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RESEARCH ARTICLE

Management of advanced uni- or bilateral retinoblastoma with macroscopic optic nerve invasion

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Abstract

Background: Retinoblastoma with macroscopic optic nerve (ON) invasion depicted by imaging at diagnosis remains a major problem and carries a poor prognosis. We sought to describe the treatment and outcome of these high-risk patients.

Methods: Retrospective mono-institutional clinical, radiological, and histological review of patients with uni- or bilateral retinoblastoma with obvious ON invasion, defined by radiological optic nerve enlargement (RONE) depicted by computed tomography scan or magnetic resonance imaging (MRI), was performed.

Results: Between 1997 and 2014, among the 936 patients with retinoblastoma treated at Institut Curie, 11 had detectable RONE. Retinoblastoma was unilateral in 10 and bilateral in one. Median age at diagnosis was 28 months (range, 11-96). ON enlargement extended to the orbital portion in three patients, to the optic canal in five, to the prechiasmatic portion in two, and to the optic chiasm in one. Nine patients received neoadjuvant chemotherapy and partial response was obtained in all. Enucleation was performed in 10/11 patients—by an anterior approach in three and by anterior and subfrontal approaches in seven. Three patients had a positive ON resection margin (2/3 after primary enucleation). All enucleated patients received adjuvant treatment (conventional chemotherapy: 10, high-dose chemotherapy: seven, radiotherapy: five). Leptomeningeal progression occurred in four patients. Seven are in first complete remission (median follow up: 8 years [3.5-19.4]).

Conclusion: Neoadjuvant chemotherapy and microscopic complete resection have a pivotal role in the management of retinoblastoma with RONE. MRI is recommended for initial and pre-operative accurate staging. Surgery should be performed by neurosurgeons in case of posterior nerve invasion. Radiotherapy is required in case of incomplete resection.

KEYWORDS
long-term effects, MRI, optic nerve, retinoblastoma, treatment

1 | INTRODUCTION

Retinoblastoma is the most frequent primary malignant intraocular tumor in children, with an incidence of 1/20 000 births.[1] Extraocular extension, often in the optic nerve (ON), is still relatively frequent in low- and middle-income countries, but occurs in less than 5% of patients in high-income countries. It is often due to diagnosis delay and is associated with a considerably higher mortality rate, especially in case of combined metastatic disease or metastatic relapse.[2,3]

The diagnosis of ON invasion is based on imaging, and magnetic resonance imaging (MRI) is the current reference technique.[4] MRI is associated with a high negative predictive value for ON invasion. Early

Abbreviations: CSF, cerebrospinal fluid; ON, optic nerve; RONE, radiological optic nerve enlargement.

stages of invasion still rely on pathology, but an enlarged ON related to macroscopic invasion is easily depicted with this technique.[5]

Patients with macroscopic ON invasion are considered high risk. However, their therapeutic management is still debated. Neoadjuvant chemotherapy can be administered in order to make ocular tumors more accessible to complete microscopic resection. Adjuvant treatment may be administered, based on chemotherapy, while radiotherapy can be performed postoperatively in the event of incomplete resection and/or surgical eyeball effraction.[2,6–10]

The aim of our study is to analyze a cohort of patients with retinoblastoma with radiological optic nerve enlargement (RONE) at diagnosis managed at our institution in order to provide treatment recommendations.

2 | PATIENTS AND METHODS

2.1 | Patients

The medical records of patients treated at Institut Curie between December 1997 and March 2014 for uni- or bilateral retinoblastoma with RONE were reviewed (four of them had been enrolled in a previous publication with short-term follow-up[7]). The inclusion criteria were nonmetastatic uni- or bilateral retinoblastoma and availability of diagnostic-quality computed tomography (CT) scan and/or MRI (performed at diagnosis or during neoadjuvant chemotherapy) and identification of ON enlargement. This retrospective study was approved by our institutional review board.

2.2 | Methods

2.2.1 | Initial pediatric and ophthalmologic evaluation

Data collected concerned patient age/gender at diagnosis, and involved the eye(s). All patients underwent an ophthalmologic examination under general anesthesia and were staged according to Reese-Ellsworth and International Intraocular Retinoblastoma classifications.

2.2.2 | Radiological review and local staging

CT scan and/or MRI of patients with RONE were retrospectively reviewed by a senior pediatric radiologist (member of the European Retinoblastoma Imaging Collaboration[4]) to assess local extension and rule out metastatic central nervous system disease. The length of ON invasion was measured and classified into the following four stages: "intraorbital" (ie, between the optic globe and the anterior ostium of the optic canal), "optic canal," "prechiasmatic" (ie, between the posterior ostium of the optic canal and the optic chiasm), or "chiasmatic."

Regarding the technique, MRI examinations were performed under sedation or general anesthesia using various 1.5-T MRI systems according to the referring hospital. Examinations included both orbits and brain analyses. MRI sequences on the orbits were performed with either head or surface coils with 1-3 mm slice thickness, and included a variable combination of T1-weighted spin-echo or gradient-echo sequences, without and with a gadolinium-based contrast agent, and T2-weighted turbo-spin echo (TSE) or constructive interference in steady state sequences obtained in the axial or oblique-sagittal plane. Brain sequences included T2 TSE, fluid-attenuated inversion recovery, and postcontrast T1-weighted sequences.

