

Results of Postoperative Adjuvant Treatment of Pediatric Locally Advanced Retinoblastoma NEMROCK Experience

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ABSTRACT

Purpose: The aim of the present study was to evaluate the role of adjuvant postoperative chemotherapy in the local control, disease free interval and overall survival by comparing retrospectively two groups of patients, group (I) received postoperative radiation therapy and the second group (II) received postoperative radiation therapy and chemotherapy.

Methods and Material: The present study is a retrospective study carried on 54 newly diagnosed patients of pediatric unilateral retinoblastoma referred to pediatric unit of KASR-EL-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period from February 1991 till February 1996 and they were followed up till February 1999. Their age ranged from 2 to 15 years, and all patients were treated by orbital exenteration. The patients were divided into 2 groups. The first group (I) included 21 patients treated by postoperative radiation therapy and the second group (II) included 33 patients treated by postoperative radiation therapy and chemotherapy in the form of Vincristine, Adriamycin and Cyclophosphamide.

Results: After a period of follow up of 3 years 6 out of 21 patients (28.6%) in group (I) versus 10 out of 33 patients (28%) in group (II) developed local recurrence, with no statistically significant difference $p = (0.100)$. Six out of 21 patients (28.2%) of group (I) versus 7 out of 33 patients (19.6%) of group (II) developed distant metastases the results were statistically insignificant ($p = 0.210$). The 3 year overall survival for group (I) was 19.25% versus 50.53% for group (II). However this difference was not statistically significant. The 3 year disease free survival for group (I) was 17% with a median (DFS) of 6 months versus 33% for group (II) with a median (DFS) of 13 months. This difference was statistically significant ($p = 0.012$). The 3 year time to local recurrence for group (I) was 51.62% versus 37.42%, for group (II) with a statistically significant difference (I) ($p = 0.031$). The 3 year time to distant metastases was 58.29% for group (I) versus (37.16%) for group (II) with a statistically significant difference (I) $p = (0.031)$. Six patients in-group (I) developed orbital infection and cellulitis (27%). Twelve patients developed grade (I) myelosuppression (54%). In group (II) all cases developed grade (II) alopecia (100%) 3 patients

developed grade (I) myelosuppression (16.8%) 12 patients developed grade (II) myelosuppression (33.6%) and 15 patients developed grade (III) myelosuppression (45.4%).

Conclusion: The role of postoperative adjuvant chemotherapy was not clear. It insignificantly reduces the incidence of distant metastases and local recurrence. On the other hand it may significantly improve disease free survival but not the overall survival.

Key Words: Retinoblastoma - Adjuvant treatment - Locally advanced

INTRODUCTION

Locally advanced retinoblastoma is a common presentation noticed in pediatric retinoblastoma patients. Retinoblastoma considered to be locally advanced when there is exophthalmous, palpable mass through eyelids, scleral involvement by tumour or scleral necrosis, tumour present at the cut end of optic nerve margins and vitreous seedlings [13].

In the past, locally advanced retinoblastoma was treated by surgery and radiation therapy. Recently, chemotherapy was added to treatment hoping to improve treatment results as regards incidence of local recurrence, distant metastases, disease free survival and overall survival rates. Some authors found no benefit of adding chemotherapy [4,5] others found little benefit [7,9].

The aim of the present study was to evaluate the role of adjuvant postoperative chemotherapy in the local control, disease - free interval and overall survival by comparing two groups of patients, who received postoperative radiotherapy with and without chemotherapy.

PATIENTS AND METHODS

This retrospective study carried out on 54 newly diagnosed pediatric patients of unilateral locally advanced retinoblastoma patients referred to pediatric unit of Kasr EL-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period from February 1991 till February 1996. These patients were followed up till February 1999.

Patients were divided into two groups. The first group included 21 patients treated by surgery and radiation therapy, second group included 33 patients treated by surgery, postoperative radiation therapy and chemotherapy.

Pretreatment evaluation

At initial presentation all patients were assessed by history taking, full clinical, laboratory and radiological assessment.

Clinical assessment included examination of the orbit for any evidence of orbital infection or cellulitis. Examination of parotid and preauricular lymph nodes were also carried out. Chest and abdominal examination were performed in addition to body surface area.

