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Accelerated Hyper Fractionated Radiotherapy in Localized Ewing's Sarcoma with or without Surgery: What's New? A Phase II Study

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Abstract

Background and aim of work: We aimed from this study to determine the response and local relapse free survival (RFS) of pediatric patients with localized Ewing's sarcoma treated with accelerated hyper-fractionated RT. **Patient and methods**: This study was a nonrandomized uncontrolled phase II study and was conducted at clinical oncology department and south Egypt cancer institute; it involved 28 patients with histologically confirmed Ewing's sarcoma; all of them were subjected to PET/CT whenever possible or MRI with contrast of the primary site, MSCT chest, bone scan, and LDH to ensure absence of metastasis followed by the protocol of accelerated hyper fractionated RT. **Results:** The overall response rate (ORR) was 92.9% by MRI with significant effect of the type of response on local RFS ($P < 0.002$). The median local RFS of 28 patients with localized Ewing's sarcoma was 30 ± 8.599 months with 95% CI = 13.147 - 46.853; the 3-year local control was 35%. **Conclusion:** Accelerated hyper fractionated RT didn't achieve better results than standard fractionation RT, but it is recommended to be done on a large sample size, and multiple centers, and continued follow up is also recommended to evaluate 5-year LRFS, 5-year OS.

Keywords

Accelerated Hyper Fractionated RT, Ewing's Sarcoma, Relapse Free Survival

1. Introduction

Ewing's sarcoma is the 2nd most common primary malignant bone tumor in

children and adolescents, with 64%, 27%, and 9% of cases occur in the 2nd, the 1st, and the 3rd decades of life respectively.

Multidisciplinary approaches including dose dense chemotherapy, surgery and radiotherapy resulted in impressive cure rates of 65% - 70% in patients with localized lesions.

Current standard treatment is neoadjuvant combination chemotherapy followed by local control in the form of either surgery or definitive RT or both surgery and postoperative RT.

Several factors affect the choice of local treatment as patient age, site, size, and local extension of tumor; however surgical resection is better than definitive RT for local control [1], namely marginal resection or wide local excision while debulking followed by RT doesn't add any benefit over definitive RT [2].

Definitive RT is employed only for inoperable tumors with a dose of 54 - 55.8 Gy given to the tumor with 2 cm safety margin including all surgical and biopsy scars [3].

According to Schuck A *et al.* [4] fractionation of RT doesn't affect the local control more than the quality of RT given, so it is advisable to be given by IMRT, stereotactic RT, or proton RT [2].

Post operative RT (PORT) is indicated whenever incomplete surgical excision [5], positive/close margin, or poor histologic response to chemotherapy exists; however the role of PORT is debatable in those patients with good histologic response to chemotherapy; Stephanie F *et al.* tried through their an observational study of the Euro-E.W.I.N.G group to solve this argument and declared that surgery plus PORT compared to surgery alone was associated with statistically significant reduction in local relapse leading to an 8-year local relapse incidence of 11.9% [6] and this benefit was marked for those with tumor volumes ≥ 200 ml and 100% necrosis following chemotherapy.

Regarding to tumor size and RT dose; despite of being predictive of local control in localized Ewing's sarcoma, CESS study [7] failed to detect a significant advantage of hyper fractionated RT over the standard fractionation and RT dose of 55.8 Gy.

Data from university of Florida [8] suggested that hyper fractionated RT was associated with lower early and late tissue toxicities.

We aimed from this study to determine the response and local relapse free survival (RFS) of pediatric patients with localized Ewing's sarcoma treated with accelerated hyper-fractionated RT.

2. Patients and Methods

This study was a nonrandomized uncontrolled phase II study and was conducted at clinical oncology department, Assiut university hospital and south Egypt cancer institute, Assiut university where children with histologically confirmed Ewing's sarcoma, localized, whether RT given as definitive therapy or postoperative for the presence of residual disease, age ≤ 18 years, any gender,

informed consent was taken from their relatives, and the study was approved by the institutional ethics committee of faculty of medicine, Assiut University.