2.2.3 | Distant staging

Assessments included bilateral bone marrow aspirate and biopsy for all patients at diagnosis. Brain MRI and lumbar puncture with cerebrospinal fluid (CSF) cytology were performed for all patients at diagnosis, before enucleation and before high-dose chemotherapy. Besides, CSF cytology was assessed each time the children had intrathecal injections of chemotherapy. In some cases, initial staging was completed with spinal MRI and/or bone scan.[11]

2.2.4 | Neoadjuvant chemotherapy

The chemotherapy used was a combination of etoposide-carboplatin, etoposide-cyclophosphamide, high-dose melphalan, and intrathecal thiotepa.[7,12,13] Doses, treatment schedules, and total number of courses were detailed. Data concerning hematological and grade 3-4 nonhematological treatment-related toxicity were collected, according to NCI-CTCAE v4.

2.2.5 | Surgical approach

The data collected were the type of surgery (classic anterior or "double" approach including both anterior and neurosurgical approaches), macroscopic aspect of ON, and intraoperative eyeball rupture.

2.2.6 | Pathology examination

Pathological review was performed by a pathologist with more than 20 years of experience in eye and orbital tumor pathology. Histopathologic risk features were evaluated according to Sastre et al.[14] A standard form was used to evaluate specimens for histopathological risk features, including tumor involvement of the choroid (minimal superficial, minimal deep, or deep), sclera (intrascleral or extrascleral), ON, and anterior segment. ON invasion was classified as prelaminar, intralaminar, postlaminar, or involving the surgical margin of the ON and/or of its meningeal sheath. Histological response to neoadjuvant chemotherapy was classified as complete (100% necrosis), major (>80% necrosis), or minor (<80% necrosis).

2.2.7 | Adjuvant treatment

Conventional chemotherapy was used, which was a combination of etoposide-carboplatin, etoposide-cyclophosphamide, cyclophosphamide-vincristine, and intrathecal thiotepa.[7,12,13,15] Intrathecal topotecan was also administered according to Potter et al.[16] The high-dose chemotherapy used was a combination of either carboplatin-etoposide-cyclophosphamide or etoposide-carboplatin-thiotepa.[6,7,9,17] Data concerning adjuvant chemotherapy were collected as described for neoadjuvant treatment. Some patients were also treated with radiotherapy and the data collected were techniques (brachytherapy[18] or external beam irradiation) and doses.

2.2.8 | Follow-up

Overall and event-free survivals were estimated using the Kaplan-Meier method. Follow-up was calculated from the date of diagnosis to last contact with the patient. The data collected were the final clinical, general, and ophthalmologic status as well as late treatment-related side effects. Data on ototoxicity were collected only if there were at least 2 years between the last treatment with carboplatin and auditory evaluation.

3 | RESULTS

Between December 1997 and March 2014, 936 patients with retinoblastoma were treated at Institut Curie. The inclusion criteria were fulfilled by 11 patients. Among them, nine were referred to our center from Africa and French overseas territories. Retinoblastoma was unilateral in 10 patients and bilateral in one. The patient with bilateral retinoblastoma had unilateral RONE. Median age at diagnosis was 28 months (11-96) and median follow-up was 8 years (0.4-19.4). Nine patients received neoadjuvant chemotherapy while two had primary enucleation (Table 1).

3.1 | Main clinical, radiological, and histological data

3.1.1 | Initial radiological involvement

Radiological investigations were performed at diagnosis for 10 patients and after four courses of neoadjuvant chemotherapy in one who was secondarily transferred to our center. MRI was performed in all patients, with additional CT scan in seven. Four patients had spinal MRI and four had a bone scan.

3.1.2 | Pre-operative assessment

Pre-operative radiological evaluation (MRI) and lumbar puncture were performed in all patients. Imaging showed partial response in all of them (Figures 1–4). Lumbar puncture showed CSF progression in one patient.

3.1.3 | Surgery

Two patients were primarily enucleated by an anterior approach—one at another hospital before being referred to our center and the second one at our institution. The second patient had the initial MRI at another center and there was a suspicion of RONE, but ON invasion was underestimated by the radiologists who considered it was not necessary to perform neoadjuvant chemotherapy. When the images were retrospectively reviewed by our pediatric radiologist, it appeared clear that there was a 15-mm ON invasion that should have required neoadjuvant chemotherapy. Among the nine remaining patients, one with CSF progressive disease persisting after second-line chemotherapy was not enucleated. Another patient needed emergency enucleation by an anterior approach (in spite of major chiasmatic involvement) due to corneal perforation. The seven remaining patients underwent secondary enucleation by a double approach. The ON was resected in one single fragment in four patients; among them, the nerve was sectioned posteriorly in the optic canal in three patients and in the prechiasmatic region in one patient with RONE involving the optic canal. In the three remaining patients, the ON was resected in two fragments; two patients had an ON section on both sides of the optic canal (one patient with intraorbital involvement and one with RONE in the optic canal) and one had sections in the prechiasmatic region and on the anterior side of the optic canal (patient with prechiasmatic invasion). No patients presented complications after surgery.

