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► **To cite this version:**

Laetitia Callec, Audrey Lardy-Cleaud, Lea Guerrini-Rousseau, Claire Alapetite, Laure Vignon, et al.. Relapsing intracranial germ cell tumours warrant retreatment. *European Journal of Cancer*, 2020, 136, pp.186 - 194. 10.1016/j.ejca.2020.06.012 . hal-03492058

HAL Id: hal-03492058

<https://hal.science/hal-03492058>

Submitted on 22 Aug 2022

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Relapsing intracranial germ cell tumours warrant retreatment

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Running title: Treatment of relapsing IGCT

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: None

ABSTRACT

Background: The optimal therapeutic strategy for relapsing intracranial malignant germ cell tumours (IGCT) has not been clearly established.

Methods: Relapses of IGCT, occurring from 01/01/1990 to 31/12/2014, were retrieved from the SFOP-TGM 90, 92, and GCT 96 protocols, and from the National Childhood Solid Tumour Registry. Refractory IGCT were excluded.

Results: Forty-four relapsing IGCT were identified: 14 were initially treated for histologically proven germinomas (germinoma group), 5 for non-histologically proven germinomas (putative germinoma group), and 25 for non-germinomatous germ cell tumours (NGGCT group).

In the germinoma group, the 5-year EFS and OS were 79% (95% CI: 47-93) and 86% (95% CI: 54-96), respectively. Only one of the 11 patients treated with reirradiation experienced a further relapse. A trend of better EFS was observed for relapses at sites that were not initially involved: 5-year EFS of 100% versus 67% (95% CI: 28-88), $p = 0.09$. In the putative germinoma group, 4/5 patients experienced a further event, leading to 2 deaths. In the NGGCT group, the 5-year EFS and OS were 56% (95% CI: 35-73) and 60% (95% CI: 38-76), respectively. A significant improvement in outcomes following high-dose chemotherapy was observed: 5-year OS of 72% (95% CI: 46-87) versus 29% (95% CI: 4-61), $p = 0.006$.

Conclusion: Relapsing germinomas are highly curable, reirradiation appears to play a key role. Histological proof at initial diagnosis if markers are negative is crucial. Despite inferior outcomes relapsing NGGCT can be cured in a significant proportion of cases provided intensive treatment including HDC is applied.

Keywords: Germinoma, Non-Germinoma Germ Cell Tumours, relapse, high-dose

chemotherapy, radiotherapy, outcome

INTRODUCTION

Malignant intracranial germ cell tumours (IGCT) are rare tumours, that segregate into germinomas and non-germinomatous germ cell tumours (NGGCT). Germinomas are extremely sensitive to chemotherapy and radiotherapy[1,2]. NGGCT are less chemo- and radiosensitive, although multimodal treatment has improved their prognosis [3–7]. Optimal salvage treatment remains a matter of debate due to the paucity of such events. Therapeutic options include surgery, standard-dose chemotherapy (SDC), high-dose chemotherapy (HDC), and radiotherapy [8–11]. The challenge lies with segregating good prognosis relapses that may not require the entire treatment armamentarium, from poor prognosis relapses that require treatment optimization. The aim of this study was hence to describe the outcomes of patients with relapsing IGCT.

MATERIAL AND METHODS

A retrospective, multicentre, French study was performed, collecting all cases of patients experiencing a relapse from IGCT before 31/12/2014. Patients of any age were retrieved either from the national SFOP (Societe Française d’Oncologie Pediatrique) TGM 90 and TGM 92 protocols (from 01/01/1990 through 31/12/1996), or from the European SIOP (Société Internationale d’Oncologie Pediatrique) GCT 96 protocols (from 01/01/1998 through 31/12/2005), or from the National Childhood Solid Tumour Registry (RNTSE; launched on 01/01/2000). Patients with refractory IGCT (i.e., progressing during first-line treatment) or not treated with curative intent were excluded.

