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Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institut Curie

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Abstract

Retinoblastoma is usually curable in developed countries. The morbidity and mortality of patients with hereditary retinoblastoma is still threatened by the occurrence of secondary tumours. Between 1971 and 1988, 427 patients with retinoblastoma were treated in the ophthalmologic, paediatric and radiotherapy departments of the Institut Curie. In this study, we report the clinical and therapeutic features and the outcome of 25 patients treated for a second malignant neoplasm, diagnosed between 1997 and 1999 at the Institut Curie. The median time interval between the diagnosis of retinoblastoma and SMN was 11.2 years (range 3.8–20.6 years). Histopathological diagnoses included: 12 osteosarcomas, 12 soft tissue sarcomas and, 1 malignant oligodendroglioma. The second malignant neoplasm was located inside the radiation field in 21 cases and outside in 4. Twenty three patients received pre-operative chemotherapy. Surgery was performed in 16 patients. Post-operative chemotherapy was administered in 12 patients and external beam radiotherapy was used in 2 patients. Response to treatment was evaluable in 24 patients: complete remissions were observed in 14/24, partial remissions in 2/24 and progressive disease in 8/24. Nineteen patients died. Six are still alive, with 4 in complete remission (median follow-up 8.8 years; range 5.8–13.9 years). Despite aggressive therapy, the prognosis of patients with second malignant neoplasm occurring after retinoblastoma is very poor. It is important to provide information to retinoblastoma patients regarding the risk of a second tumour as this may facilitate an early tumour detection.

Keywords: Retinoblastoma; Second primary neoplasm; Survival; Antineoplastic agent; Surgery

1. Introduction

Retinoblastoma is the most frequent ocular malignancy of childhood, with an incidence of 1/15,000–20,000 births [1]. An estimated 40% of retinoblastomas are genetic. The tumour is linked to RB1 gene mutations in all patients with bilateral retinoblastoma, as well as in 10–15% of those with unilateral retinoblastoma.

Although complete recovery from retinoblastoma is frequent in industrialised countries [1], the likelihood of long-term survival in the hereditary group is reduced because of the risk of second malignant neoplasms occurring years after treatment. In industrialised countries, second malignant neoplasms represent the primary cause of death in patients with hereditary retinoblastoma [2].

The cumulative incidence of second cancers after retinoblastoma reported by numerous well documented studies [3–9], ranges from 8.4% at 18 years after diagnosis to 90% after 30 years [9].

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The risk factors for second non-ocular tumours occurring after retinoblastoma have been well studied. There is a genetic predisposition in patients with hereditary retinoblastoma to develop second malignancies [9,10]. Patients treated for hereditary retinoblastoma are at an increased risk to develop non-ocular malignancies due to a mutation in the second RB1 allele in different tissues [11]. Radiation, which was a conservative treatment that was often used to treat retinoblastoma, is known to increase the incidence of second tumours [3–5,9,12–15]. Chemotherapy containing alkylating agents, alone or in combination with radiotherapy, also seems to be involved in the development of second cancers [14,16], but anthracyclines have been implicated as well [17].

Thirty five different histological types of second malignant neoplasms have been reported in treated retinoblastoma patients [8]. Osteogenic sarcomas are the predominant type identified [3–7,9,12,13]. Soft tissue sarcomas [3–6,9,13,18] as well as malignant melanomas [3,5,19] are also very common with an incidence of 6.9% [8] and 7%, respectively, having been reported [19]. Many other tumours have been described such as central nervous system (CNS) tumours [9], peripheral primitive neuroectodermal tumours (pPNET), leukaemias and lymphomas [5,9,12].

Herein, we reviewed the experience at the Institut Curie, and describe the outcome following the diagnosis and treatment of second malignant neoplasms in 25 hereditary retinoblastoma patients.

2. Patients and methods

Between 1971 and 1988, 427 patients with retinoblastoma were treated in the ophthalmological, paediatric and radiotherapy departments of the Institut Curie. A large proportion of the patients treated between 1971 and 1985 were from North Africa and were lost to follow-up. Nevertheless, we treated 25 patients (23 Europeans, 2 North African patients) who developed a second malignant neoplasm; the last patient was diagnosed in October, 1997. The end-point of the study was either the date of the last consultation if patient was still alive or the date of death.

Patients with a local relapse, a metastatic retinoblastoma or a trilateral retinoblastoma [20] were not included in our study.