3.1.4 | Histopathological results

Pathological examination found histological risk factors, including ON resection margin involvement in both primarily enucleated patients and in the patient who was enucleated in emergency. ON invasion was confirmed in all seven remaining patients and all had ON free resection margins, including the ones who had multifragmented ON resection.

3.1.5 | Adjuvant treatment

All enucleated patients were initially intended to receive high-dose chemotherapy. Two patients presented CSF progression during conventional adjuvant treatment and could not receive high-dose chemotherapy. One child could not be treated with high-dose chemotherapy because of a failure to collect peripheral stem cells and was treated with six monthly intrathecal injections of topotecan.

3.2 | Cumulative dose of chemotherapy and treatment-related toxicity

The median number of conventional chemotherapy received per patient was 7 (5-8) . Eight patients were treated with high-dose chemotherapy.

Median cumulative doses were etoposide 2750 mg/m^2 (1100-4600), carboplatin 3425 mg/m^2 (1760-4300), and cyclophosphamide 9000 mg/m^2 (1540-15 400). One patient also received 100 mg/m^2 of melphalan and three received 900 mg/m^2 of thiotepa.

Patients experienced expected hematological and nonhematological toxicities during treatment (Table 2). No patient died of acute treatment toxicity. We did not report any renal toxicity. One patient out of five evaluable presented grade 4 ototoxicity.

3.3 | Radiotherapy and treatment-related toxicity

Among the 10 enucleated patients, five were treated with additional radiotherapy. The two primarily enucleated patients received orbital irradiation with iodine-125 brachytherapy because of ON resection margin involvement. The three others received external beam radiotherapy. The patient who was enucleated in emergency was irradiated from the orbital cavity up to the optic chiasm; the patient who presented prechiasmatic RONE at diagnosis and had multifragmented ON resection was irradiated from the posterior part of the orbital cavity up to the left side of the optic chiasm because of macroscopically suspicious ON, even though pathology showed no residual tumoral cells;

TABLE 1 Clinical, radiological, and histological summary of the patients

Patient number, age at diagnosis (months), year of diagnosis	Clinical opthalmological features	Radiological features, enlarged optic nerve (ON) length	Neoadjuvant treatment	Evaluation before surgery, residual ON enlargement length	Surgery and ON length (if available)	Histological features	Adjuvant treatment: conventional chemotherapy	Adjuvant treatment: high-dose chemotherapy with ASCT	Radiotherapy	Follow-up (years)
Patient 1, 19, 1997	Exopthalmia, leukocoria, periocular soft tissue edema, conjunctival hyperemia, pain, iris heterochromia, ocular hypertonia	Prechiasmatic RONE, 42 mm	First-line treatment: 2 VP C 5d 1 VP C 5d[a] + 2 IT 1 VP E 3d + IT, second-line treatment: 1 M (high-dose chemotherapy) 1 VP	Magnetic resonance imaging (MRI): tumor reduction, ON length 5 mm Cerebrospinal fluid (CSF) (+)	No	Not evaluable	No	No CSF (+) before enucleation (but this child received neoadjuvant high-dose chemotherapy with melphalan	No	Death 5.5 months after diagnosis, CSF (+)
Patient 2, 21, 1997	Leukocoria, conjunctival hyperemia	Intraorbital RONE, 12 mm	2 VP C 5d 1 VP C 5d[a]	MRI + computed tomography (CT) scan: tumor reduction, ON length 10 mm CSF(–)	Double approach, ON length unknown	Free resection margin, no residual ON invasion, major response	2 VP E 3d	Yes CARBOPEC	No	19.4
Patient 3, 11, 1998	Leukocoria	Optic canal RONE, 22 mm	1 VP C 5d 2 VP C 3d 1 VP E 3d	MRI + CT scan: tumor reduction, ON length 10 mm CSF (–)	Double approach, ON length 10 mm	Free resection margin, postlaminar involvement (6 mm), minimal superficial choroidal involvement, major response	1 VP C 3d 1 VP E 3d	Yes CARBOPEC	No	8
Patient 4, 96, 2000	Strabismus, conjunctival hyperemia, pain	Prechiasmatic RONE, 43 mm	2 VP C 5d + IT	MRI: tumor reduction, ON length not evaluable CSF (–)	Double approach, ON length unknown	Free resection margin, no residual ON invasion, complete response	1 VP C 3d 1 VP E 3d	Yes CARBOPEC	EBRT (proton and photon therapy) (25.2 + 19.8 Gy)	18.1
Patient 5, 43, 2002	Strabismus, leukocoria	Optic canal RONE, 25 mm	No		Anterior approach, ON length 10 mm	Resection margin involvement, extrascleral involvement, minor response	1 VP C 5d 2 CO 3d 1 VP C 5d + IT 1 VP C 5d + IT[b]	No CSF (+) before high-dose chemotherapy	Brachytherapy (45 Gy)	Death 6 months after diagnosis, CSF (+)
Patient 6, 28, 2003	Leukocoria, pain	Intraorbital RONE, 15 mm	No		Anterior approach, ON length unknown	Resection margin involvement, extrascleral involvement, minor response	3 VP C 5d + IT 3 CO 3d	Yes CARBOPEC	Brachytherapy (45 Gy)	14.6
Patient 7, 36, 2012	Leukocoria	Intraorbital RONE, 10 mm	3 VP C 5d	MRI: tumor reduction, ON length 8 mm CSF (–)	Double approach, ON length 23 mm	Free resection margin, postlaminar involvement (8 mm), complete response	2 CO 3d 1 C 3d	Yes VP C T	No	4.3