The therapeutic strategy for localized germinoma and NGGCT has been reported elsewhere [1,3,6]. Briefly, tumour classification was based on the levels of tumour markers and/or histopathology. Tumours were classified as NGGCT when they were either documented by histology and/or if the serum and/or CSF levels were above 25 ng/ml for AFP and/or above 50 IU/L for HCG. The strategy for localized germinomas was similar across the three protocols. Frontline chemotherapy consisted of 2 cycles of CarboPEI (carboplatin 600 mg/m² on day 1, etoposide 100 mg/m² on day 1-3, ifosfamide 1.8 g/m² on day 22-26, etoposide 100 mg/m² on day 22-24), followed by focal 40 Gy irradiation. After January 2002, a 24 Gy whole ventricular irradiation (WVI) was implemented, because ventricular relapses were observed [12]. The strategy for NGGCT has evolved over time: in the SFOP TGM 90 protocol, patients received CarboPEI until tumour marker normalization plus two additional courses. Patients in complete remission did not receive radiotherapy. Due to the high relapse rate, systematic 54 Gy focal radiotherapy was added to the SFOP TGM 92 protocol. Patients treated in the SIOP GCT 96 protocol received four courses of PEI (cisplatin 20 mg/m² on day 1-5, etoposide 100 mg/m² on day 1-3, ifosfamide 1.5 g/m² on day 1-5). Surgery was recommended for post-chemotherapy residual masses. Systematic 54 Gy focal radiotherapy was then applied. No recommendations regarding salvage treatments were available during the study period. When applied, the HDC regimen consisted of thiotepa (300 mg/m² day 1-3) and etoposide (500 mg/m² day 1-3) followed by autologous stem cell transplant, as published elsewhere [13].

Survival curves for overall survival (OS, time from first relapse to death from any cause or censored to date of the most recent follow-up) and Event-free survival (EFS, time from the first to the second relapse or death from any cause or censored to date of the most recent follow-up) were generated using the Kaplan-Meier method. SAS version 9.4 software was used for all of the

statistical analyses (SAS Institute Inc., Cary, NC, USA). Outcome differences were assessed using the log-rank test. P-values less than 0.05 were considered significant.

This study was approved by the CCTIRS (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé) and CNIL (Commission Nationale de l'Information et des Libertés).

RESULTS

Fifty-eight patients received a second-line treatment with curative intent for IGCT. Fourteen were excluded as shown in Figure 1. Forty-four patients were hence retained: 14 patients with histologically proven germinomas (germinoma group), 5 patients treated as germinoma but without histological proof (putative germinoma group), and 25 patients with NGGCT. Among them 8 patients with proven or putative germinoma have been previously published [12].

The germinoma group

The main patient characteristics are presented in Table 1. None was metastatic at diagnosis. Of note, two patients had HCG levels above 50 IU/L (62 and 140 IU/L, respectively), but front-line complete removal of the tumour confirmed a pure germinoma histology. All but one achieved complete remission at the end of first treatment. The first relapse occurred with a median delay of 33 months (range: 9 to 69 months) from the initial diagnosis. Two relapses were focal, five were distant (one intracranial, four spinal) and seven were combined. All patients received a salvage platinum-based SDC. One had a surgery. Eleven patients were treated with reirradiation (of whom 8 received preirradiation HDC) and only 1 had a further event. Three received no reirradiation and 2 had a further event. After a median follow up of 152 months (95% CI:84-216),

the 5-year EFS and OS were 79% (95% CI:47-93) and 86% (95% CI:54-96), respectively (Figure 2). The 5-year EFS was better for distant as compared to combined or local relapses: 100% versus 67% (95% CI: 28-88); $p = 0.09$.

Putative germinoma group

All patients were males; four were included in the TGM 90, and one in the GCT96 protocol. None was metastatic. Two had a weak secretion of HCG. The primary site was pineal ($n = 3$), suprasellar ($n = 1$), and bifocal ($n = 1$). All five received two cycles of CarboPEI and focal or bifocal irradiation. All achieved complete remission after first treatment. Relapse occurred with a median delay of 30 months (range: 10 to 56 months) from initial diagnosis. One relapse was focal, one was distant (intracranial) and three were combined. All patients received SDC and HDC at relapse. None of them had reirradiation or surgery. After a median follow-up of 245 months (95% CI:203-263); one patient was alive with no evidence of tumour (NED); four experienced a further relapse: two died of the disease, and two were salvaged by reirradiation.

