Clinics in Oncology

Research Article
Published: 03 Dec, 2021

Impact of Neoadjuvant Systemic Chemotherapy and Delayed Enucleation for Eyes with Advanced Intraocular Retinoblastoma on High-Risk Pathological Features

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Abstract

Purpose: To evaluate the impact of neo-adjuvant systemic chemotherapy on High-Risk Pathologic Features (HRPF) in retinoblastoma and compare the risk with eyes that underwent primary enucleation.

Methods: A retrospective study of 121 eyes from 118 patients who underwent enucleation between November 2009 and January 2020 at the King Hussein Cancer Center (KHCC) Amman/Jordan. Data included demographics, tumor stage, and time from diagnosis to enucleation, follow-up, metastasis, and mortality.

Results: Seventy-two (60%) eyes underwent primary enucleation and 49 (40%) eyes were secondarily enucleated after failure of systemic chemotherapy. Compared to the primarily enucleated patients, those in the secondary group were significantly younger at diagnosis (p=0.0014), had bilateral disease (p=0.0001) and presented with less advanced disease (p=0.016).

Even though the overall prevalence of HRPF was nearly similar between two groups (35.5% *vs.* 37.5%), (p<0.585), eyes with primary enucleation were significantly more likely to harbor massive choroidal invasion (p=0.0315) and post-laminar optic nerve invasion (p=0.027). In the other hand, secondary enucleated eyes were significantly more likely to harbor anterior chamber invasion (p=0.013). We studied the prevalence of HRPF for International Intraocular Retinoblastoma Classification (IIRC) group D and E eyes separately, and compared between primary and secondary enucleation for each subgroup (D and E) and found that the prevalence of HRPF was similar (P=0.58, 1.0 respectively). Of interest, the difference in time from diagnosis to enucleation in secondarily enucleated eyes was not significant predictive factor for HRPF (p=0.50). In terms of metastasis and survival, there was no significant difference between primary and secondary enucleated eyes (p=0.156, 0.44 respectively).

Conclusion: Systemic chemotherapy has the capability to downstage the level of tumor extension as detected pathologically. Primary and secondary enucleated eyes are comparable in low metastatic risk only if strict protocols of management and meticulous exam to detect early signs of disease progression. Therefore, controlled ocular salvage should be tried with caution in candidate advanced intraocular retinoblastoma cases to avoid possible risk of under treatment of micro metastatic diseases and subsequent mortality.

Keywords: Retinoblastoma; Enucleation; Neoadjuvant chemotherapy; High-risk histopathological features

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Received Date: *29 Oct 2021*
Accepted Date: *25 Nov 2021*
Published Date: *03 Dec 2021*

Citation:
Mohammad M, Shehada R, Al-Nawaiseh I, Mehyar M, Al-Hussaini M, Jaradat I, et al. Impact of Neoadjuvant Systemic Chemotherapy and Delayed Enucleation for Eyes with Advanced Intraocular Retinoblastoma on High-Risk Pathological Features. Clin Oncol. 2021; 6: 1885.

ISSN: 2474-1663

Introduction

Retinoblastoma (Rb) is the most common childhood primary intraocular tumor and 90% of the cases are diagnosed before the age of 5 years world over [1]. Globally, the incidence is approximately 1 in 15,000 to 20,000 live births [2]. An earlier epidemiological study from Jordan has reported an incidence of 9.32 cases per million children among 0 to 5 years of age [3]. Approximately 20% of cases reported from Jordan are familial whereas only 10% of cases are familial in western countries

[4-6].

