier estimation and log-rank test was used for group comparisons. A Cox proportional hazards model was used to clarify independent predictive factor in multivariate analysis. Statistical significance was defined as a p-value of < 0.05.

Results

The median follow up of entire cohort was 18 months (Range 3–81 months). The various patient- and tumor-related variables of the study are shown in Table 1.

Patient characteristics

The mean age of patients was 15.29 years (SD: 10.13), with 53.1% patients aged 10–19 years and Male:Female ratio of 1.7:1. The median duration of symptoms among the patients was 5 months (Range: 1–12 months).

Tumor characteristics

The mean tumor size was 9.09 cm (SD = 3.44). The majority of cases showed presence of a soft tissue mass (85.7%) with radiological evidence of tumor necrosis in 34.6%. Most common sites of tumor location were the femur and pelvis (n = 7, 14.3% each). Most of tumors had skeletal origin (73.5%) and were centrally located (61.2%). Four patients (8.2%) had metastatic disease at diagnosis with bone metastasis being most common (3 cases).

Treatment characteristics

All 49 patients included in the study were planned with intent to cure or salvage (Fig. 1). Neoadjuvant chemotherapy was received by all except one patient. Surgery as local treatment was used in 14 cases, with 11 patients undergoing complete resection with clear margins (R0) while 3 had marginal/intralesional resection of their tumors. All patients that underwent surgery also received radiotherapy — 5 preoperative and 9 postoperatively.

Radiotherapy was the definitive local therapy planned in 71.4% (35/49) of our patients. Among them, a dose of 54 Gy or above was used in 28 patients, 5 patients received less than 54 Gy and 2 patients died before radiotherapy completion (one each from sepsis and disease progression). Radiotherapy was delivered using conventional planning techniques in majority (63.2%) of the patients (Tab. 1).

Local control and survival analysis

The 2 patients of ESFT who could not complete planned radiotherapy treatment were omitted from survival and disease specific analysis and hence the total number of cases for final evaluation was 47. The 5-year local control and overall survival for the study group was found to be 79.1% and 51.2%, respectively (Fig. 2). An important prognostic indicator of better survival was achievement of local disease control. Cases where

Table 1. Patient and tumor related characteristics

Variables	n (%)
Age	
< 18 years	38 (77.6%)
18 years and above	11 (22.4%)
Sex	
Male	31 (63.3%)
Female	18 (36.7%)
Duration of Symptoms	
< 6 months	26 (53.1%)
6 months and above	23 (46.9%)
Imaging for Staging	
CT Scan	27 (55.1%)
MRI	17 (34.7%)
PET-CT Scan	5 (10.2%)
Tumor Size	
Less than 8 cm	20 (40.8%)
8 cm and above	29 (59.2%)
Tumor Site	
Skeletal	36 (73.5%)
Extra-Skeletal	13 (26.5%)
Tumor Location	
Central	30 (61.2%)
Peripheral	19 (38.8%)
Metastasis at Diagnosis	
Yes	4 (8.2%)
No	45 (91.8%)
NACT	
Yes	48 (98%)
No	1 (2%)
Radiotherapy Technique	
Conventional	31 (63.2%)
3DCRT	14 (28.6%)
IMRT	4 (8.2%)

CT — computed tomography; MRI — magnetic resonance imaging; PET-CT — positron emission tomography-computed tomography; NACT — neo-adjuvant chemotherapy; 3DCRT — 3-Dimensional conformal radiotherapy; IMRT — intensity modulated radiation therapy