The NGGCT group

The main patient characteristics are presented in Table 2. The markers were positive in the CSF and/or serum for all patients except one, who had histopathological confirmation. None was metastatic. Fifteen were treated with carboplatin-based chemotherapy and 10 with cisplatin-based chemotherapy. Four patients did not receive radiotherapy. All but 2 achieved complete remission after first treatment. The first relapses occurred with a median delay of 18 months from initial diagnosis (range: 7 to 96 months). Nine out of the 16 patients experiencing a relapse within 2 years after initial diagnosis (early relapse) died of disease as compared to only 2 out of 9 patients who had a relapse later. Five relapses were focal, 8 were distant (6 spinal and 2 intracranial) and

12 were combined. Of note, 5 patients had no tumour marker elevation at relapse. All 25 patients received a platinum-based SDC. Six had a surgery. Ten received HDC followed by irradiation and 8/10 survived; 8 received HDC without irradiation and 5/8 survived; 4 received irradiation without HDC and 1/4 survived and 3 received neither HDC nor irradiation and none survived. Among the four patients who were not irradiated in first-line treatment, one died of disease. After a median follow up of 170 months (95% CI: 77-224), the 5-year EFS and OS were 56% (95% CI: 35-73) and 60% (95% CI: 38-76), respectively, in the entire cohort (Figure 2). When only the 10 patients relapsing after GCT 96 protocol were considered, the 5-year EFS and OS in this subgroup were 50% (95% CI: 18-75) and 58% (95% CI: 23-82), respectively. Seven out of 8 patients with “HCG only” secreting NGGCT (defined as HCG>50 UI/L at initial diagnostic) survived as compared to 8/17 with AFP secreting NGGCT. HDC had a significant beneficial effect on the outcomes (Figure 3): the five-year OS was 72% (95% CI: 46-87) for the patients who were treated with HDC versus 29% (95% CI: 4-61) for those who did not receive HDC, $p = 0.006$. Similarly, the 5-year EFS was 72% (95% CI: 46-87) versus 14% (95% CI: 1-46), respectively; $p = 0.006$. There was no significant difference in the outcomes whether or not the patients received irradiation at relapse: 5-year EFS 64% (95% CI: 34-83) versus 45% (95% CI: 17-71); $p = 0.36$, and 5-year OS 64% (95% CI: 34-83) versus 55% (95% CI: 23-78); $p = 0.029$. There was no significant influence of the type of relapse on outcome: the 5-year EFS was 59% (95% CI: 33-78) for focal or combined relapse versus 50% for distant relapse (95% CI: 15-77); $p = 0.52$, the 5 year OS was 64% (95% CI: 37-82) versus 50% (95% CI: 15-77), respectively; $p = 0.55$.

DISCUSSION

In the current series of 44 patients with relapsing IGCT, the outcomes were excellent in the germinoma group and particularly in the subgroup of patients with distant relapse. The outcomes in the NGGCT group, albeit less favourable were higher than expected and were improved by HDC.

Salvage treatments for IGCT are not consensual, as only a limited number of small and heterogenous series have been published to date. Key conclusions from those series are presented in Table 3. Platinum based chemotherapy is often reused with the potential risk of acquired resistance [14] and of cumulating toxicities [15]. The use of HDC is thus meant to increase the dose-effect while avoiding platinum derivatives [10,16]. Reirradiation is also a matter of concern [17]. Indeed, for patients relapsing in the previously irradiated volume, there is little scope for reirradiation, especially in the suprasellar region, due to dose constraints for the optic chiasm and the brainstem [2].

Relapsing germinomas are highly curable, with 5-year OS ranging from 55% to 88.9%. Murray et al. published a cohort of 11 relapsing germinomas after the SIOP CNS GCT96 protocol [8]. After platinum-based SDC, patients received additional salvage treatments with HDC or reirradiation. The 5-year EFS and OS were 45% and 55% respectively. Of note, the survival rate was lower in the subgroup of patients treated with first-line CSI, possibly explaining why our results compare favorably with theirs. Beak et al., evaluated the feasibility of tandem HDC in 9 relapsing germinomas. Four patients experienced a post-HDC relapse but survived after subsequent whole brain or craniospinal irradiation [11], emphasizing the key place of radiotherapy. This differs from a recent publication from Kubota and al. suggesting that reirradiation might be skipped and replaced by HDC [9]. Therefore, it remains difficult to define the respective roles of HDC and reirradiation. Treatment-related deaths have been reported [8,10]. HDC plus reirradiation could

hence constitute overtreatment. The data from the current series, where patients did not receive CSI in first-line, slightly favours the use of radiation over HDC whenever possible.