Risk-based management of retinoblastoma is determined by many factors including child's age at presentation, disease severity and laterality. The International Intraocular Retinoblastoma Classification (IIRC) estimated the success rate of chemotherapy combined with focal consolidation treatment, with ≥ 90% salvage rate for groups A-C eyes while 47% salvage rate for group D eyes [7,8]. Regarding group E eyes, the usual appropriate option is primary enucleation, due to irreversible intraocular damage and the higher possibility of adverse histology [9,10]. Furthermore, the management of group D eyes put the physician in a dilemma that trial at a conservative treatment for secondarily enucleated eyes may actually have High Risk Pathological Features (HRPF), raising the concern of developing metastasis. An ocular salvage and vision preservation treatment options for group D eyes includes the use of systemic chemotherapy paired with concurrent or subsequent focal consolidation therapies [11-13] or by Intra-ophthalmic Artery Chemotherapy (IAC). The latter has been a debating point due to the concern of tumor spread [13]. Moreover, the risk for intractable disease and extraocular extension still presents for children with advanced disease [6]. In some cases of advanced intraocular disease, the pathology of the enucleated eye may be under-estimated after neo-adjuvant therapy, increasing the possibility of metastasis and death due to inadequate surveillance and inappropriate management of unrecognized HRPF [14]. The presence of coexisting ocular morbidities in addition to prolonged time to enucleation has a predictive value of extraocular dissemination [15]. Massive choroidal invasion (>3 mm), post-laminar optic nerve invasion, anterior chamber, iris, sclera, ciliary body invasion and extraocular extension are considered to be HRPF for cancer spread [16-20]. All enucleated eyes are sent for histopathological assessment to define HRPF which if present mandate adjuvant chemotherapy and/or External Beam Radiation Therapy (EBRT) [21-25].

The aim of this study is to compare the prevalence of HRPF first between eyes primarily enucleated with those who received systemic chemotherapy before having the eye removed (secondary enucleation), and then to compare HRPF between early secondary enucleation (enucleation done less than 6 months since last chemotherapy) and late secondarily enucleated eyes. Moreover, we compared the frequencies of specific HRPF between the two groups.

Methods

The study was approved by the King Hussein Cancer Center (KHCC) Institutional Review Board and in accordance with the Declaration of Helsinki tenets.

It was a retrospective study of all IIRC group D and E retinoblastoma cases who underwent enucleation from November 2009 to January 2020 at the ocular oncology unit at KHCC.

We included eyes with advanced intraocular retinoblastoma, and we divided them into two groups. Group 1 were eyes that underwent primary enucleation (no previous treatment before enucleation), and group 2 were eyes that received conservative therapy (systemic chemotherapy combined with focal consolidation therapy) and were eventually enucleated for treatment failure. Furthermore, we divided group 2 into two sub groups; early group (if time between last chemotherapy and enucleation is less than 6 months), and late group (if the time period is more than 6 months). We excluded eyes that received radiotherapy (external beam or brachytherapy), and patients with extraocular retinoblastoma or distant metastasis at presentation.

The histopathology reports of all enucleated eyes were evaluated for the presence of HRPF features and the growth pattern. HRPF were defined as the presence of anterior chamber involvement, iris infiltration, ciliary muscle/body infiltration, massive (≥ 3 mm) choroidal invasion, post-laminar optic nerve invasion, combined focal choroidal and prelaminar/laminar optic nerve invasion, scleral infiltration or extraocular disease. Any patient with HRPF was assigned to additional eight cycles of adjuvant systemic chemotherapy ± External Beam Radiotherapy (EBRT).

During the study period, all patients were managed and followed by at least two retinoblastoma specialists and histopathological evaluation of the enucleated eyes was performed by ocular pathologist.

Medical chart review

From the medical charts the following data were extracted: sex, age at presentation, laterality of the disease, Reese-Ellsworth (R-E) Classification, IIRC and the 8th edition American Joint Committee on Cancer Union for International Cancer Control (AJCC/UICC) clinical staging system (8th edition cTNMH) at diagnosis, time from diagnosis to enucleation, treatments prior to enucleation and subsequent required therapies, early (less than six months from last chemotherapy) *vs.* late secondary enucleation, family history of Rb, duration of follow-up, development of distant metastatic spread and death. All Ret-Cam images that performed at presentation and during follow-up were reviewed and analyzed by two ocular oncologists to confirm the staging of each eye.

Statistical methods

Descriptive analysis of Patients' information was done. Categorical data were presented as counts and percentages. The mean, standard deviation and range were calculated for the continuous data. In general, differences in proportions were tested with χ^2 test or Fisher exact test, and differences in continuous variables were tested with a Student t test or non-parametric test depending on the assumption required for each test.