All patients were subjected to the followings prior to RT:

- Preoperative chemotherapy in the form of alternating VACA/IE (Children's Oncology Group Study INT-0091) administered every 3 weeks for 12 weeks with doses of vincristine 2 mg/m^2 (max. 2 mg) i.v. on day 1, doxorubicin 75 mg/m^2 i.v. day 1, cyclophosphamide 1200 mg/m^2 i.v. with mesna uroprotection on day 1, dactinomycin 1.25 mg/m^2 i.v. on day 1 to be substituted for doxorubicin after 375 mg/m^2 of doxorubicin was received this regimen combination was given alternating with ifosfamide 1800 mg/m^2 i.v. on days 1 - 5 with mesna uroprotection and etoposide 100 mg/m^2 i.v. on days 1 - 5, VACA/IE was continued during radiotherapy but with omission of doxorubicin.
- Surgery was planned to be done on week 12 and it was wide local excision if possible with radiotherapy planned to be given for those with incomplete excision or definitively for those with just incisional or tru-cut needle biopsy.
- PET/CT whenever possible (as it was done in some patients) or MRI with contrast of the primary site, MSCT chest, bone scan, and LDH to ensure absence of metastasis.

2.1. Radiation Treatment Protocol

RT was given in two phases without any time separation, the dose for phase I was 44.8 Gy given over 28 fractions over two weeks in two fractions daily and fraction size of 1.6 Gy and the two fractions were at least 6 hours apart, CTV = pre chemotherapy GTV (bone and soft tissue) + 2 cm safety margin (in both longitudinal and lateral axes) (Figure 1).

The dose for phase II was 19.2 Gy given over 12 fractions over 6 days, CTV = pre chemotherapy bone GTV + residual soft tissue with 1 - 2 cm safety margins in both longitudinal and lateral axes. Treatment was delivered regularly using 6 - 15 MV energy and LINAC primus machine.

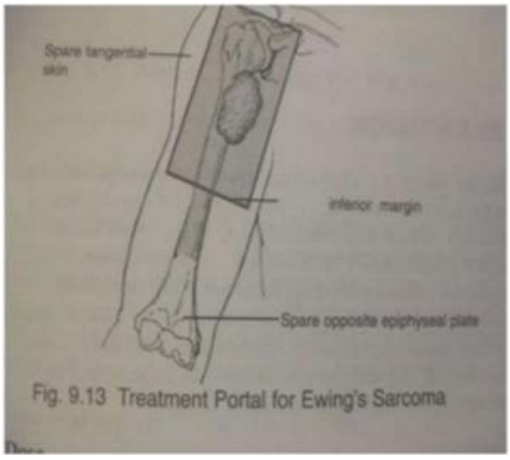

Figure 1. Treatment portals for phase I RT of Ewing's sarcoma of upper end of humerus.

Certain measures were taken to minimize potential RT side effects on normal tissues including; avoidance of circumferential limb irradiation, shielding of gonads in pelvic tumors, avoidance of Achilles tendon and uninvolved epiphyseal growth plates irradiation as possible and if difficult we limited dose of RT to less than 20 Gy, and we ensured fullness of the bladder before each session to minimize small bowel damage.

Evaluation of the response was done 4 weeks after the end of RT by MRI of the primary site and 8 - 10 weeks by PET/CT then every 3 months by MRI of the primary site.

2.2. Statistics

All data were analyzed by SPSS ver. 21, descriptive data in the form of mean, median, percentage, and standard deviation, Kaplan-Meier was used to calculate local RFS, log rank test to determine different prognostic factors on survival.

Local RFS was defined as the time length after end of RT to occurrence of local relapse, the results was significant at P value < 0.05.

3. Results

28 children with localized Ewing's sarcoma presented to pediatric oncology unit at south Egypt cancer institute and treated with chemotherapy at this unit then referred to clinical oncology department at Assiut university hospital for radiotherapy during a period of two years from January 2012 to December 2013. This study was approved by the ethical committee of faculty of medicine, Assiut University.

These patients were followed up at both centres from January 2012 and are still under follow up to determine the OS.

The demographic and clinical characteristics of these patients and their significance on local RFS were demonstrated in **Table 1**.

3.1. Response to Treatment

The overall response rate (ORR) was 92.9% as determined by MRI with significant effect of the type of response on local RFS (P < 0.002) (**Table 2**).

3.2. Local Relapse Free Survival

The median local RFS of 28 patients with localized Ewing's sarcoma was 30 ± 8.599 months with 95% CI = 13.147 - 46.853, the 3-year local control was 35%, (**Figure 2**).

4. Discussion

Ewing's sarcoma is an aggressive tumor tends to recur locally and distally, according to Gupta *et al.* [9] the 5-year survival has been improved dramatically reaching 70% - 75%.

In our study; only tumor size had a significant worse effect on LRFS with higher rates of relapses in those with large tumors ≥ 8 cm which was comparable to Karski EE *et al.* [10] that denoted higher tendency of relapses in larger tumors.