The outcomes for patients with putative germinomas were dismal. At diagnosis, 1 tumour had a low level of HCG secretion compatible with the diagnosis of germinoma but a high level (94 IU/L) of secretion at relapse, possibly indicative of an underlying choriocarcinoma. This calls for histological documentation of tumours in the setting of unclear tumour marker secretion to define adequate therapeutic strategies. Moreover, in this group for which none of the patients received irradiation at relapse, 4/5 patients experienced a subsequent event, and half of them were ultimately salvaged with radiation, again suggesting a key role for radiotherapy.

Relapsing NGGCT do not share the same good prognosis as germinomas [8,10,18]. In the cohort of 32 patients reported by Murray et al., the 5-year OS was only 9% (95% CI: 2–26). The two patients who survived with NED received both HDC and irradiation [8]. Similarly, in the experience of Modak et al., the 4 year OS was 42% for the NGGCT group and more patients survived when treated with both HDC and reirradiation [10]. International consensus for patients with relapsing NGGCT who are to be treated with curative intent is hence to apply HDC with surgery and additional radiotherapy where feasible [19]. Our cohort is in line with such a strategy and thus supports the HDC, even if the patients receiving HDC have been preselected by their chemo-sensitivity to SDC. Only a randomised control trial could demonstrate the positive impact of HDC on outcomes, but appears unrealistic due to the paucity of IGCT relapses. Patients with HCG only secreting NGGCT (defined as HCG>50 UI/L at initial diagnostic) fared better than patients with AFP secreting NGGCT. This finding was also reported by Murray and al. In this situation where no biopsy was performed and with a somewhat arbitrary cutoff, a germinoma cannot be ruled out explaining the better outcome in this subgroup. The good outcome observed

in the current series could potentially be explained by a less intensive first line treatment (carboplatin-based chemotherapy and absence of irradiation for some patients) that could render the patients more “salvageable”. Indeed the outcomes in the subgroup of patients treated according to SIOP GCT96 (with cisplatinum and systematic irradiation) is inferior to those of the whole cohort, but still superior to the previously reported outcomes. The difference in outcomes observed between the patients treated according to SIOP GCT96 in the present series and the recent publication from Murray et al. is intriguing. It can possibly be explained by a more severe population in the latter series. Indeed, in the group of NGGCT reported by Murray, 6 patients had an initially metastatic disease (implying initial craniospinal irradiation), 1 received high dose chemotherapy as initial treatment and above all, 4 had a progressive disease at the end of initial treatment, while these patients were excluded from the current report. Regarding salvage treatment, a higher proportion of patients received high dose chemotherapy in the current series, as compared to the paper from Murray et al. (18/25 and 16/32 respectively).

The current series carries some limitations. Despite being one of the largest series published to date, the limited sample size of each subgroup precludes a definite conclusive analysis; fields, doses and timing of radiotherapy to be delivered at relapse, deserve better assessment.

CONCLUSION

The outcome of relapsing germinoma is generally favourable and the current series suggests that salvage SDC and reirradiation represent the best option. HDC should probably be indicated only when reirradiation is not possible. The outcomes for patients with relapsing NGGCT albeit less favourable, are still encouraging. Proper identification of these patients at the primary diagnosis and intensive treatment at relapse with both HDC and reirradiation is required for a cure.

Acknowledgements: We wish to thank C. Patte for her contribution to the GCT protocols

design; S. Pall-Kondolf, C. Dufour, E. Sariban, P. Schneider, C. Icher, P. Leblond, J.C. Gentet, A.I. Bertozzi, I. Debroise, D. Bodet, and V. Peciulyte for providing clinical data; and B. Lacour from the French National Registry of Childhood Solid Tumor and Childhood Cancer Observation Platform.