A significance criterion of $p \leq 0.05$ was used in the analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Demographics and disease stage

Record review identified 137 eyes were enucleated at KHCC over the study period from November 2009 to January 2020. After exclusion of 16 eyes for patients who were given radiotherapy before enucleation or those with extraocular or metastatic disease at diagnosis, we identified 121 eyes (118 patients); 72 eyes (60%, 70 patients (59%)) of which underwent primary enucleation and 49 eyes (40%, 48 (41%) patients) were secondarily enucleated (Figure 1). Of the enucleated eyes, 68 (56%) were classified as group D, 53 (44%) were group E. The mean of follow up was 47 ± 37 months, range 1 to 155, with a median 40 months.

Sixty-two (52.5%) patients were males and 56 (47.5%) were females, and 3 patients had positive family history of Rb (all were from the secondary enucleation group). The median age at presentation was 18.0 months (mean: 24.0, range: 1-86). Half 59 (50%) of patients presented with bilateral disease. Of the bilateral cases, the fellow eye was IIRC group A in 10 cases, B in 9, C in 11, D in 12 and E in 4, the rest had the eye previously enucleated outside our center. Eight patients had bilateral enucleation, among six of them the first eye

Table 1: Demographic and clinical characteristics by treatment group.

Parameter	Primary Enucleation Patients (n=70) (%)	Secondary Enucleation Patients (n=48) (%)	Significance: P-value
Sex			
Male	34 (49)	28 (58)	0.297
Female	36 (51)	20 (42)	
Age at diagnosis (m)			
Mean ± SD	28 ± 21	17 ± 16	0.0014
Median	24	13	
Range	1-86	1-80	
Duration of follow up (m)			
Mean ± SD	45 ± 36	51 ± 38	0.245
Median	38	45	
Range	1-144	5-155	
Laterality of tumor			
Unilateral	49 (70)	10 (21)	0.0001
Bilateral	21 (30)	38 (79)	
Mortality			
Yes	3 (4.2)	4 (8.3)	0.44
No	67 (95.8)	44 (91.7)	
Mortality			
IIRC D	0	1	
IIRC E	3	3	
Metastasis			
NO	67 (96)	42 (88)	0.156
Yes	3 (4)	6 (12)	
CNS	3	3*	
Lymph node	0	2	
Bone marrow	0	4*	
Family history			
Yes	0	3 (6)	0.065
No	70	46 (94)	
	Primary Enucleation Eyes (n=72) (%)	**Secondary Enucleation Eyes (n=49) (%)**	
Laterality			
RE	42 (58)	24 (49)	0.31
LE	30 (42)	25 (51)	
Time from diagnosis to enucleation (m)			
Mean ± SD	2 ± 6	13 ± 12	<.0001
Median	0	9	
Range	0-3	2-57	
Time from last primary treatment to enucleation (m)			
Mean ± SD	Not applicable	5 ± 7	NA
Median		2	
Range		0-24	
International Classification Group			
D	34 (47)	34 (69)	0.016
E	38 (53)	15 (31)	
cTNM			
T2a	2	3	0.099
T2b	24	27	
T3a	3	3	
T3b	17	5	
T3c	8	5	
T3d	10	2	
T3e	2	2	
Missing	6	2	
Reese-Ellsworth Group			
Va	20	16	0.599
Vb	48	31	
Missing	4	2	

Table 2: Histopathologic findings among primarily *vs.* secondarily enucleated eyes.