Radio-induced tumours were defined as reported by Cahan in [21] and characteristics included the histological diagnosis of sarcoma, external beam radiation therapy history, tumour location in the field of radiation and a disease-free interval of more than 5 years between the end of radiotherapy treatment and the diagnosis of the second tumour.

This definition was extended to the other histological types of tumours developing in the radiation field more than 5 years after the diagnosis of retinoblastoma. We also considered a malignant oligodendroglioma that developed in the radiation field 9 years after the initial diagnosis of retinoblastoma to be radio-induced.

The median age of the 25 patients included in our study at the time of the diagnosis of retinoblastoma was 10 months (range 3–30 months). There were 10 girls and 15 boys. Twenty three patients presented with bilateral retinoblastoma and two with a multifocal unilateral form. Of these 25 patients, the disease was familial in 6 cases (Table 1).

2.1. Treatment for retinoblastoma

2.1.1. Surgery

Twenty three patients have undergone enucleation (33 eyes) (Table 1). Enucleation was the first treatment for 15 eyes and was performed secondarily after failure of a conservative treatment in 18 eyes.

2.1.2. Radiotherapy

All the patients received external beam radiation therapy of the eye at a mean dose of 45 Grays (range 45–55 Grays). The median age at the time of radiation therapy was 11 months (range 3.5–24 months). Interstitial irradiation with iodine plaque [22] was used in 4 patients and with cobalt60 in one patient.

2.1.3. Chemotherapy

Chemotherapy was used in 12 patients: neoadjuvant chemotherapy in six patients, adjuvant treatment in 5 patients because of histopathological risk factors [23] and in one patient because of a delayed relapse. All of the patients received alkylating agents. Various chemotherapy regimens were used during this time period (Table 1).

2.2. Second malignant neoplasms

2.2.1. Latency period from diagnosis of retinoblastoma

The median time interval between the diagnosis of retinoblastoma and the second cancer was 11.2 years (range 3.8–20.6 years) (Table 2). The median age at diagnosis of the second cancer was 11.9 years (range 4.4–21.7 years).

2.2.2. Histology

The diagnosis of second cancer was made using biopsies in all cases (Fig. 1). The central histological examination results were:

- osteogenic sarcomas (OS): 12 cases
- malignant mesenchymatous tumours (MMT): 12 cases
  - 3 spindle cell sarcomas
  - 1 undifferentiated sarcoma
  - 3 pleiomorph sarcomas

Table 1
Characteristics of patients with Retinoblastoma and treatment received

Patient	Age (months)	Laterality	Familial	Enucleation	External beam RT	Interstitial RT	Chemotherapy
1	7	Bilateral	Yes	Right in second treatment	RE 50 Gy/LE 50 Gy		
2	11	Bilateral	Yes	Bilateral secondary LE, RE	RE 45 Gy/LE 45 Gy	RE	PE/CAdO
3	19	Bilateral	Yes		RE 52 Gy/LE 48 Gy		VAC
4	8	Bilateral	No	Right in first treatment	LE 45 Gy		
5	8	Bilateral	No	first for RE, secondary for LE	LE 45 Gy		CO
6	8	Bilateral	No	Left in first treatment	RE 45 Gy		
7	8	Bilateral	No	Right in first treatment	LE 50 Gy		
8	10	Bilateral	No	first for LE, secondary for RE	RE 47.5 Gy		VAC
9	11	Bilateral	No	Right in first treatment	LE 45 Gy		
10	22	Bilateral	No	Bilateral secondary RE, LE	RE 45 Gy/LE 45 Gy		VAC/IVA
11	8	Bilateral	No		RE 45 Gy/LE 45 Gy		VAC
12	15	Right	No	Right in second treatment	RE 45.5 Gy		
13	15	Bilateral	No	first for LE, secondary for RE	RE 45 Gy	RE	
14	4	Bilateral	No	Left in first treatment	RE 45 Gy		
15	18	Bilateral	No	Left in second treatment	RE 45 Gy/LE 50 Gy		
16	13	Bilateral	No	first for LE, secondary for RE	RE 51 Gy	RE	PE/ CAdO
17	13	Bilateral	Yes	first for RE, secondary for LE	RE 55 Gy/LE 55 Gy		
18	8	Bilateral	No	Bilateral secondary LE, RE	RE 45 Gy/LE 45 Gy		CO/PE CAdO
19	5	Bilateral	No	Left in second treatment	RE 45 Gy/LE 45 Gy		VAC
20	12	Bilateral	No	Right in first treatment	RE 45 Gy/LE 45 Gy		PE/CAdO
21	3	Bilateral	No	Right in first treatment	RE 45 Gy/LE 45 Gy		
22	15	Bilateral	No	first for LE, secondary for RE	RE 45 Gy		VAC
23	5	Bilateral	No	Left in first treatment	RE 45 Gy	RE, Cobalt 60	
24	30	Left	Yes	Left in first treatment	LE		
25	7	Bilateral	Yes	Bilateral secondary for RE, LE	RE 45 Gy/LE 45 Gy	RE	VAC