Declarations of interest: none

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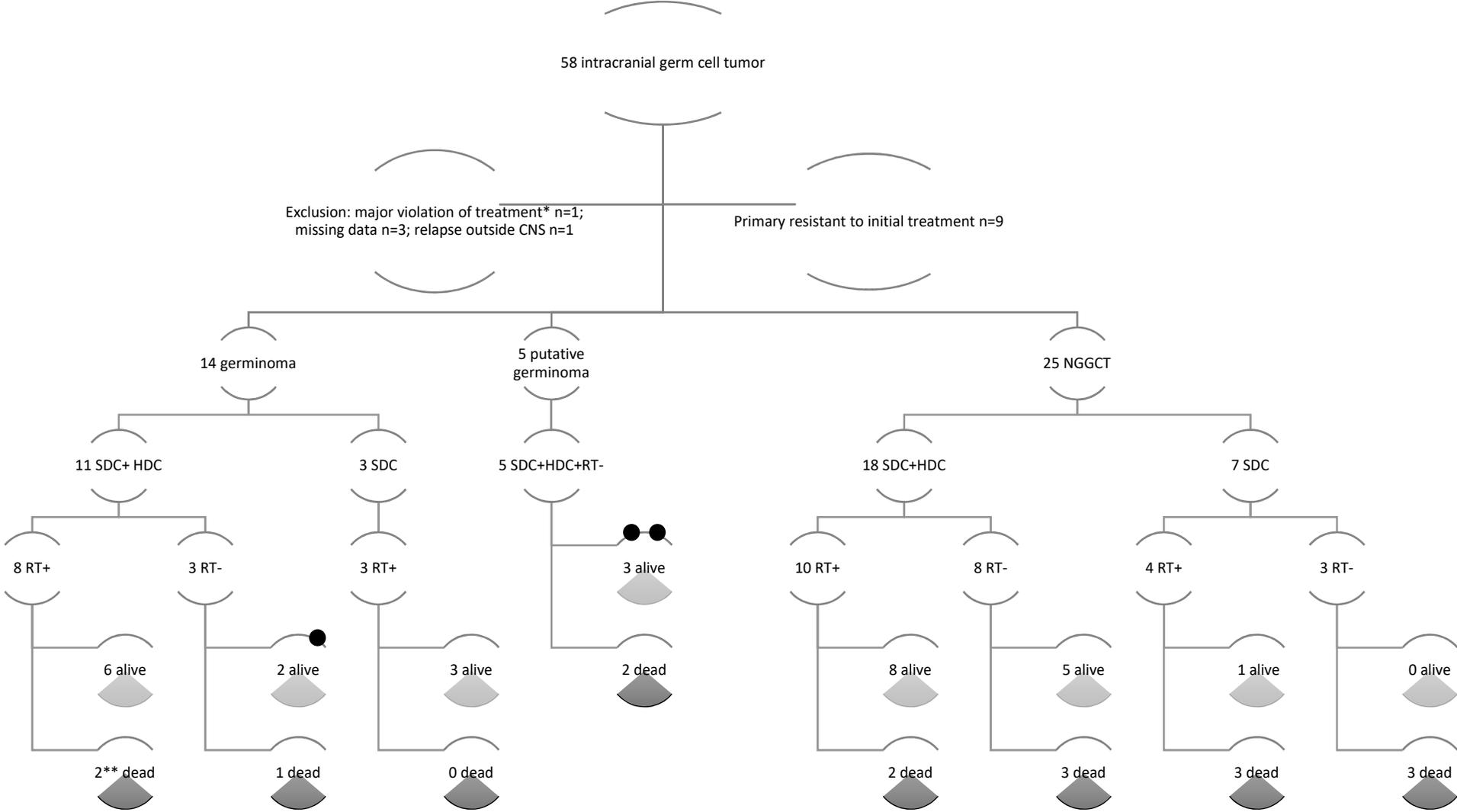
Figure Legends

Figure 1

Figure 2

Figure 3

Figure 1: Consolidated standard of Reporting Trials Diagram



*this patient with non germinomatous germ cell tumor received no chemotherapy as initial treatment

**One patient died of unknown reason while in complete remission

● Further relapse, salvaged with radiotherapy

SDC standard-dose chemotherapy, HDC high-dose chemotherapy, NGGCT non-germinoma germ cell tumor, RT radiotherapy

Figure 2: Post-relapse OS for patients with relapsing IGCT according to the initial group