Parameter	Primary Enucleation Eyes (n=72) (%)	Secondary Enucleation Eyes (n=49) (%)	Significance: P-value
High-Risk Histopathologic Features (HRPF)			
NO	45 (62.5%)	33 (67.3)	0.585
YES	27 (37.5%)	16 (32.7%)	
IIRC group D	34 (47%)	34 (69%)	
HRPF			
Yes	11 (32%)	8 (24%)	0.58
No	23 (68%)	26 (76%)	
IIRC group E	38 (53%)	15 (31%)	
HRPF			
Yes	19 (50)	8 (53%)	1
No	19 (50)	7 (47%)	
Growth pattern			
Endophytic	31 (43.1%)	11 (22%)	0.018
Exophytic	17 (23.6%)	14 (28.6%)	
Combined	18 (25%)	11 (22.4%)	
Necrotic	6 (8.3%)	13 (26.5%)	
Anterior chamber iris, ciliary body, scleral invasion and extraocular disease invasion			
NO	66 (91.6%)	38 (77.5%)	0.013
YES	5 (6.94)	11 (22.5%)	
Choroid invasion:			
NO	35 (48.6%)	33 (65.3%)	0.0315
Focal (<3 mm)	16 (22.2%)	7 (16.3%)	
Massive (>3 mm)	21 (29.16)	9 (18.4%)	
Optic nerve invasion			
NO	30 (41.66%)	34 (69.3%)	0.027
ANT to Lamina Cribrosa (LC)	14 (19.4%)	6 (12.2%)	
AT LC	13 (18%)	5 (10.2%)	
POST to LC	15 (20.8%)	4 (8.3%)	

Table 3: Demographic and clinical characteristics for early *vs.* late secondarily enucleated eyes.

Parameter	Early Secondary Patients (n=35) (%)	Late Secondary Patients (n=13)	Significance: P-value
Sex			
Male	21 (60)	7 (54)	0.701
Female	14 (40)	6 (46)	
Age at diagnosis (m)			
Mean ± SD	17 ± 17	17 ± 13	0.797
Median	12	13	
Range	1-80	1-48	
Duration of follow up (m)			
Mean ± SD	50 ± 38	55 ± 37	0.479
Median	45	44	
Range	5-147	11-155	
Laterality of tumor			
Unilateral	8 (23)	2 (15)	0.706
Bilateral	27 (77)	11 (85)	
Mortality			
Yes	3 (9)	1 (8)	1
No	32 (91)	12 (92)	
Metastasis			
NO	31 (89)	11 (85)	0.572
Yes	4 (11)	2 (15)	
CNS	*2	1	
Lymph node	0	*2	
Bone marrow	*3	*1	
Family history			
Yes	2 (6)	1 (8)	1
No	33 (94)	12 (92)	
	Early Secondary Eyes (n=36) (%)	Late Secondary Eyes (n=13) (%)	
Laterality			
RE	16 (44)	8 (62)	0.345
LE	20 (56)	5 (58)	
Time from diagnosis to enucleation (m)			
Mean ± SD	9 ± 7	23 ± 15	0.003
Median	8	19	
Range	2-36	4-57	
Time from last primary treatment to enucleation (m)			
Mean ± SD	2 ± 2	15 ± 6	<0.0001
Median	1	12	
Range	0-6	8-24	
International Classification Group			
D	24 (67)	10 (77)	0.727
E	12 (33)	3 (23)	
cTNM			
T2a	3	0	0.878
T2b	18	9	
T3a	3	0	0.878
T3b	4	1	
T3c	4	1	
T3d	2	0	
T3e	2	0	
Missing	0	2	
Reese-Ellsworth Group			
Va	14	2	0.287
Vb	22	9	
Missing	0	2	

was previously enucleated outside, one patient had one eye primarily enucleated and the remaining eye secondarily enucleated and the last one both eyes were primarily enucleated at KHCC. In terms of the 8th edition cTNMH, the majority 51 (45.1%) of enucleated eyes were classified as cT2b, 22 (19.5%) as cT3b, 13 (11.5%) as cT3c, 12 (10.6%) as cT3d and the rest were cT3a, cT2a, cT3e (Table 1).

Significant differences in age at diagnosis, laterality of the tumor, IIRC group and time from diagnosis to enucleation were observed between the two groups. Compared to the primarily enucleated patients, the patients undergoing secondary enucleation were more likely to be younger at diagnosis (P value 0.0014), had bilateral disease (P value 0.0001) and more IIRC group D (69% secondary *vs.* 47% primary) less group E (31% of secondary *vs.*, 53% primary) (p<0.016). The mean time from diagnosis to enucleation of the secondarily enucleated eyes was 13 ± 12 months, range 2-57, with a median 9 months (p<0.001).

