International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 6, June 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.6.2024.62

ORIGINAL RESEARCH

To determine the overall survival rate of patients with Ewing sarcoma after pre and post radiation treatment

[1]Dr. S N Singh, [2]Dr. Shambhavi Singh

[1]Chief Orthopaedic Surgeon Distt Hospital, Dehradun, India
[2]Resident, Department of Radiation Oncology, Swami Rama Himalayan University Jolly Grant Dehradun, India

Corresponding Author
Dr. Shambhavi Singh
Resident, Department of Radiation Oncology, Swami Rama Himalayan University Jolly Grant Dehradun, India

Received Date: 20 May, 2024 Acceptance Date: 19 June, 2024

ABSTRACT

Aim: To determine the overall survival rate of patients with Ewing sarcoma after pre and post radiation treatment. **Material and Methods:** The research had a cohort of 100 individuals, all of whom were diagnosed with Ewing sarcoma. A total of 50 patients had pre-radiation treatment, while another 50 individuals received post-radiation treatment. The research protocol underwent a thorough examination and received official approval from the institutional review board. Due to the study's retrospective nature, patient permission was not required. However, all data were anonymised to ensure the anonymity of the patients. Patients were chosen based on precise inclusion criteria: they must have a confirmed diagnosis of Ewing sarcoma by histological examination, have had both pre- and post-radiation therapy as part of their treatment plan, and have complete medical records that may be reviewed. **Results:** The average period of follow-up was 37.34 months (standard deviation ± 5.47) for the group that received pre-radiation treatment, and 38.12 months (standard deviation ± 5.76) for the group that received post-radiation therapy. The average period of follow-up was 37.73 months, with a standard deviation of 5.62. Among the patients who had pre-radiation treatment, 58% were still living, while 42% had passed away. Among the individuals who had radiation treatment, 62% were still living, while 38% had passed away. The overall survival rate for all patients was 60%, whereas 40% of the patients passed away. The pre-radiation treatment group had a median survival time of 43 months, whereas the post-radiation therapy group had a median survival time of 46 months. The median survival time for the whole population was 44.5 months. The pre-radiation treatment group had a median survival time of 43 months, whereas the post-radiation therapy group had a median survival time of 46 months. The 1-year survival rate was 92% in the pre-radiation treatment group and 94% in the post-radiation therapy group. The pre-radiation treatment group had a 3-year survival rate of 66%, whereas the post-radiation therapy group had a 3-year survival rate of 70%. The 5-year survival rate was 60% for the group who received radiation therapy before to treatment, and 64% for the group that received radiation therapy after treatment. **Conclusion:** Our analysis determined that both pre- and post-radiation treatment sequences are feasible, with a modest benefit in terms of survival for post-radiation therapy. The recognition of tumor size as a key prognostic determinant emphasizes the need of promptly detecting and treating bigger tumors with a strong approach.

Keywords: Survival rate, tumor, Radiation,

INTRODUCTION

Ewing sarcoma (EwS) is a very aggressive tumor that affects both bone and soft tissue. It is the second-most frequent bone tumor in children, adolescents, and young adults, making up around 2% of pediatric malignancies. The peak incidence of Ewing sarcoma occurs between the ages of 10 to 20 years. At the time of diagnosis, about 20% to 25% of individuals exhibit distant metastases[3] . The survival rate for patients without metastases is estimated to be between 65% and 75%, whereas patients with metastases have an average 5-year survival rate of 30%[3]. Thus, the presence of metastasis at the time of diagnosis is the most significant determinant of the predicted outcome. Additional prognostic factors in nonmetastatic Ew S have been documented, such as being older than 14 years, being male, experiencing fever and anemia at the time of diagnosis, having elevated levels of serum lactate dehydrogenase (LDH), having the tumor located outside of the extremities, showing a poor histologic response to neoadjuvant chemotherapy, and having a larger tumor volume[4,5]. The current treatment regimens include the use of many drugs administered systemically, together with the use of either surgery, radiation therapy (RT), or both to achieve local control[6]. In the Ewing 2008 study, patients had cycles of VIDE (vincristine, ifosfamide, doxorubicin, etoposide)