Table (1): Patients characteristics of the 2 groups.

No.	Clinical presentation	Group (I)		Group (II)	
		No	%	No	%
1	Exophthalmous	12	56.8	20	56
2	Palpable mass through eyelids	3	14.2	4	11.2
3	Scleral involvement by the tumor	3	14.2	3	8.7
4	Globe rupture during surgery	3	14.2	3	8.7
5	Tumor present at cut end of the optic nerve histologically.	-	-	2	5.6
6	Vitreous seedlings.	-	-	1	2.8

Laboratory assessment was performed including complete blood picture, renal and liver profiles. CSF cytology as well was performed for patients presented by optic nerve involvement.

Radiological assessment including postoperative orbital CT scan to rule out local recurrence, chest X-ray and abdominal sonar was done to exclude liver metastases.

All patients underwent orbital exenteration and received postoperative radiation therapy by 2 oblique fields using tele-cobalt 60 machine at a source skin distance of 80 cm. A total dose of 50 Gy over 25 sessions, 5 sessions per week for 5 weeks were given to all patients. Patients with optic nerve involvement received whole brain radiation up to 30 Gy over 10 fractions over 2 weeks followed by orbital radiation up to 50 Gy.

Patients in group (II) received additional postoperative chemotherapy in the form of Vincristine 1.4 mg/m² IV D1. Adriamycin 40 mg/m² IV D1 and cyclophosphamide 650 mg/m² D1 every 3 weeks for 1 year.

Intrathecal chemotherapy in the form of methotrexate (12mg/m²) once weekly till CSF is clear was given for patients presented by positive C.S.F. cytology or patients presented by optic nerve involvement.

Patients who relapsed either locally or systemically received second line chemotherapy using Cisplatinum containing regimen and/or palliative radiation therapy [15].

Follow up patients was performed by chest X-ray, abdominal sonogram, C.T. scan of the orbit and C.S.F cytology were performed every three months during follow up period.

The 2 groups were compared as regard overall survival, disease free interval, pattern and incidence of local recurrence and distant metastases.

Statistical evaluation

Kaplan meier method was used for estimating survival and log rank test for comparing the survival in the 2 groups [14].

RESULTS

54 newly diagnosed paediatric patients of unilateral locally advanced retinoblastoma were divided into 2 groups.

Group (I) included 21 patients, who received adjuvant postoperative orbital radiation therapy. Group (II) included 33 patients, who received adjuvant postoperative orbital radiation therapy, in addition to adjuvant chemotherapy.

Clinical, radiological and laboratory assessment of patients, revealed normal chest and heart in all studied patients. Metastatic work up

were free in all patients apart from 3 patients who had positive involvement of C.S.F. with tumor cells. All patients were of normal percentile as regards age and sex.

Thirty patients were males (54%) and 24 patients were females (46%). Ten patients had positive family history of consanguinity (18%).

Six out of 21 patients (28.6%) of group (I) developed local recurrence in the same orbit versus 10 out of 33 patients (28%) in group (II), the difference was statistically insignificant $p = (0.110)$.

Six out of 21 patients (28.6%) of group (I) developed distant metastases, 3 patients in the brain (14.29%), 2 patients in the lungs (9.4%), 1 patient in the bone (4.7%). In group (II) 7 out of 33 patients (19.6%) developed metastases, 2 patients in the lung (5.6%), 3 patients in the brain (8.7%) and 2 patients in the bone (56%). The differences were statistically insignificant $p = (0.113)$.

The 3 year overall survival for group (I) patient was 19.25% of (14.0 - 19.9). In group (II) the 3 year overall survival was (50.53%) with 95% confidence interval of (46.7 - 53.2). The difference between the 2 groups was not statistically significant ($p = 0.221$) (Fig. 1).

The 3 year disease free survival (DFS) rate in group (I) patients was 17%, with 95% (CI) of (6.35 - 19.65) the median DFS was 6 months while the 3 year DFS in group (II) was 33% with 95% CI of (28.2 - 34.6) with median (DFS) of 13 months. The difference was statistically significant ($p = 0.012$) (Fig. 2).