HRPF prevalence and type

HRPF were detected in 43 (35.5%) eyes in the entire cohort. Of the 72 eyes that underwent primary enucleation, HRPF were detected in 27 (37.5%). Of the 49 eyes that underwent secondary enucleation, HRPF were detected in 16 (32.7%), with non-significant difference (p<0.585) between the two groups.

We separated patients with IIRC group D and E, and then compared the overall risk of HRPF between those primarily and secondarily enucleated in each sub-group. For group D, 34 eyes (47%) were primarily enucleated, 8 eyes (24%) of those had HRPF, while 34 eyes (69%) were secondarily enucleated, 8 eyes (24%) of which had HRPF, with no significant difference between both groups (P=0.58).

For IIRC group E eyes of 38 eyes (53%) in primary enucleation group 19 eyes (50%) had HRPF which was not significantly different than those with positive HRPF in the secondarily enucleated eyes (8 eyes (53%)) (p=1.0).

The most prevalent HRPF in the entire study was massive choroidal invasion in 30 eyes (24.8%) followed by post-laminar optic nerve invasion in 19 eyes (15.7%), and the least one is anterior chamber, iris, ciliary body, scleral invasion in 16 eyes (13.2%) (Figure 2). Of the primarily enucleated group, the prevalence of massive choroidal invasion was 29.16% which was significantly higher than for secondarily enucleated eyes 18.4% (9 eyes) (p<0.0315). Also of the primarily enucleated group, the prevalence of post-laminar optic nerve invasion (15 eyes) was significantly higher than secondarily enucleated eyes (4 eyes) (p<0.027). On the other hand, the prevalence of anterior chamber, iris, ciliary body, scleral invasion was significantly higher among secondarily enucleated eyes (11 *vs.* 5 eyes)

Table 4: Histopathologic findings among early or late secondarily enucleated eyes.

Parameter	Early Secondary Eyes (n=36) (%)	Late Secondary Eyes (n=13) (%)	Significance: P-value
HRPF			
NO	25 (69)	8 (62)	0.733
YES	11 (31)	5 (38)	
Growth pattern			
Endophytic	9 (25)	2 (15)	0.174
Exophytic	11 (30.5)	3 (24)	
Combined	5 (14)	6 (46)	
Necrotic	11 (30.5)	2 (15)	
Anterior Chamber, iris, ciliary body, scleral invasion and extraocular disease invasion			
NO	30 (83)	8 (62)	0.133
YES	6 (17)	5 (38)	
Choroid invasion:			
NO	25 (69)	7 (54)	0.513
Focal (<3 mm)	5 (14)	3 (23)	
Massive (>3 mm)	6 (17)	3 (23)	
Optic nerve invasion			
NO	26 (72)	8 (62)	0.832
Anterior to LC	4 (12)	2 (15)	
At LC	3 (8)	2 (15)	
Posterior to LC	3 (8)	1 (8)	

(p<0.013). Regarding the histological growth pattern in the entire study, 42 (34.7%) of eyes were endophytic, 19 (15.7%) were necrotic, 31 (25.6%) were exophytic and combined in 29 (24.0%) patterns. The primary and secondary enucleated eyes differ significantly in histological growth pattern (p<0.018). Among primary enucleated eyes, endophytic pattern was the highest 31 eyes (43.1%) while the necrotic pattern was the lowest 6 eyes (8.3%). On the other hand, the distribution among secondarily enucleated eyes among all patterns was nearly the same ranging from 22.4% to 28.6% (Table 2).

The secondary enucleation eyes were divided into two groups: Early and late enucleation. Analysis for both groups showed that there is no significant difference between two groups in terms of demographic and clinical characteristics (Table 3), and the presence of HRPF (Table 4).