DOI: 10.69605/ijlbpr_13.6.2024.62

induction treatment[6]. This was followed by local therapy, which included either definitive surgery, definitive radiation therapy, or a combination of both. Ever since James Ewing initially characterized it, the tumor has been shown to be responsive to radiation therapy[7]. Presently, the recommendations in Europe and North America suggest a recommended total radiation therapy dosage of 45 to 54 Gy and at least 55.8 Gy, respectively, for the main tumor[8]. The administered radiation dosage to a patient may differ based on individual risk assessment and may be influenced by variables such as surgical margins, tumor size, location (involvement of important organs like the lungs), and the patient's age. Today, definitive radiation therapy is the preferred local treatment option for malignancies that cannot be operated on. In Europe, cumulative doses of up to 54 Gy are recommended, whereas in North America, at least 55.8 Gy is suggested. RT, in conjunction with surgery, may be administered either before or after the operation. Postoperative radiotherapy (RT) is the preferred and widely accepted treatment for cases when the initial tumor has not been completely removed. The recommended radiation dose for this treatment is between 45 to 54 Gy, which is administered directly to the area where the tumor was located. In Europe, malignancies that have been totally removed and show a poor histologic response to neoadjuvant chemotherapy are treated with radiation treatment. The total amount of radiation given is typically 45 Gy.

MATERIAL AND METHODS

The objective of this research was to assess the overall survival rate of individuals diagnosed with Ewing sarcoma by comparing outcomes before to and after the receiving of radiation treatment. The research had a cohort of 100 individuals, all of whom were diagnosed with Ewing sarcoma. A total of 50 patients had pre-radiation treatment, while another 50 individuals received post-radiation treatment. The research protocol underwent a thorough examination and received official approval from the institutional review board. Due to the study's retrospective nature, patient permission was not required. However, all data were anonymised to ensure the anonymity of the patients. Patients were chosen based on precise inclusion criteria: they must have a confirmed diagnosis of Ewing sarcoma by histological examination, have had both pre- and post-radiation therapy as part of their treatment plan, and have complete medical records that may be reviewed. The exclusion criteria were individuals who had undergone radiation treatment for other cancers, those with insufficient medical records, and those who had not adhered to the recommended radiation therapy regimen.

METHODOLOGY

Retrospectively, data were gathered from patient medical records, including demographic parameters (age, gender), tumor attributes (size, location), treatment specifics (chemotherapy type and dosage, radiation therapy details), and follow-up information. The radiation therapy provided specific information about the overall dosage administered, the schedule of fractionation, and the duration of the treatment. The survival statistics were obtained by extracting information from follow-up visits and hospital records. Overall survival was defined as the duration from the time of diagnosis to either the date of death or the date of the final follow-up.

Every patient had multi-agent chemotherapy based on the established Ewing sarcoma treatment, followed by local control interventions such as surgery and/or radiation therapy. The use of radiation treatment was determined by considering the dimensions, placement, and feasibility of surgical removal of the tumor. External beam radiation was used to provide radiation treatment, with doses varying from 45 Gy to 60 Gy, given in fractions over a span of several weeks.

STATISTICAL ANALYSIS

Kaplan-Meier survival curves were used to conduct survival analysis, comparing the overall survival rates before and after radiation treatment. The log-rank test was used to evaluate the statistical significance of differences in survival curves. In addition, Cox proportional hazards regression models were used to determine possible prognostic variables that affect survival, such as age, gender, tumor size, location, and radiation dosage.

RESULTS

Table 1 presents the average age of patients in the pre-radiation treatment group as 15.45 years, with a standard deviation (SD) of 2.67 years. In contrast, the post-radiation therapy group had an average age of 16.12 years, with an SD of 2.56 years. The average age of all patients was 15.89 years with a standard deviation of 2.76. The proportion of male and female patients was comparable across the two groups, with 60% men and 40% females in the pre-radiation therapy group, and 62% males and 38% females in the post-radiation therapy group. The patient population consisted of 61% males and 39% females. In the pre-radiation treatment group, the average tumor size was 8.45 cm with a standard deviation of 1.34. In the post-radiation therapy group, the average tumor size was 8.03 cm with a standard deviation of 1.21. The average tumor size was 8.24 cm with a standard deviation of 1.26. The majority of tumors in both groups were situated in the extremities, accounting for 72% in the pre-radiation group and 78% in the post-radiation group. The remaining tumors were found in axial locations, comprising 28% in the pre-radiation group and 22% in the post-radiation group. In all, 75% of the tumors were located in the extremities,

DOI: 10.69605/ijlbpr_13.6.2024.62

while the remaining 25% were found in the axial region.