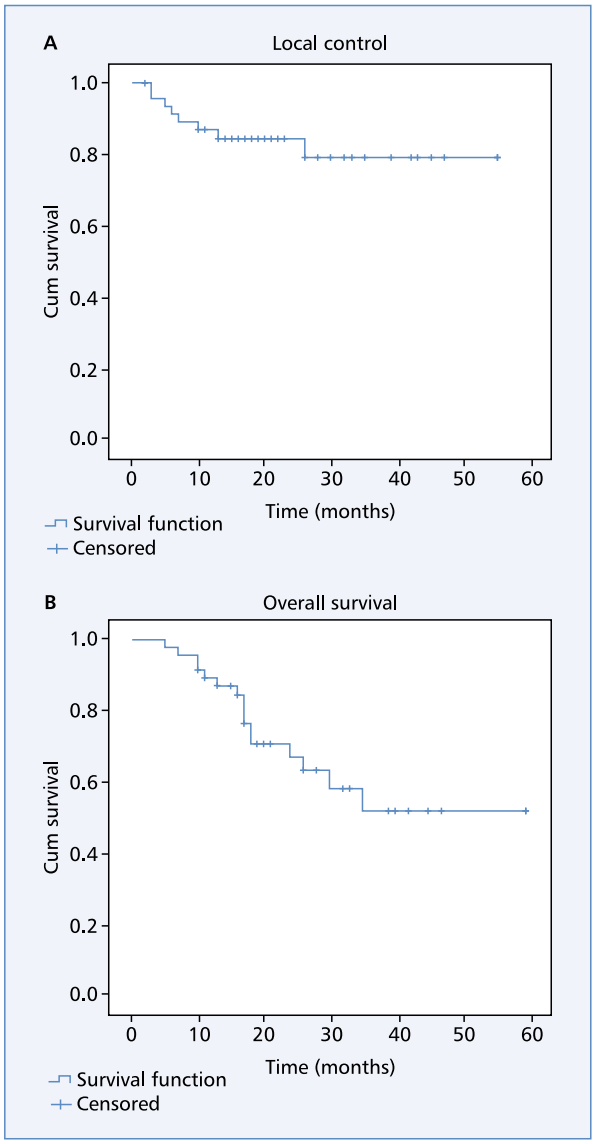

Figure 2. Kaplan-Meier curves showing local control (A) and overall survival (B) of study group (n = 47)

primary tumor was locally controlled following multimodality therapy had significantly better 5-year overall survival (53.3% *v.* 33.3%, p = 0.038, Fig. 3).

Univariate analysis of the patient-, tumour- and treatment-related characteristics with local control was carried out and is depicted in Table 2. Univariate and multivariate analysis of various prognostic factors with survival for these patients are shown in Table 3.

Local control rates did not differ significantly among the different enlisted prognostic variables (all p-values > 0.05). A subset analysis was performed to look into the impact of local treatment modality with respect to tumor size (< 8 cm *v.* 8 cm and above) and location (central vs peripheral), which is shown in Figure 4. Local control with combined surgery and radiotherapy was better compared to definite radiotherapy irrespective of these variables, but the difference was statistically insignificant.

A favorable response to neoadjuvant chemotherapy (p-value = 0.044) and combined surgery and radiotherapy as local treatment therapy (p-value = 0.022) were also associated with better survival in patients with non-metastatic ESFT. On multivariate analysis, response to neoadjuvant chemotherapy was found to be the only independent prognostic factor for OS (HR: 0.301, 95% CI: 0.093–0.970, p-value: 0.044).

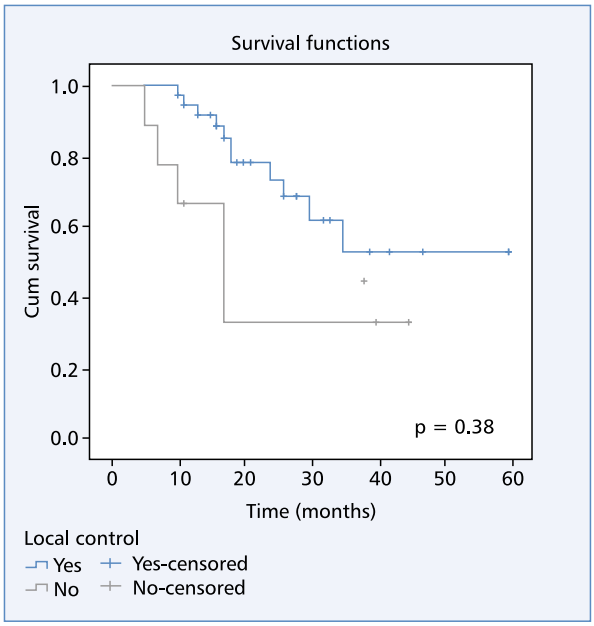

Figure 3. Kaplan-Meier curves showing overall survival based on local disease control status for study group (n = 49)