Metastatic disease and mortality

Among the study patients, eight had metastatic disease and seven of those patients passed away (three patients in primary group and all had IIRC group E, four patients in secondary group: 1 IIRC group D and the rest group E). In terms of disease related mortality, there was no statically significant difference between patients in primary versus secondary enucleation groups (p=0.44) or for those with early versus late secondary enucleation (p=1.00).

Discussion

There are many treatment modalities of retinoblastoma and the choice of the appropriate treating strategy is determined by several factors. Nowadays there is a shift toward globe salvage therapy given the recent advanced experience with systemic chemotherapy, focal therapies or Intra-Arterial Chemotherapy (IAC) [26]. This shift towards globe salvage therapies put the treating physician at a dilemma when we try to avoid enucleation and keep an eye harboring an active disease, mainly for IIRC group D eyes, this dilemma is whether we endanger the child's life by delaying enucleation in attempts with globe salvage therapies [13,14]. For those cases extra- precautions should be followed to identify when treatment fails and to offer enucleation to avoid metastatic spread and subsequent mortality. The predictors of tumor metastasis post-enucleation are invasion of post-

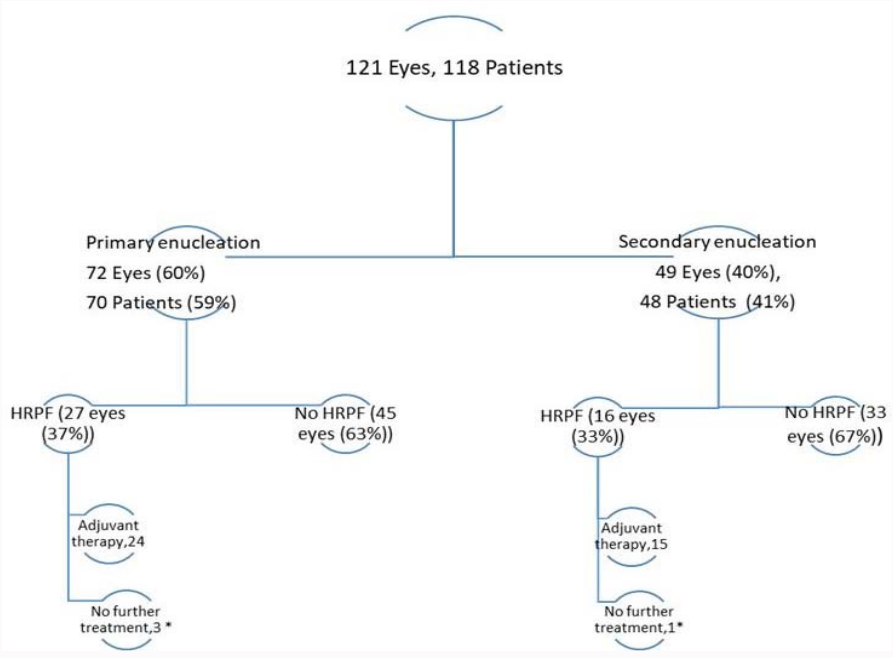

Figure 1: The prevalence of high-risk pathological features among primary and secondary enucleation groups.
*Patients did not continue the planned protocol due to parental request or because they travel back home