The 3 year time to local control (Fig 3), for group (I) was 51.62% versus 37.42% for group (II) with a median time to local recurrence of 8.5 months for group (II) with 95% CI of (5.3 - 9.7). The difference was statistically significant favoring group (I) ($p = 0.031$).

The 3 year distant metastases free rate for group (I) was 58.29% versus 37.16% for group (II) with a median time to distant metastases of 8 months for group (II) with 95% CI of (5.3 - 9.7) the difference was statistically significant ($p = 0.031$).

Six patients in group (I) developed orbital infection and cellulitis (27%), 12 patients developed grade (I) myelosuppression (54%).

In group (II) all patients developed grade (II) alopecia (100%), 3 patients developed orbital infection (8.4%), 6 patients developed grade (I) myelosuppression (16.8%), 12 patients developed grade (II) myelosuppression (33.69) and 15 patients developed grade (III) myelosuppression (45.5%) according to Miller & Hogastatin grading system [10].

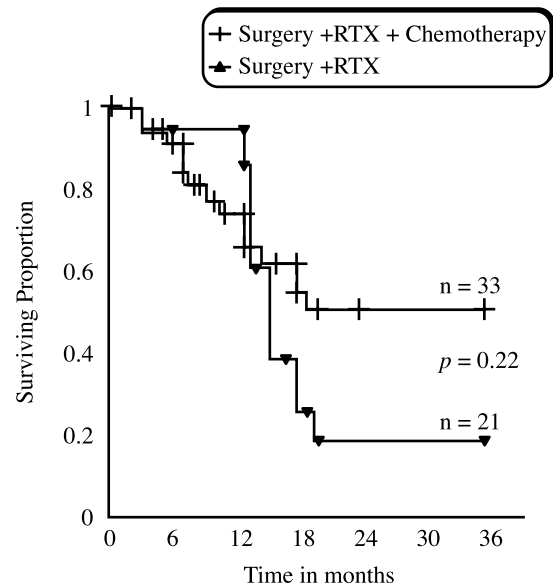


Fig. (1) Overall survival of 54 patients with retinoblastoma classified by line of management.

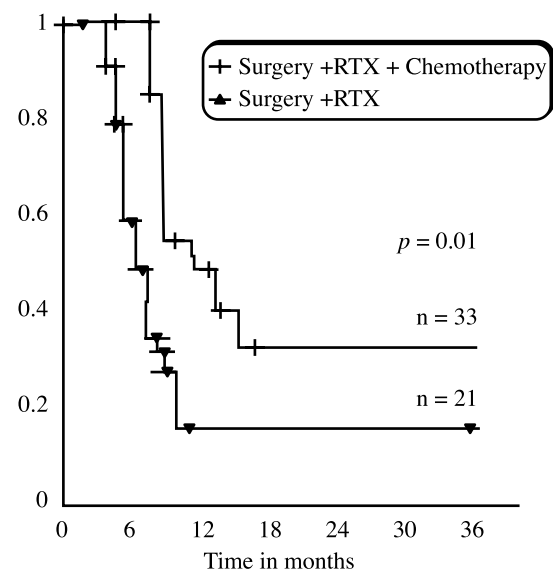


Fig. (2) Disease free survival of 54 patients with retinoblastoma classified by line of management.

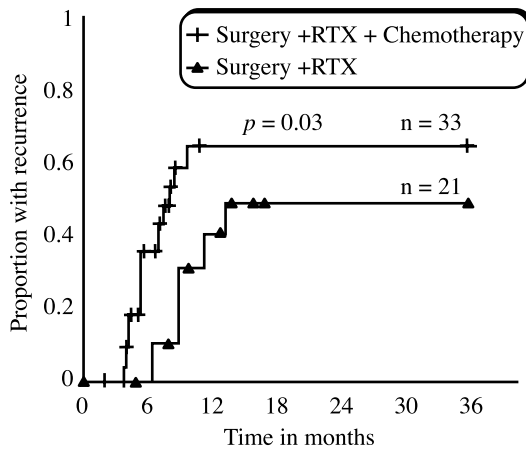


Fig. (3) Time to local recurrence of 54 patients with retinoblastoma classified by line of management.