Discussion

ESFTs are comparatively rare in Asian population [4, 14]. Chakraborty et al. [15] reported that ESFT comprises 15% of all bone malignancies in India. They found 68% of the cases in 0–19 years age group with male preponderance (1.6:1) and a higher risk of tumor in the bones of limbs (1.6 times) compared to other bones. Our findings (Tab. 1) correlate with their observation except that most of our cases had tumors located in the axial skeleton and pelvis (61.2%) rather than in the limb bones. The median duration from symptoms to definitive diagnosis in our patients was 5 months, which correlates with the findings by Sneppen et al. [16] who reported a median duration of 3 to 9 months. The majority of patients in our study (59.2%) had large tumor size (≥ 8 cm) which is an established poor prognostic factor [9, 17, 18]. Another observation to be noted was the high percentage of patients with good response to neoadjuvant chemotherapy (76.5%) — a prognostic indicator of better survival [19–21]. Around one fourth of Ewing's sarcoma patients have metastatic disease upfront and often show a dismal prognosis. [3] In our study, however, the proportion of metastatic cases were low (n = 4, 8.2%). This was because the majority of metastatic ESFT cases often presented with poor general condition and hence received palliative therapy, which made them ineligible for inclusion in this study.

The role of chemotherapy in successful treatment of ESFT has evolved considerably over last few decades and is still evolving. [12] The Intergroup Ewing's Sarcoma Studies (IESS) I and II [5, 6] and the study by Grier et al. [7] established the role of multidrug chemotherapy in the management of ESFT. The Childrens Oncology Group AEWS-0031 study [8] subsequently demonstrated the

Table 2. Univariate analysis of local control of the localized Ewing's Sarcoma Family Tumor cases

Variables	n (%)	Univariate Analysis	
		5-year Local Control (%)	p-value
Age			
< 18 years	36 (76.5)	90.9	0.52
18 years & above	11 (23.5)	76.9	
Tumor Size			
< 8 cm	19 (40.4)	87.5	0.103
8 cm & above	28 (59.6)	75.3	
Tumor Location			
Central	28 (59.5)	80.9	0.756
Peripheral	19 (40.5)	78.3	
Response to NACT			
Yes	36 (76.5)	82.2	0.592
No	10 (21.2)	78.8	
Type of Local Treatment			
Surgery + RT	14 (29.8)	92.3	0.214
RT alone	33 (70.2)	71.0	
RT Dose (Definitive RT only)			
< 54 Gray	5 (15.2)	69.4	0.996
54 Gray and above	28 (84.8)	80.0	

NACT — neoadjuvant chemotherapy; RT — radiotherapy

Table 3. Univariate and Multivariate Analysis of Overall Survival of the Localized ESFT cases

Prognostic Factors	n (%)	Univariate Analysis		Multivariate Analysis	
		5-year OS (%)	p-value	HR (95% CI)	p-value
Age					
< 18 years	36 (76.5)	51.2	0.96	1.020 (0.273–3.809)	0.977
18 years & above	11 (23.5)	39.0			
Tumor Size					
< 8 cm	19 (40.4)	62.8	0.264	2.205 (0.627–7.753)	0.218
8 cm & above	28 (59.6)	41.5			
Tumor Location					
Central	28 (59.5)	32.9	0.055	0.283 (0.076–1.055)	0.060
Peripheral	19 (40.5)	78.9			
Duration of Symptoms					
< 6 months	25 (53.2)	60.5	0.463	1.302 (0.453–3.743)	0.624
6 months and above	22 (46.8)	43.4			
Response to NACT					
No	10 (21.2)	19.0	0.044	0.301 (0.093–0.970)	0.044
Yes	36 (76.5)	61.4			
Type of Local Treatment					
Surgery + RT	14 (29.8)	83.3	0.022	0.387 (0.079–1.887)	0.240
RT alone	33 (70.2)	31.1			