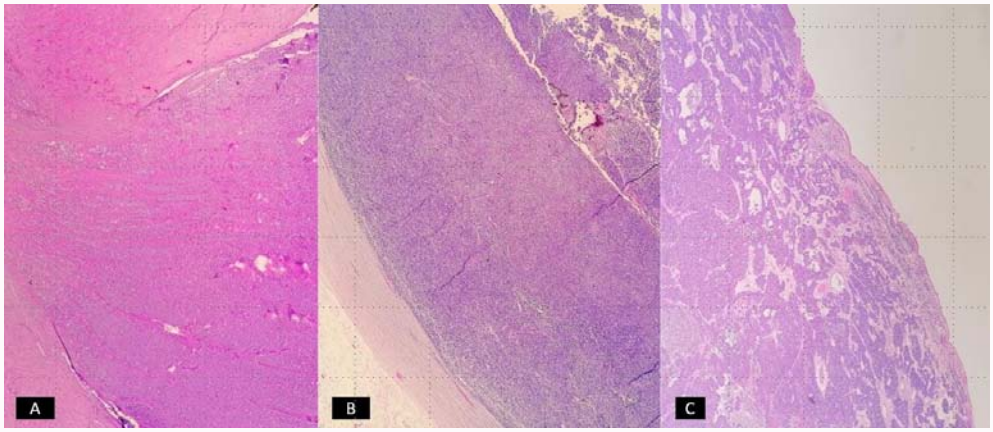

Figure 2: Retinoblastoma with HRPF, Hematoxylin and Eosin (H&E) stain. A) tumor posterior to lamina cribrosa, B) massive choroidal invasion, C) retinoblastoma invading the cornea with surface ulceration.

laminar optic nerve, anterior chamber or massive choroidal invasion, as these may constitute the portals of tumor spread outside the eye. The presence of any of those HRPF mandates adjuvant chemotherapy ± radiotherapy.

Our protocol is that any group D eye is assigned to either trial salvage therapy or primary enucleation [27]. The decision of trial salvage took into consideration the size of the tumor, the presence of good visual potential depending on the tumor location relative to the optic disc or the macula, the status of the fellow eye, parents' compliance for treatment and finally parents' consent after meticulous discussion of advantages and disadvantages of both options of treatment. Trial salvage includes either systemic chemotherapy (6 to 8 cycles Vincristine/Carboplatin/Etoposide (CVE)) followed by necessary consolidation focal therapies. Secondary enucleation is performed in case of tumor progression or unresponsiveness despite of the aforementioned treatment. If tumor showed signs of progression while the patient is on systemic chemotherapy, we perform enucleation and then continue the planned chemotherapy regimen irrespective of the histopathology results. For IIRC group E eyes, our protocol is to do upfront enucleation without pre-enucleation chemotherapy. However, we had cases with IIRC group E eyes, where we tried globe salvage therapy, as for patients referred from other countries with the other eye is already enucleated and the remaining single eye had group E retinoblastoma, or when there is a strong parent refusal for enucleation. We counsel those families very thoroughly about the risk of metastasis with group E eyes. After enucleation, all patients with positive high risk pathological features are given adjuvant systemic chemotherapy (8-cycles CVE/doxorubicin) ± radiotherapy to the orbit if the tumor involves the cut edge of optic nerve or for scleral invasion.

There is no consensus regarding the definition of HRPF [15-18], but the majority of physicians agree that post-laminar optic nerve invasion, massive choroidal infiltration, scleral and anterior chamber invasion, and tumor spread at the cut end of the optic nerve are considered HRPF harboring a high risk of metastatic disease and mandating subsequent adjuvant therapy. Most previous studies described the prevalence of HRPF after enucleation in general but in the current review, we looked into the effect of neoadjuvant systemic chemotherapy on the detection of HRPF after enucleation [9,28] and compared this risk with primarily enucleated eyes. Moreover, we divided the secondary enucleation group into early and late subgroups to seethe if the effect of systemic chemotherapy differs between both subgroups. In this study the overall risk of the presence of HRPF for both primary and secondary enucleation is 35.5%. Our incidence of HRH features is comparable with previous reports [8,15,20]. In 2014, Yousef et al. [8] analyzed 50 eyes post primary enucleation for retinoblastoma in our center and found the risk of HRPF to be 36%. Importantly, of 121 enucleated eyes, the overall risk of HRPF was similar between eyes with primary and secondary enucleation. Similar to this, Brennan et al. [29] compared the risk of HRPF between eyes with primary versus secondary enucleation and found that in spite of more favorable classification for eyes in the secondary group, the risk of HRPF was comparable with eyes in the primary group. Fabian et al. [30] evaluated the rate of HRPF for group D eyes for both primary and secondary enucleation subgroups and found the overall risk of HRPF 16%: 13% for primary, and 21% for secondary. Because the overall risk of HRPF is higher for IIRC group E eyes, we separated eyes with IIRC group D and E eyes, and compared the risk between eyes with primary and secondary enucleation for each subgroup; we found that the risk of HRPF is comparable between primary and secondary enucleated eyes in IIRC group D and E eyes separately.