(Continues)

TABLE 1 (Continued)

Patient number, age at diagnosis (months), year of diagnosis	Clinical opthalmological features	Radiological features, enlarged optic nerve (ON) length	Neoadjuvant treatment	Evaluation before surgery, residual ON enlargement length	Surgery and ON length (if available)	Histological features	Adjuvant treatment: conventional chemotherapy	Adjuvant treatment: high-dose chemotherapy with ASCT	Radiotherapy	Follow-up (years)
Patient 8, 13, 2012	Bilateral retinoblastoma,[c] leukocoria, periocular soft tissue oedema, conjunctival hyperemia, exopthalmia	Right eye: optic canal RONE, 29 mm; left eye: no RONE	2 VP C 5d + IT	MRI: tumor reduction, ON length 10 mm CSF (–)	Double approach, ON length unknown	Free resection margin, postlaminar involvement (5 mm), deep choroidal and scleral involvement, anterior segment involvement, major response	3 CO 3d 1 VP C 5d + IT[b]	No CSF (+) before high-dose chemotherapy	No	0.4 Lost-to-follow-up after CSF progression
Patient 9, 59, 2013	Leukocoria, pain, exopthalmia	Optic canal RONE, 34 mm	Chemotherapy in Nigeria,[d] 3 VP C 5d + IT	MRI: tumor reduction, ON length 30 mm CSF (–)	Double approach, ON length 33 mm	Free resection margin, no residual ON invasion, complete response	1 CO 5d 3 CO 3d	Yes VP C T	EBRT (proton therapy) (45 Gy)	4
Patient 10, 29, 2013	Strabismus, exopthalmia, leukocoria, periocular soft tissue oedema, conjunctival hyperemia, pain	Optic canal RONE, 27 mm	2 VP C 5d + IT 1 VP C 5d[e] + IT	MRI: tumor reduction, ON length 10 mm CSF (–)	Double approach, ON length 20 mm	Free resection margin, postlaminar involvement (8 mm), deep choroidal and scleral involvement, meningeal sheath involvement, complete response	3 CO 3d 1 VP C 5d + To IT 1 CO 3d + To IT 4 To IT	No, because of a failure to collect peripheral stem cells	No	3.5
Patient 11, 22, 2014	Exopthalmia	Chiasmatic RONE, 60 mm	2 VP C 5d	MRI: tumor reduction, ON length 41 mm CSF (–)	Anterior approach (emergency enucleation), ON length 5 mm	Resection margin involvement, postlaminar involvement (5 mm), extrascleral involvement, meningeal sheath involvement, anterior segment involvement, major response	1 CO 3d 1 VP C 5d + IT 2 CO 3d	Yes VP C T	EBRT (proton therapy) (45 Gy)	Death 16 months after diagnosis, CSF (+)

Abbreviations: ASCT, autologous stem cell transplant; AUC, area under the curve; C 3d, cyclophosphamide 1 g/m^2/day D1 to D3 without vincristine because of peripheral neuropathy; CARBOPEC, carboplatin 350 mg/m^2/day D1 to D5 + etoposide 350 mg/m^2/day D1 to D5 + cyclophosphamide 1.6 g/m^2/day D2 to D5 with autologous stem cell infusion D8; CO 3d, cyclophosphamide 1 g/m^2/day D1 to D3 + vincristine 1.5 mg/m^2/day D1; CO 5d (mistake in administration), cyclophosphamide 150 mg/m^2/day D1 to D5 (instead of 300) + vincristine 1.5 mg/m^2/day D1 (instead of D1 and D5); EBRT, external beam radiotherapy; IT, thiotepa 15 mg intrathecal D1; M, melphalan 100 mg/m^2/day D1 with autologous stem cell infusion D3; To IT, topotecan 0.40 mg intrathecal D1; VP, etoposide 100 mg/m^2/day 3 days/week 3 weeks/4; VP C T, carboplatin maximum 500 mg/m^2 D1 and dose adjustment with AUC 7/day D2 to D3 + etoposide 250 mg/m^2/day D4 to D6 + thiotepa 300 mg/m^2/day D4 to D6 with autologous stem cell infusion D9; VP C 3d, etoposide 150 mg/m^2/day D1 to D3 + carboplatin 200 mg/m^2/day D1 to D3; VP C 5d, etoposide 100 mg/m^2/day D1 to D5 + carboplatin 160 mg/m^2/day D1 to D5; VP E 3d, etoposide 150 mg/m^2/day D1 to D3 + cyclophosphamide 1 g/m^2/day D1 to D3; 2 IT, thiotepa 10 mg intrathecal D2 and D5.