Table 1. Demographic and clinical characteristics of 28 patients with localized Ewing's sarcoma and their significant effects on RFS.

characteristics	NO	%	P value
Age			
Median ± SD	13 ± 3.707		P = 0.858 N.S.
Min - max	5 - 19 y		
Sex male	15	53.6%	P = 0.248 N.S.
Female	13	46.4%	
Site axial	4	14.3%	
Pelvic	8	28.6%	P = 0.156 N.S.
peripheral	16	57.1%	
ECOG PS 0	2	7.1%	
1	10	35.7%	P = 0.079 N.S.
2	16	57.1%	
Presentation			
Palpable mass	22	78.6%	P = 0.248 N.S.
No palpable mass	6	21.4%	
Type of biopsy			
Core needle	12	42.9%	P = 0.794 N.S.
Incisional	10	35.7%	
Excisional	6	21.4%	
CD 99 not done	6	21.4%	P = 0.180 N.S.
Positive	22	78.6%	
LDH high	22	78.6%	P = 0.795 N.S.
Normal	6	21.4%	
Size < 8 cm	11	39.3%	
8 cm	4	14.3%	P < 0.001
>8 cm	13	46.4%	
Pretreatment MRI			
Only bone lesion	12	42.9%	P = 0.543 N.S.
Bone and soft tissue	16	57.1%	
Surgery			
Incomplete excision	6	21.4%	P = 0.180 N.S.
No surgery	22	78.6%	

N.S. = nonsignificant. * = moderately significant.

Table 2. Type of response among 28 patients with Ewing's sarcoma and their significance.

Response	NO	%	
By MRI			
CR	14	50%	P < 0.002
PR	12	42.9%	
SD	2	7.1%	
By PET/CT			
Not done	2	7.1%	P < 0.02
Negative	21	75%	
Positive	5	17.8%	

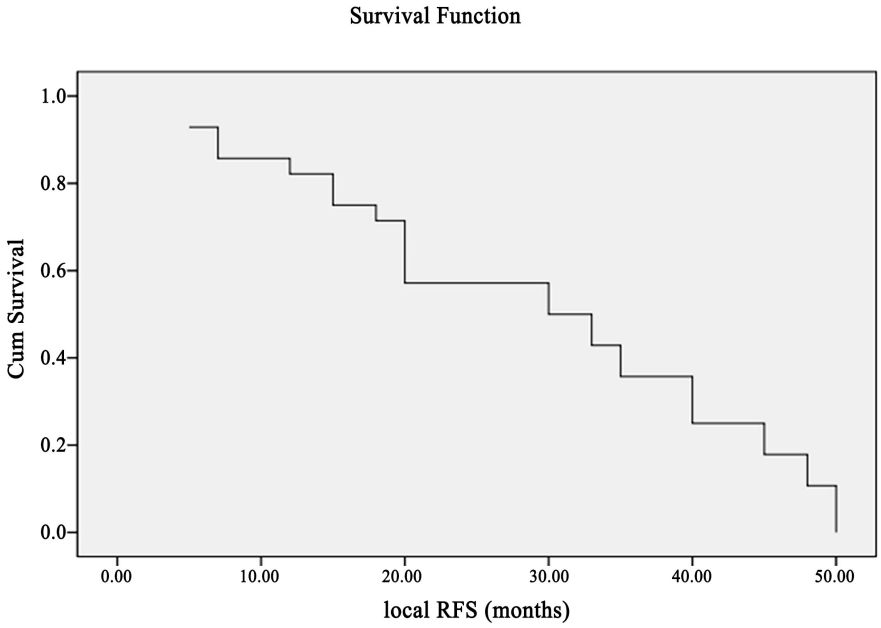

Figure 2. Local RFS among 28 patients with localized Ewing's sarcoma treated with accelerated hyper fractionated RT.

Unfortunately, no other demographic or clinical characteristics had a prognostic impact on LRFS; but it may be logic to have no impact of age, sex, PS, presentation, biopsy type, CD 99, pretreatment MRI.

In this study; site of the tumor had no significant effect and this was contrary to Karski EE *et al.* also no significant impact of surgery on LRFS which wasn't comparable to Ricardo G *et al.* [11] that detected a 5-year event free survival of 30.8% for patients received definitive RT, 64.1% for surgery plus RT and 71.7% for surgery alone.

3-year LC in our study was 35% which was comparable to DuBois SG [1] that denoted high incidence of local relapses in those received definitive RT and in ours; the local control was low as no complete surgical excision was done.