For the secondary enucleation patients: compared with early secondary enucleation group, the time from last salvage trial to enucleation is significantly longer for the late secondary group, however there is no significant difference in the prevalence of HRPF between those two groups. In contrast to this finding, Zhao et al. [14] found pre-enucleation chemotherapy will mask the presence of HRPF and increase the risk for metastasis if enucleation was done more than 3 months after the diagnosis. This was not the case here, we tried to achieve tumor control by chemotherapy followed by focal consolidation, and according to our protocol we give patients with HRPF adjuvant chemotherapy ± radiotherapy. Also, we continued the planned systemic chemotherapy regimen irrespective of the final histopathology findings, while Zhao et al. [14] treated their patients with chemotherapy alone.

Even though the overall risk of HRPF was similar between study groups, we found difference in the distribution of HRPF between primary and secondary enucleated eyes. For example, primary enucleated eyes were significantly more likely to have massive choroidal invasion and/or post-laminar optic nerve invasion, this may be attributed to the fact that we offer primary enucleation if there is any clinical or radiological suspicion for choroidal or optic

nerve invasion and this is reflected that eyes in the primary group had more advanced disease at presentation, the other possible explanation for this difference is that systemic chemotherapy may mask features of extraocular extension causing under staging and under treating of systemic disease . In the secondary enucleation group, anterior chamber, iris, ciliary body, scleral invasion was significantly higher than for the primary enucleation group, which was consistent with what Brennan et al. [29] and Fabian et al. [30] reported before in a previous study. This finding can be explained by the fact that the spectrum of HRPF may be affected by the prolonged therapy and the action of systemic treatment. All patients that underwent secondary enucleation had previously received systemic chemotherapy which may have preferentially targeted invasion of the choroid and the optic nerve due to their complex and rich vascular supply. Moreover, focal treatment modalities as cryotherapy and laser may damage the choroid allowing direct access of tumor cells to the inner sclera. In addition, Abramson and Gombos [31] demonstrated that more advanced tumors anterior to the equator usually develop at a later age. Therefore, recurrences or treatment-resistant disease preferentially grown beyond the choroid to the sclera allowing special patterns of HRPF such as scleral invasion associated with ciliary body infiltration like what was observed in this study.

In this study, eight patients developed metastatic disease, seven of those patients passed away (three patients from primary enucleation group, all of them had IIRC group E). Of note, four out of seven patients who passed away had HRPF and did not continue the planned systemic chemotherapy schedule, either because they travelled back home or due to parents' refusal to continue with systemic chemotherapy after enucleation. There is no significant difference between primary and secondary enucleated eyes, early and late secondary enucleated eyes and between HRPF and non-HRPF eyes in terms of metastasis and mortality. Also, prolonged time to enucleation in secondary enucleation group was not associated with higher mortality, which we believe is that is due to the fact that with prompt recognition of recalcitrant disease progression, enucleation and further adjuvant therapy that addresses the high risk of metastatic spread may still achieve a cure. It is important to note here that six out of seven patients who passed away had IIRC group E, even though the difference in mortality was not significant between primary and secondary enucleation but still this high risk for group E eyes is alarming and should be taken into consideration if we tried globe salvage therapies for IIRC group E eyes.

Conclusion

Systemic chemotherapy may downstage the disease in retinoblastoma and masks the presence of HRPF. This is dangerous if we did not apply strict protocols of management to identify the presence of HRPF and give adjuvant therapy. Secondary enucleated eyes with high-risk histopathological features more commonly involved anterior structures, mandating meticulous clinical and histological examinations for this type of patients. Primary and secondary enucleated eyes are comparable in low metastatic risk and effectivity of tumor control if we follow strict guidelines of treatment and surveillance.

Acknowledgement

The authors acknowledge the great efforts of Ms. Ayat Taqash and Ms. Dalia Al-Rimawi for their valuable help in statistical analysis of data.

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