[a]Dose reduction to 3/5 because of hematotoxicity.

[b]Treatment stopped after 1 day because of CSF progression.

[c]Only results concerning the eye with RONE are summarized in this table.

[d]Four courses of unknown chemotherapy before arrival at Institut Curie.

[e]Dose reduction to 2/3 because of hematotoxicity.

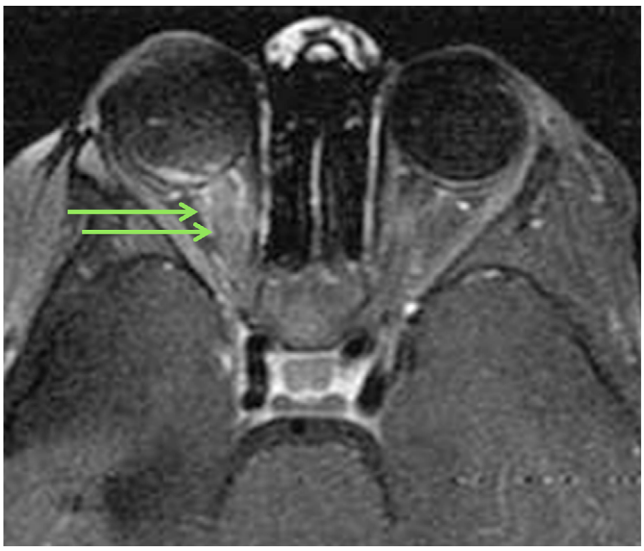

FIGURE 1 MRI pattern of intraorbital optic nerve involvement (patient 6); intraorbital radiological optic nerve enlargement at diagnosis (contrast-enhanced T1-weighted sequences)

the patient who had the first MRI after four courses of neoadjuvant chemotherapy was irradiated from the orbital cavity up to the optic chiasm because the pathological analysis of the enucleated eye could not rule out possible initial chiasmatic involvement, and MRI at diagnosis was not available.

All patients received a total dose of 45 Gy. Among the three patients treated with external beam radiotherapy, two exclusively received protontherapy and one a combination of proton and photontherapy.

The patient who was treated with brachytherapy and survived had few esthetic sequelae such as enopthalmia, smaller orbital cavity, and palpebral retraction. Two out of three patients treated with external beam radiotherapy survived and presented palpebral retraction or ptosis, enopthalmia, loss of eyelashes, and moderate temporal bone hypoplasia.

3.4 | Follow-up

Median follow-up was 8 years (0.4-19.4) with seven patients still alive at last follow-up, in first complete remission (Table 1). Overall and event-free survival were respectively 80% and 72% at 1 year and 70%

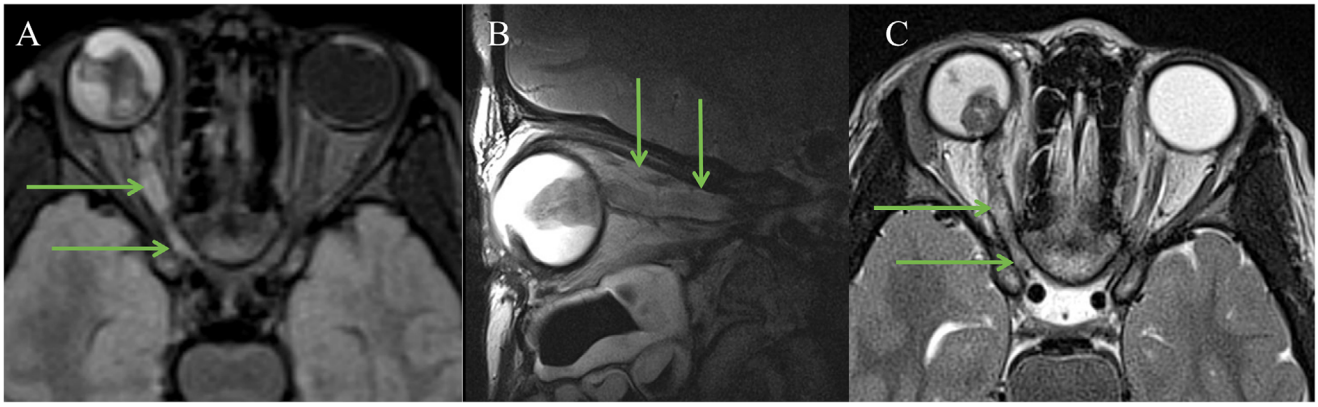

FIGURE 2 MRI patterns of optic nerve involvement in the optic canal (patient 9); (A-C) optic canal radiological optic nerve enlargement at diagnosis (A: FLAIR, B-C: T2-weighted sequences). Abbreviation: fluid-attenuated inversion recovery