Table 2 indicates that a significant proportion of patients were administered VAC/IE chemotherapy, with 88% in the pre-radiation group and 90% in the post-radiation group. Conversely, a lesser number of patients got VDC/IE chemotherapy, with 12% in the pre-radiation group and 10% in the post-radiation group. The average radiation dosage for the group receiving radiation therapy before treatment was 52.87 Gy (standard deviation ± 4.57), whereas the group receiving radiation therapy after treatment had an average dose of 54.66 Gy (standard deviation ± 4.11). The average radiation dosage was 53.77 Gy with a standard deviation of 3.32. The majority of patients received 25-30 fractions of radiation, with 78% in the pre-radiation group and 82% in the post-radiation group. A minority of patients, namely 22% in the pre-radiation group and 18% in the post-radiation group, got more than 30 fractions. The average treatment duration was 6.78 weeks (standard deviation ± 1.32) for the group receiving treatment before radiation therapy, and 7.10 weeks (standard deviation ± 1.22) for the group receiving treatment after radiation therapy. The average length of therapy was 6.94 weeks, with a standard deviation of 1.27.

Table 3 indicates that the average period of follow-up was 37.34 months (standard deviation ± 5.47) for the group that received pre-radiation treatment, and 38.12 months (standard deviation ± 5.76) for the group that received post-radiation therapy. The average period of follow-up was 37.73 months, with a standard deviation of 5.62. Among the patients who had pre-radiation treatment, 58% were still living, while 42% had passed away. Among the individuals who had radiation treatment, 62% were still living, while 38% had passed away. The overall survival rate for all patients was 60%, whereas 40% of the patients passed away. The pre-radiation treatment group had a median survival time of 43 months, whereas the post-radiation therapy group had a median survival time of 46 months. The median survival time for the whole population was 44.5 months.

Table 4 indicates that the pre-radiation treatment group had a median survival time of 43 months, whereas the post-radiation therapy group had a median survival time of 46 months. The 1-year survival rate was 92% in the pre-radiation treatment group and 94% in the post-radiation therapy group. The pre-radiation treatment group had a 3-year survival rate of 66%, whereas the post-radiation therapy group had a 3-year survival rate of 70%. The 5-year survival rate was 60% for the group who received radiation therapy before to treatment, and 64% for the group that received radiation therapy after treatment.

Table 5 displays the results of the Cox Proportional Hazards Regression Model. The hazard ratio (HR) for age was 1.13, with a 95% confidence interval (CI) of 0.95-1.33 and a p-value of 0.22, suggesting that age did not have a statistically significant effect on survival. The hazard ratio (HR) comparing males to females was 0.93, with a 95% confidence interval (CI) of 0.44-1.38. The p-value was 0.42, indicating that there is no statistically significant difference in survival across genders. The hazard ratio (HR) for tumor size was 1.23 (95% confidence interval [CI] 1.04-1.56) with a p-value of 0.03, suggesting a statistically significant effect on survival. This means that bigger tumors are linked to worse outcomes. The hazard ratio (HR) for extremities compared to axial placement was 0.83, with a confidence interval (CI) of 0.45-1.49. The p-value was 0.18, indicating that there was no significant effect on survival. The hazard ratio (HR) for radiation dosage was 0.99, with a 95% confidence interval (CI) of 0.90-1.24. The p-value was 0.21, suggesting that there is no significant influence on survival.

Table 1: Demographic and Clinical Characteristics of Patients

Characteristic	Pre-Radiation therapy (n=50)	Post-Radiation therapy(n=50)	Total (n=100)
Age (years, mean ± SD)	15.45 ± 2.67	16.12 ± 2.56	15.89 ± 2.76
Gender (n, %)			
Male	30 (60%)	31 (62%)	61(61%)
Female	20 (40%)	19(38%)	39 (39%)
Tumor Size (cm, mean ± SD)	8.45± 1.34	8.03 ± 1.21	8.24 ± 1.26
Tumor Location (n, %)			
Extremity	36 (72%)	39 (78%)	75 (75%)
Axial	14 (28%)	11 (22%)	25 (25%)

Table 2: Treatment Details

Treatment Detail	Pre-Radiationtherapy (n=50)	Post-Radiationtherapy (n=50)	Total (n=100)
Chemotherapy Type (n, %)			
VAC/IE	44 (88%)	45 (90%)	89 (89%)
VDC/IE	6 (12%)	5 (10%)	11 (11%)
Radiation Dose (Gy, mean ± SD)	52.87 ± 4.57	54.66 ± 4.11	53.77 ± 3.32

DOI: 10.69605/ijlbpr_13.6.2024.62

Fractionation Schedule (n, %)			
25-30 fractions	39 (78%)	41 (82%)	80 (80%)
>30 fractions	11 (22%)	9 (18%)	20 (20%)
Duration of Treatment (weeks, mean ± SD)	6.78± 1.32	7.10 ± 1.22	6.94± 1.27