RB, retinoblastoma; RT, radiotherapy; RE, right eye; LE, left eye.
VAC: vincristine, 1.5 mg/m^2 at day 1; actinomycin D, 1.5 mg/m^2 at day 1; cyclophosphamide, 1 g/m^2 at day 1.
CAdO: cyclophosphamide, 300 mg/m^2 day 1–5; doxorubicin, 60 mg/m^2 at day 5; vincristine, 1.5 mg/m^2 at day 1 and 5.
PE: cisplatin, 100 mg/m^2 at day 1; VM26 (teniposide), 150 mg/m^2 at day 3.
CO: cyclophosphamide, 5 mg/kg day 1–5, vincristine, 0.05 mg/kg at day 1.
IVA: ifosfamide, 3 g/m^2 at day 1 and 2; vincristine, 1.5 mg/m^2 day 1, day 8 and day 15; actinomycin D, 1.5 mg/m^2 day 1.

2 malignant fibrous histiocytomas
3 rhabdomyosarcomas: 1 alveolar and 2 undefined
- malignant oligodendroglioma: 1 case.

2.3. Topography of the second malignant neoplasm

The second tumour was located inside the radiation field in 21 cases and outside it in 4 cases (Table 2). Four patients had metastatic disease at the time of diagnosis of the second tumour: locoregional nodes in 2 cases associated in one of them with subcutaneous metastases and pulmonary metastasis in 2 cases.

2.4. Treatment of second malignant neoplasm

2.4.1. Pre-operative chemotherapy

Twenty three patients received a pre-operative chemotherapy adapted to the histological type of the second tumour. Various chemotherapy regimens were used, according to different protocols (Table 3).

Nevertheless, with the exception of one patient who underwent treatment for osteosarcoma, the chemotherapy administered was high-dose methotrexate alternating with different drug combinations [24,25]. Patients who underwent treatment for mesenchymatous tumours received vincristine, actinomycin D and cyclophosphamide or ifosfamide. The ''eight drugs in one day'' regimen [26] was administered to the patient with a malignant oligodendroglioma.

2.4.2. Surgery

A surgical treatment was performed in 16 patients with a macroscopically complete resection in 9 patients, but this was incomplete in 7. Nine of twelve osteosarcoma patients underwent surgery, 8 after pre-operative chemotherapy.

2.4.3. Post-operative chemotherapy

Post-operative chemotherapy was administered in 12 patients, according to the histological response in 6 patients, or correlated to the clinical and radiological responses to pre-operative treatment. High-dose chemotherapy followed by autologous bone marrow transplantation was performed in one patient with MMT.

Table 2
SMN histological types and metastatic SMN

Patient	Histology	Years after RB	SMN outside RT field	SMN inside RT field	Metastatic disease
1	Osteogenic sarcoma	4		Right orbit	
2	Osteogenic sarcoma	10		Zygomatic bone	
3	Osteogenic sarcoma	11		Ethmoid bone	Pulmonary
4	Osteogenic sarcoma	11		Left orbit	
5	Osteogenic sarcoma	7		Left orbit	
6	Osteogenic sarcoma	13		Right upper jaw-bone	
7	Osteogenic sarcoma	4		Left orbit	
8	Osteogenic sarcoma	17		Left fronto temporal site	
9	Osteogenic sarcoma	12	Right femur		
10	Osteogenic sarcoma	7	Left humerus		
11	Osteogenic sarcoma	12	Right tibia		
12	Osteogenic sarcoma	11	Right femur		Pulmonary
13	Rhabdomyosarcoma	6		Right temporal site	
14	Rhabdomyosarcoma	8		Left orbit	Nodal metastases
15	Alveolar rhabdomyosarcoma	8		Left temporo zygomatic bone	
16	Spindle cell sarcoma	21		Right orbit	
17	Spindle cell sarcoma	16		Orbit	
18	Spindle cell sarcoma	6		Right orbit	
19	Pleiomorph sarcoma	20		Sphenoïd	
20	Pleiomorph sarcoma	8		Right orbit	
21	Pleiomorph sarcoma	11		Right ethmoïd	
22	Malignant fibrous histiocytoma	12		Superficial face	
23	Malignant fibrous histiocytoma	18		Right orbit	
24	Undifferentiated sarcoma	11		Left maxillary sinus	Cutaneous, nodes metastases
25	Malignant oligodendroglioma	9		Right temporo parietal CNS tumour	