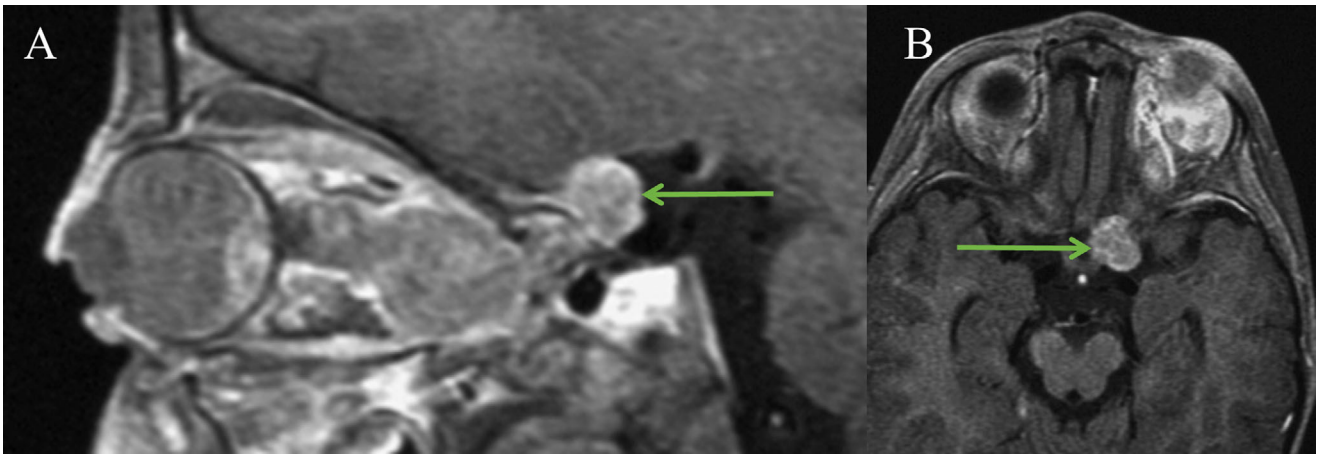

FIGURE 3 MRI patterns of prechiasmatic optic nerve involvement (patient 1); (A-B) prechiasmatic radiological optic nerve enlargement at diagnosis (contrast-enhanced T1-weighted sequences)