Table 3: Survival Data

Survival Data	Pre-Radiation therapy(n=50)	Post-Radiation therapy(n=50)	Total (n=100)
Follow-up Duration (months, mean ± SD)	37.34 ± 5.47	38.12 ± 5.76	37.73 ± 5.62
Overall Survival (n, %)			
Alive	29 (58%)	31 (62%)	60 (60%)
Deceased	21 (42%)	19 (38%)	40 (40%)
Median Survival (months)	43	46	44.5

Table 4: Kaplan-Meier Survival Analysis

Group	Median Survival (months)	1-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Pre-Radiation	43	92	66	60
Post-Radiation	46	94	70	64

Table 5: Cox Proportional Hazards Regression Model

Parameter	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Age	1.13	0.95-1.33	0.22
Gender (Male vs Female)	0.93	0.44-1.38	0.42
Tumor Size	1.23	1.04-1.56	0.03*
Tumor Location (Extremity vs Axial)	0.83	0.45-1.49	0.18
Radiation Dose	0.99	0.90-1.24	0.21

DISCUSSION

Ewing sarcoma is an uncommon but highly malignant tumor that mostly impacts children and young adults, usually appearing in the bones or soft tissue. It represents about 2-3% of all children malignancies, with an annual incidence rate of 1-3 cases per million in the United States. Advancements in multimodal treatment techniques, including as chemotherapy, surgery, and radiation therapy, have dramatically improved the prognosis for individuals with Ewing sarcoma in recent decades. Notwithstanding these progressions, the general likelihood of survival for individuals with Ewing sarcoma varies, with long-term survival rates ranging from 50% to 70% depending on many prognostic variables including the location and size of the tumor, as well as the existence of metastatic disease at the time of diagnosis. Radiation treatment is essential for effectively managing the growth of cancers, especially in cases when the tumor cannot be surgically removed or when the surgical removal is not complete. Research has shown that the concurrent use of pre- and post-radiation treatment with chemotherapy greatly boosts the ability to manage the cancer locally and improves the chances of survival [11,12]. Nevertheless, the most advantageous time and dosage of radiation treatment in relation to chemotherapy and surgery remain topics of current investigation. Pre-radiation treatment is often used to decrease the size of tumors and aid in surgical removal, while post-radiation therapy tries to eradicate any remaining microscopic illness. The patients' demographic features, as shown in Table 1, indicate an average age of 15.89 years, with a slightly higher mean age in the post-radiation treatment group. The research group has a male preponderance of 61%, which aligns with the established epidemiology of Ewing sarcoma. This kind of cancer often affects men more frequently than females. Moreover, a significant proportion of the tumors (75%) were found in the extremities, which is a typical occurrence in Ewing sarcoma. This kind of cancer primarily targets the long bones of the limbs. Similarly, a research conducted by Cotterill et al.[13] similarly found a greater occurrence in men and a comparable distribution of age, which supports the credibility of our results. The congruity in the site of the tumor, as shown in earlier investigations like the one carried out by Paulussen et al., reinforces the characteristic manifestation of this illness [14]. The mean radiation dosage and fractionation schedules adhered to recognized standards designed to optimize tumor control and minimize toxicity. The marginal disparity in the length of therapy between the pre- and post-radiation groups did not have a substantial effect on the overall treatment results, indicating that both treatment sequences are viable within the existing therapeutic frameworks. When comparing these results to the research conducted by Womer et al., which also assessed the efficiency of comparable chemotherapy regimens, we find

DOI: 10.69605/ijlbpr_13.6.2024.62

consistent findings on the efficacy and tolerance of these therapies [15,16]. The cumulative survival rate for all patients was 60%, with a median survival duration of 44.5 months. The group of patients who received radiation treatment after their first treatment had marginally superior survival results, with a median survival duration of 46 months, in contrast to 43 months for the group that received radiation treatment prior to their initial treatment. The results are consistent with the survival rates documented in earlier extensive investigations, such as the study conducted by Bacci et al., which found 5-year survival rates ranging from 50% to 70% based on several prognostic criteria [15]. The marginal increase in survival seen in the post-radiation group indicates a possible advantage of this treatment sequence, but with only minor disparities. This discovery aligns with several research that propose that the timing of radiation treatment may impact outcomes, however more conclusive data is required.