NACT — neoadjuvant chemotherapy; RT — radiotherapy; OS — overall survival; HR — hazard ratio; CI — confidence interval

benefit of dose intensification and interval compression of chemotherapy regimen without increased toxicity. So, the current standard of care is initial cytoreductive chemotherapy to eliminate micrometastasis followed by local therapy of primary disease and then consolidation chemotherapy to reduce tumor recurrence. In our study, all but one patient received treatment as per the Ewing Family of Tumors 2001 protocol. One patient did not receive neoadjuvant chemotherapy but underwent upfront surgery followed by adjuvant radiotherapy and chemotherapy. The reason for declining neoadjuvant chemotherapy for this patient could not be ascertained owing to the retrospective nature of this study.

Effective local treatment of the primary tumor plays a crucial role in the outcome of ESFT patients. In our study, local control showed significant correlation with survival: 5 year overall survival 53.3% in locally controlled patients as opposed to 33.3% in local failures or relapsed cases (p-value = 0.038). Till date, there are no randomized controlled trials comparing surgery versus radiotherapy in ESFT and all data available are retrospective in nature [9, 17, 18].

Schuck et al. [9] reviewed 1058 patients of localized ESFT for the impact of local therapy on local control and event free survival. Definitive radiotherapy showed higher incidence of local failure and poorer EFS after 5 years as compared to surgery with or without radiotherapy groups (p value < 0.05). They also demonstrated that intralesional or debulking surgeries followed by adjuvant radiotherapy offered no advantage over definitive radiotherapy and hence should be avoided.

Choi et al. [17] from South Korea reviewed 91 localized ESFT patients and reported higher local control rates with combined surgery and radiotherapy versus definitive radiotherapy (90.2% *v.* 64.8%, p value = 0.052). The superiority was found to be significant for tumors 8 cm or more in size (p value= 0.033) but not for smaller tumors (p value = 0.374).

Biswas et al. [18] in a single institution retrospective review have published the largest reported data on localized ESFT (224 cases) from India. They observed 5-year overall survival of 52.4% (± 4.3%) and local control rate of 63% (± 4.3%). On subgroup analysis, combined surgery and radiotherapy showed a hazard ratio of 2.5 (95% CI 1.2–5.19, p-valu e= 0.01) compared to radiotherapy alone for local control and also significantly improved 5-year event-free survival (50.4% *v.* 32.1%) and overall survival (69.1% *v.* 46.9%).

In our study, ESFT cases (n = 47) showed a 5-year local control rate of 79.1% and overall survival of 52.1%. Local control rates did not differ significantly among the various prognostic groups like age, tumor size, tumor location or response to neoadjuvant chemotherapy (all p-values > 0.05) as shown in Table 2. Fourteen patients (29.8%) underwent resection of their tumors in our study — 5 patients received radiation preoperatively and 9 patients postoperatively. Radiotherapy was delivered preoperatively in large tumors of resectable locations