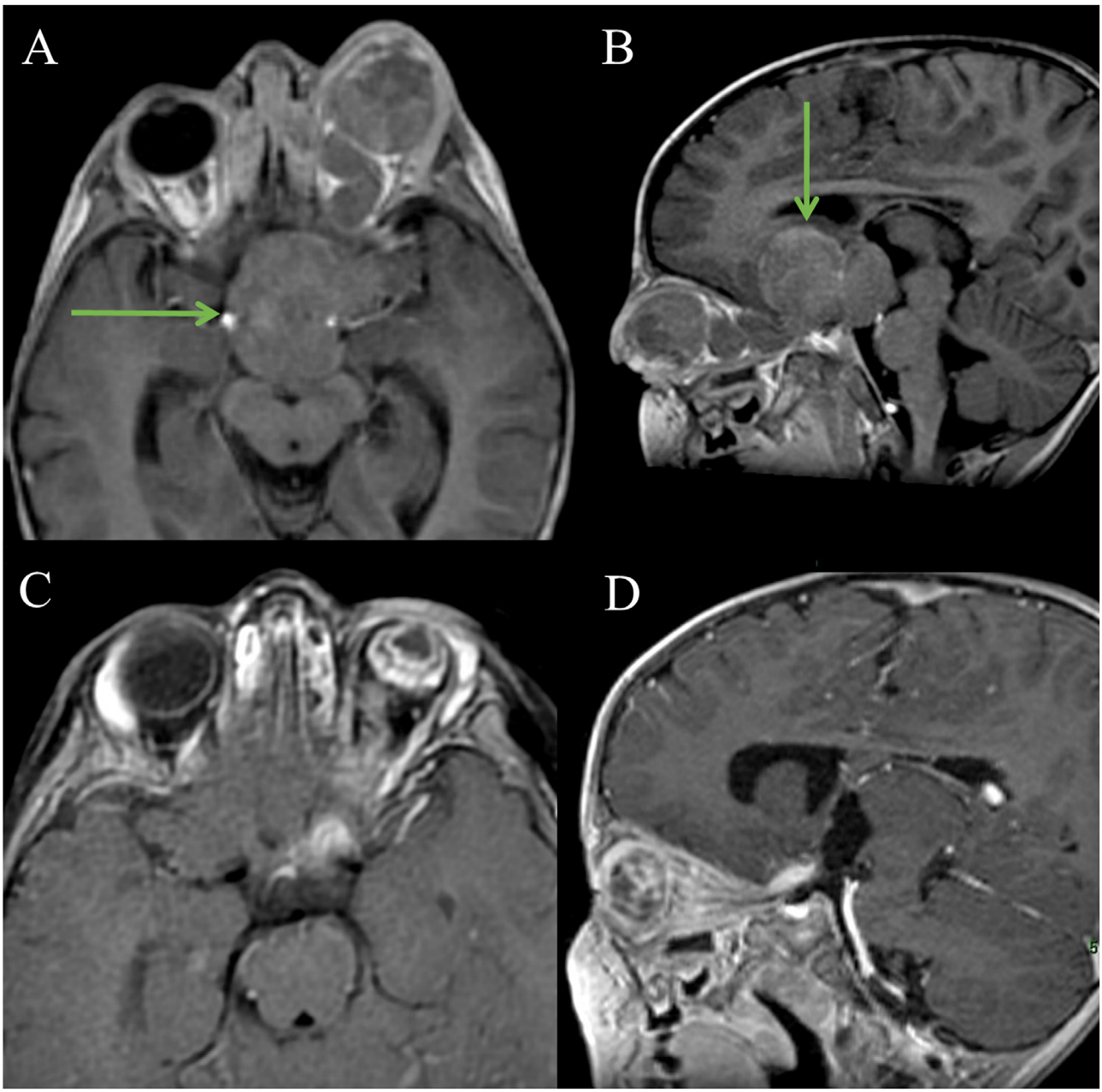

FIGURE 4 MRI pattern of chiasmatic optic nerve involvement (patient 11); chiasmatic radiological optic nerve enlargement at diagnosis (A-B) and after two courses of neoadjuvant chemotherapy (C-D) (contrast-enhanced T1-weighted sequences)

and 64% at 2 years (Figures S1 and S2). At last follow-up, no second tumour occurred in our patients.

4 | DISCUSSION

Retinoblastoma with RONE at diagnosis has become rare in high-income countries, but is still relatively frequent in low- and middle-income countries and carries a poor prognosis. Literature on the management of retinoblastoma with RONE is limited. Most patients have been treated with different approaches, making therapeutic recommendations difficult.[2,8,19]

An accurate pretreatment assessment is mandatory with brain MRI, lumbar puncture with CSF cytology, and bilateral bone marrow aspirate and biopsy.[19,20] Bone scan should only be performed in case of clinical suspicion of bone metastasis. Imaging at diagnosis plays an essential role in assessing extraocular invasion, especially high-resolution MRI.[4,5,21] Reassessment before surgery and before high-dose chemotherapy is also recommended with imaging and CSF cytology. One of our patients had a positive CSF cytology before planned surgery, emphasizing the need for frequent evaluations, in order to avoid aggressive treatments in the palliative phase. MRI is also useful to assess the efficacy of neoadjuvant chemotherapy and can help in preparing surgery. In our study, we confirm the good

TABLE 2 Chemotherapy-related toxicity

	After conventional chemotherapy (11 patients)	After high-dose chemotherapy (8 patients)
Febrile neutropenia	22 episodes including 6 bacteriologically documented Median number of episodes per patient: 1 (0-5)	8 episodes including 1 bacteriologically documented One episode per patient after each course
Median number of red cell transfusions per patient	2 (1-9)	1.5 (0-3)
Median number of platelet transfusions per patient	3 (1-11)	2 (1-9)
Peripheral neuropathy	1 patient after 2 courses of cyclophosphamide-vincristine (full recovery after stopping administration of vincristine)	None
Severe nausea and vomiting	None	1 patient (grade 3)
Oral mucositis	None	1 patient (grade 2) 4 patients (grade 3) including 3 requiring total parenteral nutrition and 1 requiring an orogastric tube
Urinary electrolyte wasting	None	1 patient (grade 2) with full recovery
Ototoxicity	None	1 patient (grade 4) out of 5 evaluable

correlation between MRI and pathological analysis regarding the length of ON invasion, especially with no underestimation by MRI.[5,21] In case of RONE with an ON involvement of 4 mm or more in length, we suggest that surgery should be performed by a double team—ophthalmological and neurosurgical—in order to ensure microscopic complete resection.

In our study, both primarily enucleated patients (anterior approach) had ON resection margin involvement whereas none of the seven secondarily enucleated patients (double approach) had ON resection margin involvement. Chemoreduction made interpretation of histological risk factors more difficult but, combined with double-approach surgery, it allowed a free ON resection margin, thus reducing the use of radiotherapy.[1] These results show the importance of the combination of chemoreduction and double-approach surgery to allow an ON free resection margin. Surgery must be performed under optimal conditions, by an experienced team, to allow an ON section as posterior as possible.

The literature remains very controversial about histopathological risk factors in retinoblastoma and the benefit of neoadjuvant chemotherapy before enucleation.[20,22–32] However, extrascleral and ON resection margin involvement are widely accepted high-risk factors. ON resection margin involvement is associated with a mortality rate between 50% and 81%.[26] Khelfaoui et al,[23] Honavar et al,[24] and Aerts et al[29] also consider postlaminar ON invasion and massive choroidal involvement as risk factors, alone or in combination. Zhao et al[32] suggested that neoadjuvant chemotherapy downstages pathological evidence of extraocular extension, thus increasing the risk of metastatic death. This was not confirmed by our study neither by Chantada et al,[33] who suggested that delayed enucleation, as well as a low-intensity adjuvant treatment that omitted orbital radiotherapy might explain the occurrence of relapse in Zhao's study. In our study, there was no therapy de-escalation, even when pathology examination showed no residual risk factors, and even if patients had a complete chemotherapy-induced tumor necrosis.[33] Enucleated patients were all intended to receive high-dose chemotherapy even if its efficacy remains unproven. High-dose chemotherapy administered in this study was either carboplatin-etoposide-cyclophosphamide for the oldest patients or etoposide-carboplatin-thiotepa for the more recent patients. This switch of high-dose chemotherapy regimen was due to changes in institutional practices over decades.