CNS tumour, central nervous system tumour; SMN, second malignant neoplasm RT, radiotherapy; RB, retinoblastoma.

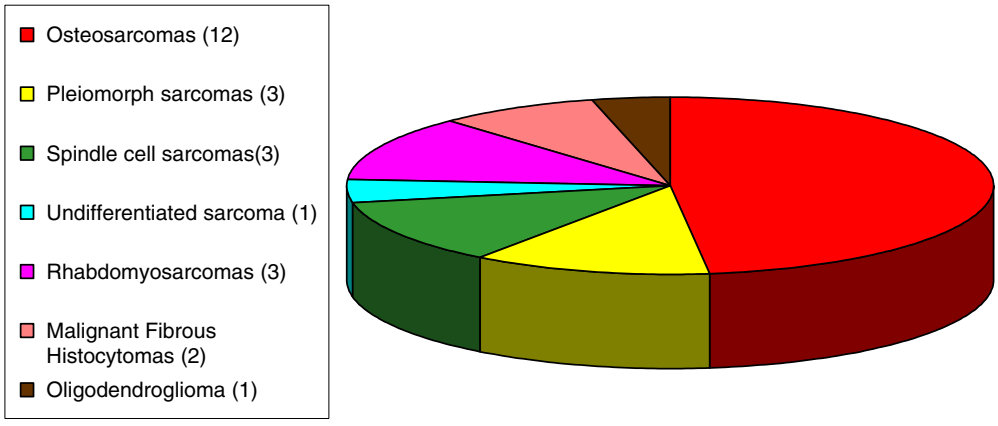

Fig. 1. Histology of the 25 second neoplasms.

2.4.4. External beam radiotherapy

Post-operative external beam radiotherapy was performed in 2 patients as palliative therapy.

3. Results

3.1. Response to therapy

For the patients with an osteosarcoma as their second tumour, the histological response according to Huvos grading [27] was evaluated: this was good in 5/8 patients, poor in 2/8 patients and unknown in the other 1/8 patient.

The response of the second malignancies was evaluable in 24 patients. One patient was not evaluable because he died from toxic complications two days after starting chemotherapy. Complete remission following the initial therapy was achieved in 14 patients. Partial remission was obtained in 2 patients. Despite treatment, 8 patients had progressive disease.

Table 3
SMN treatment

Patient	Histology	Pre-operative CT	Surgery	Tumoural cells (%)	Post-operative CT	RT (Gy)	Response	Survival
1	OS	No	Complete		VCR MTX Endoxan/ Adria/Cisplat	45	PD	Dead
2	OS	MTX/VP Ifo	Incomplete	ND	MTX/VP Ifo		PR	Alive
3	OS	MTX/VP Carbo 5 days	No		No		PD	Dead
4	OS	MTX/VP Ifo	Incomplete	5–10	VP Ifo		CR	Dead
5	OS	Help	No		No		NE	Dead
6	OS	MTX/VP Ifo	Complete	0	MTX/VP Ifo		CR	Alive
7	OS	IVA	Complete		MTX/Help Adria		CR	Dead
8	OS	VP Ifo/Adria Cisplat	No		No		PR	Dead
9	Distant OS	MTX/VP Ifo	Complete	0	MTX/VP Ifo		CR	Alive
10	Distant OS	MTX/Help Adria	Complete	5	MTX/Help Adria		CR	Dead
11	Distant OS	MTX/Help Adria	Complete	5	Help Adria		CR	Dead
12	Distant OS	MTX/VP Ifo	Complete	<5	MTX/VP Ifo		CR	Dead
13	MMT	IVA/CEV/IVE	No		No		CR	Dead
14	MMT	No	Incomplete		CAdO /HDCT (Bcnu Vm26 Carbo)		CR	Alive
15	MMT	IVA/CEV/IVE	No		No		CR	Alive
16	MMT	VCR Adria Det End SFOT	Complete		No		CR	Dead
17	MMT	VADIC/IVA	No		No		PD	Dead
18	MMT	VAC/VINCAEPI/IVA	No		No		PD	Dead
19	MMT	IVA	Incomplete		IVE/CEV		CR	Dead
20	MMT	IVA	No		No		PD	Dead
21	MMT	VAC/VADIC	Incomplete		VAC/VADIC		CR	Alive
22	MMT	IVA	No		No		PD	Dead
23	MMT	VP Ifo/Help Adria	Complete		No		CR	Dead
24	MMT	IVA/Vd I Cisplat	Incomplete		No		PD	Dead
25	Oligo-dendroglioma	8 in 1	Incomplete		No	37.8	PD	Dead