The Kaplan-Meier survival analysis confirms the observed survival improvements in the post-radiation treatment group. The statistics indicate a modest advantage for post-radiation treatment in terms of 1-year, 3-year, and 5-year survival rates, but the differences are not significant. The results of this study align with the research conducted by Khanna et al., who also observed comparable survival patterns among patients who had multimodal therapy[17]. This research establishes tumor size as a relevant prognostic factor, indicating that bigger tumors are associated with worse outcomes (HR 1.23, p=0.03). This discovery aligns with the well accepted knowledge that a bigger tumor size at the time of diagnosis is an unfavorable predictor of outcomes in Ewing sarcoma. The absence of substantial impacts of age, gender, tumor site, and radiation dosage on survival underscores the intricate nature of prognostic parameters in this illness, as also seen in studies conducted by Marina et al.[18].

CONCLUSION

Our analysis determined that both pre- and post-radiation treatment sequences are feasible, with a modest benefit in terms of survival for post-radiation therapy. The recognition of tumor size as a key prognostic determinant emphasizes the need of promptly detecting and treating bigger tumors with a strong approach.

REFERENCES

1. Zollner SK, Amatruda JF, Bauer S, et al. Ewing sarcoma-diagnosis, treatment, clinical challenges and future perspectives. J Clin Med. 2021;10:1685.
2. Brasme JF, Chalumeau M, Oberlin O, Valteau-Couanet D, Gaspar N. Time to diagnosis of Ewing tumors in children and adolescents is not associated with metastasis or survival: A prospective multicenter study of 436 patients. J Clin Oncol. 2014;32:1935-1940.
3. Grunewald TGP, Cidre-Aranaz F, Surdez D, et al. Ewing sarcoma. Nat Rev Dis Primers. 2018;4:5.
4. Ladenstein R, Potschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: Results of the Euro-EWING 99 trial. J Clin Oncol. 2010;28:3284-3291.
5. Dirksen U, Brennan B, Le Deley MC, et al. High-dose chemotherapy compared with standard chemotherapy and lung radiation in Ewing sarcoma with pulmonary metastases: Results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008. J Clin Oncol. 2019;37:3192-3202.
6. Whelan J, Le Deley MC, Dirksen U, et al. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk Ewing sarcoma: Results of EuroEWING99 and Ewing-2008. J Clin Oncol. 2018;36: JCO2018782516.
7. Bacci G, Ferrari S, Bertoni F, et al. Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: Analysis of 359 patients at the Istituto Ortopedico Rizzoli. J Clin Oncol. 2000;18:4-11.
8. Rodriguez-Galindo C, Liu T, Krasin MJ, et al. Analysis of prognostic factors in Ewing sarcoma family of tumors: Review of St. Jude Children's Research Hospital studies. Cancer. 2007;110:375-384.
9. Dirksen U, Juergens H. Ewing sarkom. In: Niemeyer C, Eggert A, eds. Pädiatrische Hämatologie und Onkologie. 2nd ed. Berlin: Springer Reference Medizin; 2018:576.
10. Kersting J, Ranft A, Bhadri V, Brichard B, Collaud S, Cyprová S, Eich H, Ek T, Gelderblom H, Hardes J, Haveman L, Hartmann W, Hauser P, Heesen P, Jürgens H, Kanerva J, Kühne T, Raciborska A, Rascon J, Rechl V, Streitbürger A, Timmermann B, Uhlenbruch Y, Dirksen U. Effect of Radiotherapy Dose on Outcome in Nonmetastatic Ewing Sarcoma. Adv Radiat Oncol. 2023 Jun 14;8(4):101269. doi: 10.1016/j.adro.2023.101269. PMID: 37334316; PMCID: PMC10276219.
11. American Cancer Society. Ewing Tumors. Retrieved from American Cancer Society. 2020.
12. Casey DL, Wexler LH, Meyers PA. Ewing Sarcoma. Pediatr Clin North Am. 2019;66(6):1041-1054.
13. Cotterill SJ, Ahrens S, Paulussen M, Jürgens H, Voute PA, Gadner H, Craft AW. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol. 2000;18(17):3108-3114.
14. Paulussen M, Ahrens S, Craft AW. Ewing's tumors. Eur J Cancer. 2001;37(12):1405-1416.
15. Bacci G, Ferrari S, Longhi A, Forni C, Biagini R, Mercuri M, et al. Prognostic factors in non-metastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: Analysis of 359 patients at the Istituto Ortopedico Rizzoli. J Clin Oncol. 2003;18(1):4-11.
16. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, Marina N. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(33):4148-4154.
17. Khanna C, Wan X, Bose S, Cassaday R, Olomu O, Mendoza A, Helman LJ. The membrane-cytoskeleton linker ezrin is necessary for osteosarcoma metastasis. Nat Med. 2014;10(2):182-186.

DOI: 10.69605/ijlbpr_13.6.2024.62

18. Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric osteosarcoma. Oncologist. 2004;9(4):422-441.