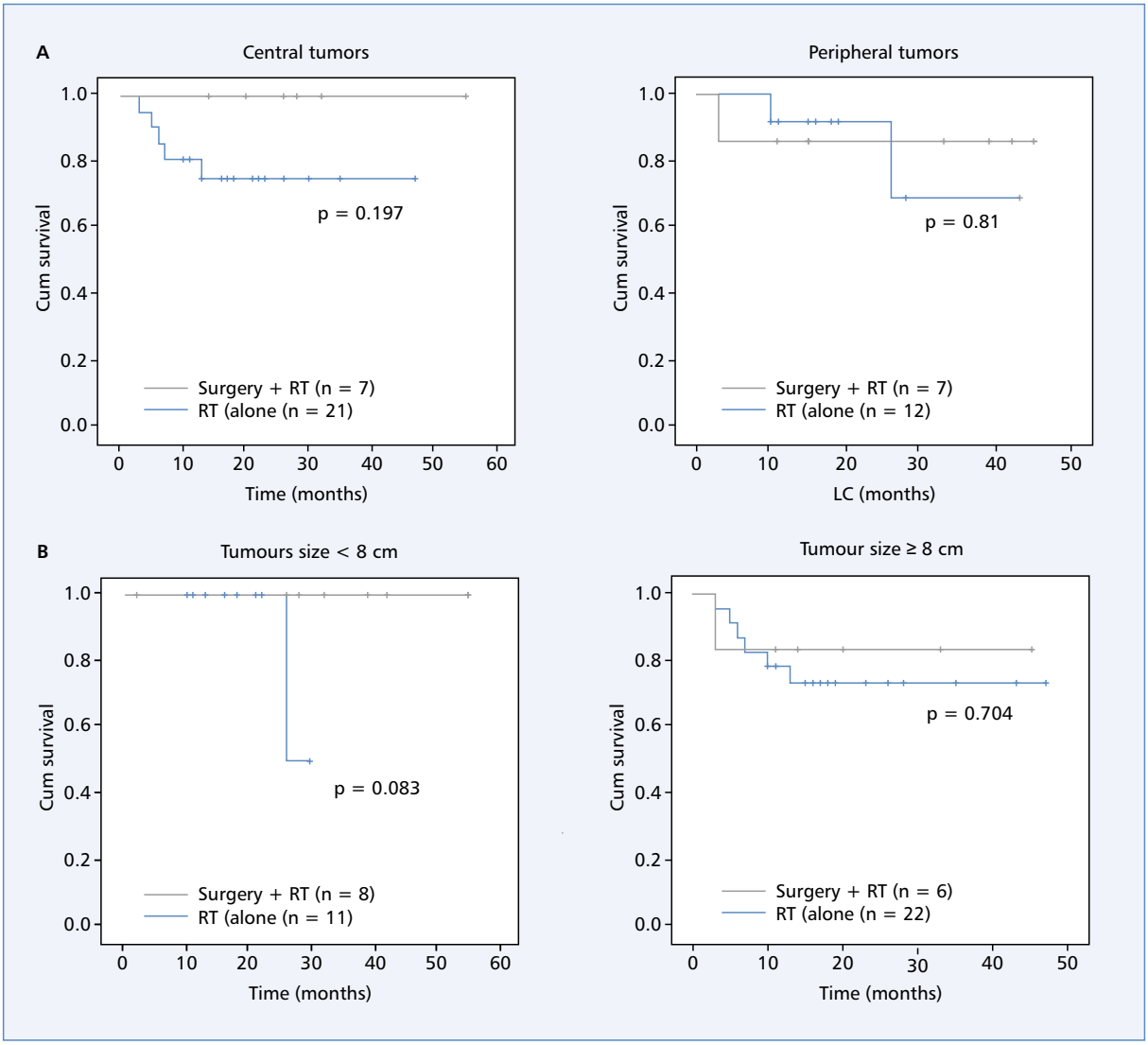

Figure 4. Subset analysis of local control according to treatment methods: Surgery and adjuvant radiotherapy versus radiotherapy alone; **A.** Comparison based on tumor location: central versus peripheral; **B.** Comparison based on tumor size: less than 8 cm versus 8 cm and above; LC — local control; RT — radiotherapy

(e.g. distal extremity) while the indications of postoperative radiotherapy were positive/close margins and poor histologic response (< 90% necrosis in resected tumor) after chemotherapy [9, 10, 22]. Surgery and RT showed superior local control rates than RT alone (92.3% versus 71%, p-value = 0.214), although the difference was not statistically significant unlike the results of Schuck et al. [9] and Biswas et al. [18].