MMT, Malignant Mesenchymal Tumour; OS, Osteosarcoma.
MTX: methotrexate, 12 g/m^2 day 1.
VP Ifo: VP16 (etoposide), 75 mg/m^2 day 1–4; ifosfamide, 3 g/m^2 day 1–4.
Adria Cisplat: doxorubicin, 70 mg/m^2 day 1; cisplatin, 120 mg/m^2 day 2.
IVA: ifosfamide, 3 g/m^2 day 1 and 2; vincristine, 1.5 mg/m^2 day 1, 8 and 15; actinomycin D, 1.5 mg/m^2 day 1.
CEV: carboplatin, 500 mg/m^2 day 1; epirubicin, 75 mg/m^2 day 1 and 2; vincristine, 1.5 mg/m^2 day 1, 8 and 15.
IVE: ifosfamide, 3 g/m^2 day 1–3; vincristine, 1.5 mg/m^2 day 1; VP16, 150 mg/m^2 day 1–3.
VAC: vincristine, 1.5 mg/m^2 day 1; actinomycin D, 1.5 mg/m^2 day 1; cyclophosphamide, 1 g/m^2 day 1.
VINCAEPI: vincristine, 1.5 mg/m^2 day 1; carboplatin, 600 mg/m^2 day 3; VM26 (teniposide), 150 mg/m^2 day 4.
Help Adria: ifosfamide, 3 g/m^2 day 1 and 2; vindesin, 4 mg/m^2 day 1; cisplatin, 100 mg/m^2 day 3; doxorubicin, 30 mg/m^2 day 1 and 2.
VADIC: vincristine, 1.5 mg/m^2 day 1; doxorubicin, 30 mg/m^2 day 1 and 2; DTIC, 150 mg/m^2 day 1–5.
CAdO: cyclophosphamide, 300 mg/m^2 day 1–5; doxorubicin, 60 mg/m^2 day 5; vincristine, 1.5 mg/m^2 day 1 and 5.
VP Carbo: VP16, 100 mg/m^2 day 1–5; carboplatin, 160 mg/m^2 day 1–5.
Vd I Cisplat: vindesin, 4 mg/m^2 at day; ifosfamide, 3 g/m^2 at day 1 and 2; cisplatin, 100 mg/m^2 at day 1.
8 in 1: HO, vincristine, 1.5 mg/m^2; BCNU, 100 mg/m^2; methylprednisolone, 100 mg/m^2; H1: procarbazine, 75 mg/m^2; H2: hydroxyurea, 1500 mg/m^2; H3: cisplatin, 60 mg/m^2; H6: methylprednisolone, 100 mg/m^2; H9: aracytine, 300 mg/m^2; H12: cyclophosphamide, 300 mg/m^2; methylprednisolone, 100 mg/m^2.
VCR, vincristine; HDCT, high dose chemotherapy; RT, radiotherapy; Gy, gray; ND, not done; CR, complete response; PR, partial response; NE, not evaluable; PD, progressive disease.

3.2. Relapse

Among the 16 patients in complete or partial remissions, relapses occurred in 11 patients. Ten of these 11 patients were in complete remission and one in partial remission after the initial treatment. Only one of these 11 relapsed patients is still alive, with a follow-up period of 19 years after the diagnosis of the second malignancy. This patient is currently being treated for a new recurrence. Two patients, now deceased, developed successively several tumours of different histological types.