Definitive RT without surgery especially in tumors ≥ 8 cm demonstrated inferior local control (P = 0.033) and progression free survival (P = 0.016) [12] and this was clear in our study as tumors ≥ 8 cm represented 60.7%

The median LRFS and 3-year Local control in our study was lower to previous studies that utilized definitive RT with standard fractionation which implied inferiority of accelerated hyper fractionation, but this conclusion couldn't be confirmed because of small sample size, cases came only from single center and no complete surgical excision was done.

5. Conclusion

Accelerated hyper fractionated RT didn't achieve better results than standard fractionation but it is better to be done on a large sample size, and multiple centers, and continued follow up is recommended to evaluate 5-year LRFS, and 5-year OS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] DuBois, S.G., Krailo, M.D., Gebhardt, M.C., *et al.* (2015) Comparative Evaluation of Local Control Strategies in Localized Ewing's Sarcoma of Bone: A Report from the Children's Oncology Group. *Cancer*, **121**, 467-475.

[2] Schuck, A., Ahrens, S., Paulussen, M., *et al.* (2003) Local Therapy in Localized Ewing's Tumors: Results of 1058 Patients treated in CESS 81, CESS 86, and EICESS 92 Trials. *International Journal of Radiation Oncology, Biology, Physics*, **55**, 168-177.

[3] Donaldson, S.S., Torrey, M., Link, M.P., *et al.* (1998) A Multidisciplinary Study Investigating Radiotherapy in Ewing's Sarcoma: End Results of POG #8346. *International Journal of Radiation Oncology, Biology, Physics*, **42**, 125-135. https://doi.org/10.1016/S0360-3016(98)00191-6

[4] Schuck, A., Rube, C., Konemann, S., *et al.* (2002) Postoperative Radiotherapy in the Treatment of Ewing's Sarcoma: Influence of Interval between Surgery and Radiotherapy. *Strahlentherapie und Onkologie*, **178**, 25-31. https://doi.org/10.1007/s00066-002-0883-1

[5] Granowetter, L., Womer, R., Devidas, M., *et al.* (2009) Dose-Intensified Compared with Standard Chemotherapy for Nonmetastatic Ewing's Sarcoma Family of Tumors: A Children's Oncology Group Study. *Journal of Clinical Oncology*, **27**, 2536-2541. https://doi.org/10.1200/JCO.2008.19.1478

[6] Stephanie, F., Benadette, B., Nathalie, G., *et al.* (2016) Can Postoperative Radiotherapy Be Omitted in Localized Standard-Risk Ewing Sarcoma? An Observational Study of the Euro-E.W.I.N.G Group. *European Journal of Cancer*, **61**, 128-136. https://doi.org/10.1016/j.ejca.2016.03.075

[7] Dunst, J., Jurgen, H., Sauer, R., *et al.* (1995) Radiation Therapy in Ewing's Sarcoma: An Update of the CESS 86 Trial. *International Journal of Radiation Oncology, Biology, Physics*, **32**, 919-930. https://doi.org/10.1016/0360-3016(95)00016-R

[8] Indelicato, D.J., Keole, S.R., Shahlaee, A.H., *et al.* (2008) Definitive Radiotherapy for Ewing Tumors of Extremities and Pelvis: Long-Term Disease Control, Limb Function, and Treatment Toxicity. *International Journal of Radiation Oncology, Biology, Physics*, **72**, 871-877. https://doi.org/10.1016/j.ijrobp.2008.02.023

[9] Gupta A., Pappo, A., Saunder, N., *et al.* (2010) Clinical Outcome of Children and Adults with Localized Ewing's Sarcoma—Impact of Chemotherapy Dose and Timing of Local Therapy. *Cancer*, **116**, 3189-3194. https://doi.org/10.1002/cncr.25144

[10] Karski, E.E., McIlvaine, E., Segal, M.R., *et al.* (2016) Identification of Discrete Prognostic Groups in Ewing's Sarcoma. *Pediatric Blood & Cancer*, **63**, 47-53. https://doi.org/10.1002/pbc.25709

[11] Ricardo, G.B., Lauro, J.G., Carlos, R.G., *et al.* (2017) What Is the Impact of Local Control in Ewing Sarcoma: Analysis of the First Brazilian Collaborative Study Group—EWING1. *BMC Cancer*, **17**, 420. https://doi.org/10.1186/s12885-017-3391-5

[12] Yunseon, C., Do Hoon, L., Soo, H., *et al.* (2015) Role of Radiotherapy in the Multimodal Treatment of Ewing Sarcoma Family Tumors. *Cancer Research and Treatment*, **47**, 904-912. https://doi.org/10.4143/crt.2014.158