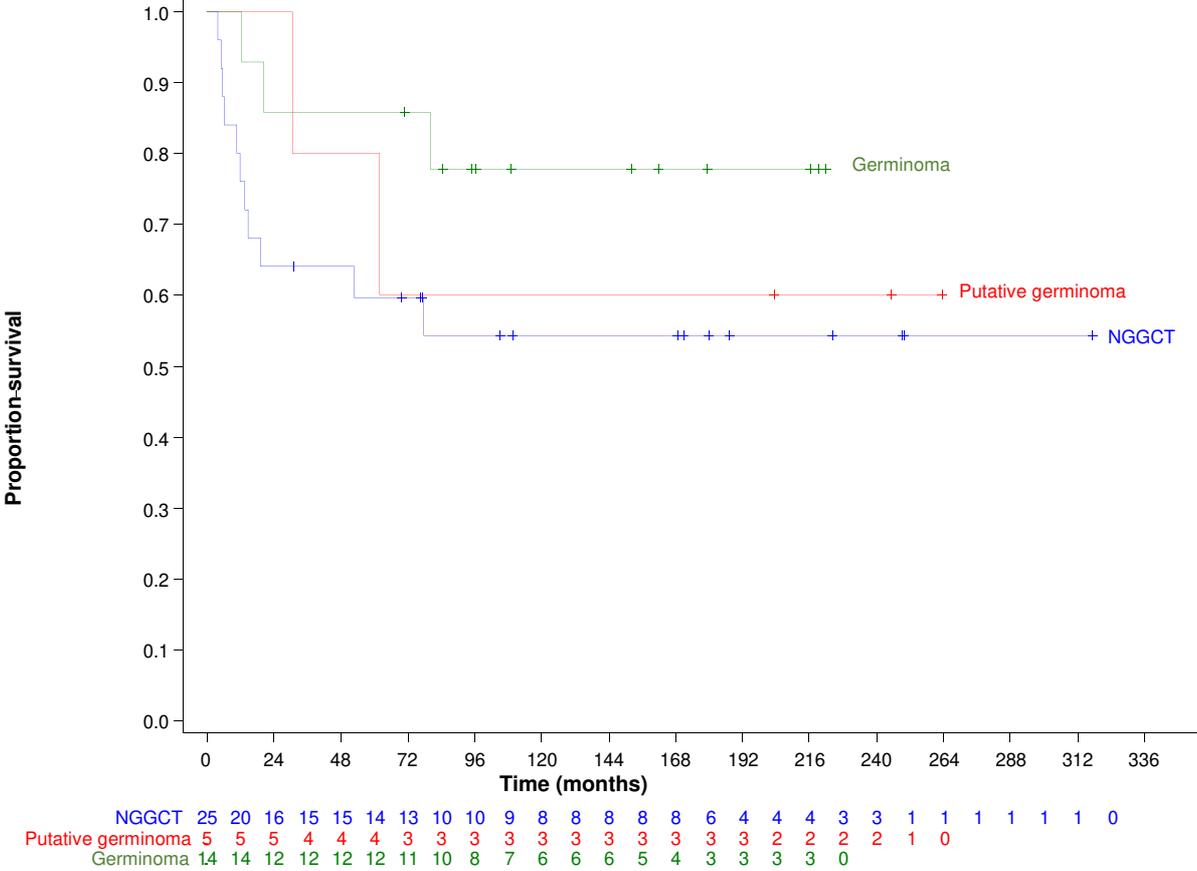


Table I: The main characteristics at diagnosis and at relapse of the patients with a germinoma