3.3. Overall survival and disease-free interval

Nineteen patients died, one from toxicity, 18 from their second malignancies. The median survival time from diagnosis of the second malignancy was 2 years (range 5 days to 19 years) (Fig. 2).

Only six patients are still alive. Four are in first complete remission with a median follow-up of 8.8 years after the diagnosis of their second malignancy (range 5.8–13.9 years) (Fig. 3). Histological diagnoses include 2 osteosarcomas, one in the radiation field and one out-

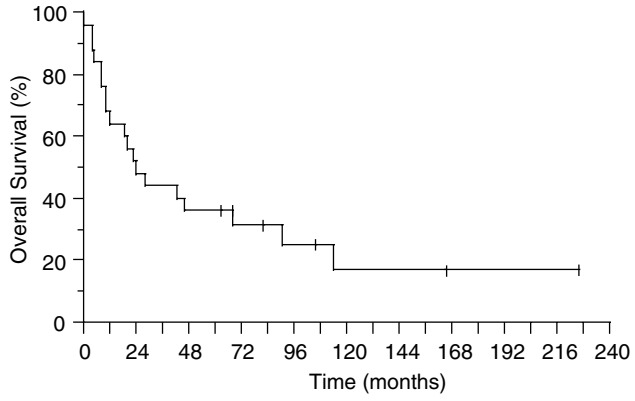

Fig. 2. Overall survival of the 25 patients treated for second malignant neoplasm after hereditary retinoblastoma.

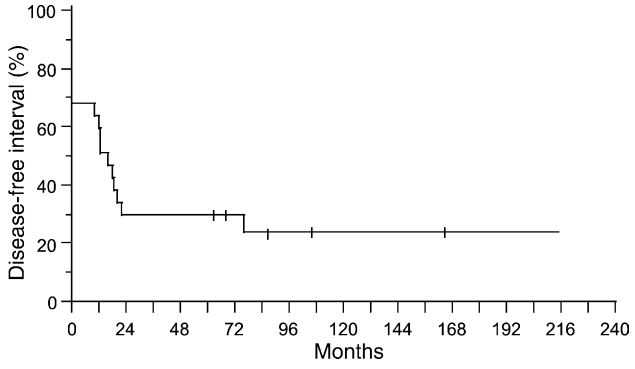

Fig. 3. Disease-free interval of the 25 patients treated for second malignant neoplasm after hereditary retinoblastoma.

side with a good response to pre-operative treatment, and 2 malignant mesenchymatous tumours. High-dose chemotherapy was administered to one of these patients, treated for a rhabdomyosarcoma of the left orbit with nodal metastases. Among the four metastatic patients at diagnosis of their second cancer, this patient is the only one who is alive in complete remission 13.9 years after treatment of their second tumour. One of the six patients is in partial remission 63 months after diagnosis of their second tumour and 56 months after the end of treatment (osteosarcoma). Palliative radiotherapy is currently being given to one patient because of a recurrence.

4. Discussion

In industrialised countries, second malignant neoplasm is the primary cause of death in patients with hereditary retinoblastoma. Despite recognition that the occurrence of second neoplasms is an important problem, there are very few studies addressing the outcome [2,3,7,13] and therapeutic management [4,13] of these patients following their diagnosis with a second malignancy. The few published studies have reported a very poor patient prognosis. Our study of 25 patients treated for second malignant neoplasms occurring after hereditary retinoblastoma represents, to our knowledge, one of the largest with regard to the management and outcome.

Numerous articles [3–9] have been published regarding the occurrence of second malignant neoplasms in retinoblastoma patients, with a considerable variety in the reported cumulative incidence.

Multiple factors can explain this variability: the population size; selection bias; the proportion of patients with hereditary and non-hereditary retinoblastoma; the number of patients treated with prior radiotherapy and the time period covered by the study; the definition of the radiation field and the radiotherapy techniques used; the use of chemotherapeutic agents (chemotherapy indications also varied over time); the definition of the second malignant neoplasms (some authors consider that pinealoblastomas are second tumours); the follow-up; the statistical methods used. In our population, no incidence data can be obtained because of the number of patients lost to follow-up.