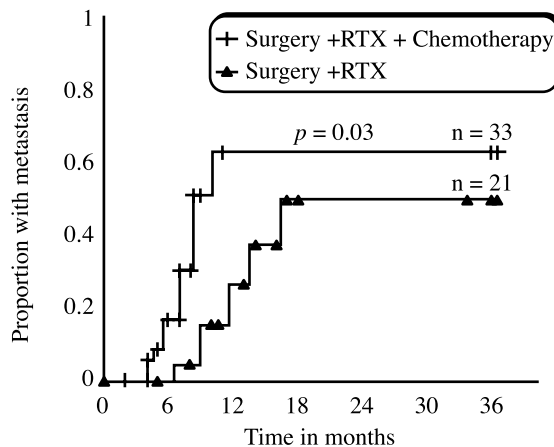


Fig. (4) Time to distant metastasis in 54 patients with retinoblastoma classified by line of management.

DISCUSSION

The use of adjuvant chemotherapy was recently introduced in the treatment of locally advanced pediatric retinoblastoma in addition to surgery and radiation therapy.

In the present study the role of adjuvant chemotherapy was assessed as regards its influence on the rate and incidence of local recurrence and distant metastases, disease free survival and overall survival by comparing 2 groups of patients in a retrospective study. The first group (I) received postoperative radiation therapy and the second group (II) received postoperative radiation therapy together with chemotherapy.

In the present study the 3-year overall survival was 19.25% for group (I) versus 50.53% for

group (II). However, this difference was statistically insignificant ($p = 0.221$).

In a similar work performed by Bitgic and Poisk [3] 23 patients received postoperative radiotherapy and 27 patients received postoperative radiation and chemotherapy. All forms of treatment achieved survival of more than 5 years. The 5-year survival was 77% and 86% respectively. The difference between the 5-year survival of the 2 groups was also statistically insignificant. In a Turkish study performed by Arslan & Gunlap [2] the 5-year survival rate was 62.8% for the group received adjuvant postoperative chemoradiotherapy versus 53% for the group received adjuvant postoperative radiation therapy. This difference was again statistically insignificant.

In a work done by Pradham et al. [12] on 46 patients, the 5 year survival was 52% for radiotherapy arm versus 61% for chemoradiotherapy arm with a statistically insignificant difference between the 2 arms. In a study performed by Mustafa et al. [11] on 55 patients the 5 year survival was 58% for chemoradiotherapy arm versus 53% for radiotherapy arm, the difference was statistically insignificant ($p = 0.123$).

The low survival of our patients was probably due to the late presentation and extreme advanced stage of the disease in most of our patients.

In the present study distant metastases occurred in 28.6% of patients in group (I) versus 19.6% for group (II).

The 3-year rate of distant metastases was 58.29% for group (I) versus 37.16% for group (II). This difference between the 3-year cumulative distant metastasis rates was statistically significant ($p = 0.031$).

The same incidence of local recurrence was experienced by the 2 groups as it occurred in 28.6% of patients in group (I) versus 28% for group (II). However, the 3 year local control rate was 51.62% for group (I), versus 37.4% for group (II) which is a statistically significant difference favoring group (I) ($p = 0.031$).

The results coincides with the work of Goble et al. [6] who found that local recurrence occurred in 14% of patients for chemoradiotherapy arm versus 21% for radiotherapy arm which is a statistically insignificant difference ($p = 0.101$).

The result coincides with the work of Advanie et al. [1] where the study was carried on 40 patients. The incidence of local recurrence was 10% and distant metastases was 14% for chemoradiotherapy arm versus 15% and 19% respectively for radiotherapy arm, the results were statistically insignificant $p = (0.112)$.

Also the present study coincides with the work of Kingstom and Hungerfert [8], where the study was carried on 44 patients, the incidence of local recurrence was 9% and that of distant metastases was 10% in chemoradiotherapy arm versus 11% and 12% in radiotherapy arm which is a statistically insignificant difference $p = (0.111)$.

Conclusion

The role of postoperative adjuvant chemotherapy was not clear. It insignificantly reduces incidence of distant metastases and local recurrence. In the other hand it may significantly improve disease free survival but it insignificantly improves overall survival.

Aggressive combination chemotherapy with or without bone marrow transplantation should be further studied in attempt to improve treatment results.

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