Patients with RONE are at greater risk of central nervous system relapse. Among our 11 patients, three died of early leptomeningeal progression and one was lost-to-follow-up after CSF dissemination. These results emphasize the very poor prognosis of central nervous system involvement despite aggressive multimodality therapy (including high-dose chemotherapy and radiotherapy), as confirmed by several studies.[2,8–10,34,35] This also shows the need for repeated CSF evaluations.

In our cohort, one child out of two who presented a prechiasmatic RONE is still alive after 18 years whereas the second one presented CSF dissemination before enucleation and died. Besides, among our two primarily enucleated patients who presented resection margin involvement, one is still alive after 14 years and after having received adjuvant chemoradiation therapy, whereas the second one presented leptomeningeal progression and could not receive high-dose chemotherapy. Because of our small sample size and our patients' different evolutions, it is impossible to assure that having prechiasmatic or chiasmatic RONE or resection margin involvement is always associated with bad evolution, although one would intuitively think this is the case.[19]

Considering the high risk of leptomeningeal progression in these extensive forms of retinoblastoma, prophylactic intrathecal injections of chemotherapy were administered. Only eight out of 11 patients received intrathecal chemotherapy because treatment modalities changed throughout the years and it was probably not recommended for our oldest patients. Now, we would recommend intrathecal chemotherapy for all patients presenting with RONE. Seven patients out of eight received intrathecal thiotepa and one patient received thiotepa during neoadjuvant chemotherapy and topotecan during adjuvant chemotherapy because of a failure to collect peripheral stem cells. Indeed, Schaiquevich et al[36] showed that topotecan, alone or in combination, is active against retinoblastoma and Potter et al[16] showed that intrathecal route of administration is tolerable and active against recurrent or refractory leptomeningeal leukemia. It

was therefore used in this patient because we could not intensify treatment with high-dose chemotherapy. Three out of seven patients who received thiotepa died of leptomeningeal progression and the fourth was lost-to-follow-up after leptomeningeal progression. The three remaining patients are still alive as well as the patient who received intrathecal topotecan. These results emphasize the need for central nervous system prophylaxis because, despite our intensive treatment, four patients presented leptomeningeal progression and were switched to palliative care. Intrathecal topotecan was only used in one of our patients but could be a good therapeutic option in the upcoming years for patients with RONE.

Treatment was intensified with additional radiotherapy in five patients. Three patients out of five had ON resection margin involvement whereas the two others received irradiation in spite of a free resection margin. One of these two patients had a macroscopically suspicious ON and in the second one, pathology could not rule out initial chiasmatic involvement, and MRI at diagnosis was not available. Our current recommendations regarding radiotherapy would be to perform radiotherapy only when resection is microscopically incomplete. These discrepancies in the therapeutic management of patients with RONE emphasize the need for standardized therapeutic recommendations. Orbital brachytherapy was used whenever possible to try to reduce esthetic sequelae.[37] In our cohort of children treated with radiotherapy, no severe complications occurred, especially no secondary tumors, although the follow-up is still short. Friedman et al[38] reported 32% of second tumours, but mostly, as expected, in patients with bilateral/hereditary retinoblastoma.

Owing to the intensified treatment performed, survival in this series is relatively favorable taking into account the initial disease extension. Nevertheless, all the patients who survived showed no progressive disease and were cured with intensive first-line chemotherapy. All the patients who presented a progressive disease had leptomeningeal progression and died or were lost-to-follow-up after switching to palliative care. It remains difficult to provide therapeutic recommendations because our study has limitations, mainly because of the small sample size with many covariables. The treatments administered here allowed good survival but, considering the small sample size, we can only provide weak treatment recommendations, at best. Retinoblastoma with RONE remains a major problem in low- and middle-income countries with poor survival rates.[3,8] This is mainly due to delay in diagnosis, poor awareness among the public and health-care professionals, poor access to health-care services, and parental refusal of enucleation and care.[3,8,39] Efforts have to be made with awareness campaigns to try to reduce the frequency of extraocular retinoblastoma.[40]

5 | CONCLUSIONS

According to our data, we recommend specific intensified management of patients with retinoblastoma with macroscopic ON invasion at diagnosis. Pretreatment accurate staging should include orbital and brain/spine MRI, CSF cytology, as well as pre-operative reassessment and assessment before high-dose chemotherapy. Neaodjuvant chemotherapy should be the first-line treatment. Secondary surgery is a very important step and should be performed by experienced ophthalmologists and neurosurgeons in order to obtain microscopic complete resection. Adjuvant chemotherapy should be employed, even when histological analysis shows no residual risk factors and complete tumor necrosis, as well as radiotherapy in case of positive resection margin.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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