A multitude of factors determine the choice of local therapy in ESFT. Smaller tumors in favorable locations (e.g. distal extremities) with significant response following neoadjuvant chemotherapy are treated more often with surgery. Tumors of large size or in central location (paravertebral, pelvic primaries) end up being treated with definitive radiotherapy. So we performed a subset analysis of local control according to local treatment modality with respect to tumor size (< 8 cm *v.* 8 cm and larger) and location (central versus peripheral). Among central tumors 25% (7/28) underwent resection, while for peripheral tumors the resection rate was 36.8% (7/19). With regards to tumor size, 21.4% (6/28) with dimension 8 cm or more underwent surgery while for tumors less than 8 cm size the rate of surgery was 42.1% (8/19). It was observed that local treatment with surgery and radiotherapy combined resulted in better 5-year local control rates than definitive radiotherapy alone for ESFT irrespective of tumor size and location (Fig. 4), even though statistical significance (all p-values > 0.05) was lacking. However, it must be understood that surgery as local treatment modality in ESFT requires special

expertise, especially in young children with growing bones. For tumors in critical locations like in the axial skeleton or advanced tumors in limbs, an organ preservation approach is often not feasible with surgery. Definitive radiotherapy remains the only local treatment option for such cases [23]. It can be expected that with the use of better imaging and treatment planning, newer techniques of precise radiation delivery and daily image guidance for treatment, radiotherapy to high doses can be safely and effectively delivered for optimum outcome in ESFT patients.

Patients receiving combined modality local therapy also had improved survival compared to radiotherapy alone (83.3% *v.* 31.1%, p = 0.022) as seen in results of our study (Tab. 3). Good response to neoadjuvant chemotherapy was another prognostic factor that translated into improved OS on both univariate and multivariate analysis (hazard ratio 0.301, 95% CI: 0.093–0.970, p = 0.044). Thus our study also shows that ESFT cases which respond favorably to cytoreductive chemotherapy and subjected to combined modality local treatment have significantly improved survival, even though the difference was not forthcoming in terms of local control.

Ours is a single institution retrospective review from a resource constrained region of the world, yet the results are not far from the studies in western population [4, 5, 11] and also correlate well with reports from Asia [17] and India [18]. However, our study is not without its limitations. There is a high rate of non-compliance to treatment among our patients, an issue that has previously been analyzed in pediatric population of our region by Hazarika et al. [24] who found that residence in rural areas, lack of maternal education, low socioeconomic status, age > 5 years and female sex were associated with higher risk of treatment abandonment. As evident from Figure 1, the non-compliance to diagnosis and treatment was 21% (15/72) in this study. Also, many patients could not receive treatment with curative intent and hence the final analysis of disease control and survival could be carried out for a cohort of 47 patients in our study. As a consequence of limited sample size, specific subset analysis based on tumor site, stage and patterns of failure could not be carried out in this study.

The retrospective nature of this study invariably allows for bias in choosing surgery versus radiotherapy as local treatment modality which might have affected the final outcome. There is a need for a randomized controlled trial to address this issue. However, in light of the available data demonstrating superiority of surgery over radiotherapy and also with the rapid advances in surgical techniques, whether any leading group in the world comes forward with such a comparative randomized trial remains to be seen.

Conclusions

Effective primary control significantly improves survival in ESFT. Favorable tumor response to neoadjuvant chemotherapy is also an independent prognostic factor that translates into better outcomes in ESFT as observed in our study. Our study results demonstrate that combined surgery and radiotherapy as local treatment provides better overall survival in these patients. However, for unresectable tumors definitive radiotherapy remains the only option which also can achieve effective local control, albeit with inferior survival rates. Thus a multidisciplinary treatment approach based on the prognostic factors and functional outcome should be made for optimum results. Radiotherapy, with or without surgery, remains an important component to achieving better local control in patients with ESFT.

Conflict of interest

All authors declare that they have no conflict of interest.

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