In agreement with others, the histological types reported in our study were mainly osteogenic sarcomas [3,5–7,9,12,13] and malignant mesenchymatous tumours [3–6,9,13,18]. Additionally, we detected a CNS tumour as reported in [9]. Malignant melanomas have also been reported in the literature [3,5,19] but we did not find this tumour in our population, probably because malignant melanomas appear after a longer latency period [3].

We also did not report any case of pPNET (Ewing's sarcomas) [3,5,7], but it is possible that some cases were not recognised and were identified as late retinoblastoma recurrences [28]. In the future, immunohistochemical and molecular studies may be helpful in distinguishing recurrences from second tumours [18].

Finally, we have not considered trilateral retinoblastomas as second tumours, because some are trilateral at diagnosis. Nevertheless, this cannot totally exclude the secondary nature of these tumours especially because the radiation dose at the pineal level is not negligible after external beam radiotherapy for retinoblastoma [20]. In our institution, we have very few patients treated for a trilateral retinoblastoma which may be due to the use of external beam radiotherapy which delivers very low intracranial radiation doses.

In our population, mortality was quite high. Among 25 patients, only 6 are still alive with a median follow-up of 8.8 years after diagnosis of their second malignancy. Four are in complete remission. One is in partial remission 63 months after diagnosis, which is longer than the median interval to death from diagnosis of the second neoplasm (2 years). The other patient has relapsed. In view of data reported in the literature, these poor results are most likely due to two main factors: a high

percentage of tumours were not curable due to local non-resectability and the biology of many of these lesions is more aggressive than in similar tumours arising "de novo". The more aggressive nature of these neoplasms may be due, in part, to genetic mutations present at the time of the initial diagnosis and/or due to DNA damage resulting from irradiation or the administration of alkylating agents [10]. As few reports have studied the outcome of patients who developed second malignancies after treatment for retinoblastoma, it is difficult to evaluate the survival of patients with second cancers after retinoblastoma [2,3,7,13]. However, when patients get older and death due to second malignancies occurs, the difference in the survival curves between hereditary and non-hereditary retinoblastoma becomes statistically significant with a much high number of hereditary retinoblastoma patients being affected [5]. Moll et al. evaluated the cumulative survival of these patients to be 22% 15 years after diagnosis of the second cancer.

Some studies report details about the therapeutic management of these second tumours [4,7,13]. All strongly recommend an aggressive therapeutic approach, particularly in patients at high risk of uncontrolled local disease. In one of these studies [4], an aggressive approach with combined modality therapy including radical resection, re-irradiation and/or chemotherapy was used to treat second malignant neoplasms in five of eight patients. In four of the five patients, there was no evidence of disease at 22–72 months following treatment. In the three patients who did not receive aggressive combined treatment, there were no survivors. Nevertheless, the use of external beam radiation for the treatment of partially radiation-induced tumour is debatable. Radical resection remains the primary therapeutic modality for optimal tumour control and cure. However, it is often difficult to achieve clear surgical margins in this region because of the proximity of the tumour to critical structures. In our population, five of the six survivors received pre-operative chemotherapy. Among the nine patients who did not receive surgery, only one is still alive in complete remission. It seems that pre-operative chemotherapy combined with radical resection may increase the survival rate of patients treated for second malignancies occurring after hereditary retinoblastoma.

Despite aggressive therapeutic modalities, mortality in our population remained very high. For this reason, we try to limit the indication of external beam radiotherapy, even though radiation therapy is not the only factor involved in the occurrence of second malignant neoplasms [29].

5. Conclusion

In conclusion this risk of developing a second malignancy after treatment for hereditary retinoblastoma suggests that the current therapeutic strategy in retinoblastoma should consist of limiting the indications for external beam radiotherapy. For these reasons, conservative ophthalmological treatments, brachytherapy and limited adjuvant chemotherapy after enucleation have been developed. However, the long-term cumulative incidence of second tumours after hereditary retinoblastoma will never be zero because of the genetic predisposition of these patients to develop second cancers. By decreasing the use of external beam radiotherapy, the proportion of tumours inside the radiation field will certainly decrease [30].

The prognosis of patients with second malignancies occurring after hereditary retinoblastoma could be improved by aggressive therapeutic management, but currently still remains very poor. In order to increase the survival rate of these patients, it appears to be important to diagnose the second tumour early. Therefore, it is important to inform parents and children that they must rapidly seek medical advice if bony pain or bone surface abnormalities develop. Physicians have to ensure that a careful and long-term follow-up of these patients is maintained.

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