Nº	Sex Age (y)	Site of primary tumour	Tumour marker at diagnosis	Initial treatment	Surgery	courses of CT	RT	Time to relapse	Site of relapse	Tumour marker at relapse	CT at relapse	HDC at relapse	Surgery at relapse	RT at relapse Field and dose in Gy	Response and event	RT for further relapse	Outcome Follow-up (m)
G1	M 36	SS	HCG +	GCT 96	partial	2	WVI	5.7 y	distant	HCG +	PEI	yes	No	CSI-24	CR		Alive (109)
G2	M 7	Pineal	HCG ++	TGM 90-92	total	6	focal	0.8 y	combined	HCG +	PEI	yes	No	CSI-? Boost-36	relapse (1 y)		DOD (12)
G3	M 14	Pineal	none	TGM 90-92	partial	4	focal	3.1 y	combined	none	CarboPEI	no	No	CSI-30	CR		Alive (84)
G4	F 15	SS	none	TGM 90-92	total	4	focal	3.3 y	combined	none	PEI	yes	No	no	relapse (3 y)	yes	Alive (216)
G5	M 19	Bifocal	none	TGM 90-92	total	4	focal	2.3 y	focal	HCG +	PEI	yes	No	Focal-40	CR		Alive (152)
G6	M 15	Pineal	none	TGM 90-92	partial	4	focal	3.6 y	distant	HCG +	PEI	yes	No	CSI-45	PR		Alive (223)
G7	M 9	Pineal	HCG +	GCT 96	biopsy	4	focal	0.7 y	distant	none	PEI	yes	No	CSI-23	CR		Alive (162)
G8	M 14	Bifocal	none	TGM 90-92	biopsy	6	focal	4.8 y	distant	none	PEI	yes	No	no	CR		Alive (180)
G9	M 17	Bifocal	HCG ++	TGM 90-92	total	4	focal	1.3 y	combined	none	PEI	yes	No	Focal-40	CR		Alive (219)
G10	F 13	SS	none	GCT 96	biopsy	4	focal	4.7 y	distant	none	PEI	no	Yes	CSI-24 Boost-12	CR		Alive (96)
G11	M 7	Pineal	HCG +	GCT 96	partial	4	focal +WVI	1.3 y	combined	none	PEI	yes	No	CSI-24 Boost-16	CR		Alive (95)
G12	F 12	SS	HCG +	GCT 96	biopsy	4	focal	3.1 y	combined	NA	PEI	no	No	CSI-24 Boost-18	CR		Alive (71)
G13	M 14	SS	none	GCT 96	biopsy	4	focal +WVI	2.2 y	combined	HCG ++	PEI	yes	No	no	relapse (1 y)		DOD (20)
G14	M 7	Bifocal	none	GCT 96	Partial	4	focal	2 y	focal	none	VP16 cisplatin	yes	No	Focal-?	dead UKN		Dead (80)

The HCG level is designated (++) when > 50 IU/L and (+) when positive but < 50 IU/L. NA: not available; CR: complete response; CSI: cerebrospinal irradiation; CT: chemotherapy; Dead UKN: dead of unknown (non-tumoral) cause; DOD: dead of disease; F: female; Gy: Gray; HDC: high-dose chemotherapy; M: male; m: months; PR: partial response; SS: suprasellar; RT: radiotherapy; y = year; WVI: whole ventricular irradiation

Table II: The main characteristics at diagnosis and at relapse of the patients with NGGCT

Nº	Sex Age (y)	Site of primary tumour	Tumour marker at diagnosis	Initial treatment	Surgery	Courses of CT	RT	Time to relapse	Site of relapse	Tumour marker at relapse	CT at relapse	HDC at relapse	RT at relapse Field and dose in Gy	Surgery at relapse	Response and event	RT for further relapse	Outcome Follow-up (m)
NG1	M 16	pineal	AFP and HCG	TGM TC 90-92	second look	6	focal	1 y	distant	AFP	PEI	yes	Focal-50	No	CR		Alive (187)
NG2	M 12	pineal	AFP	TGM TC 90-92	second look	6	focal	1.5 y	combined	AFP	PEI, VBP	yes	no	No	CR		Alive (77)
NG3	F 4	SS	HCG ++	TGM TC 90-92	no	8	focal	1.5 y	distant	AFP and HCG	PEI	yes	Focal-40	No	CR		Alive (250)
NG4	M 10	pineal	AFP	TGM TC 90-92	total	6	focal	0.7 y	distant	none	PEI	no	no	No	PD before HDC		DOD (6)
NG5	M 16	pineal	AFP and HCG	TGM TC 90-92	no	6	focal	1 y	focal	AFP	PEI	no	no	No	PD before HDC		DOD (6)
NG6	M 18	pineal	AFP	TGM TC 90-92	second look	8	focal	1 y	distant	NA	PEI	no	CSI-36	No	PD		DOD (14)
NG7	F 11	bifocal	AFP	TGM TC 90-92	no	7	focal	2.6y	combined	HCG +	PEI	yes	no	Yes	PR		Alive (224)
NG8	F 10	V3	AFP and HCG	TGM TC 90-92	second look	7	focal	1.4 y	focal	HCG ++	PEI	yes	no	No	PD		DOD (12)
NG9	M 20	pineal	AFP and HCG	TGM TC 90-92	no	10	focal	6.1 y	distant	HCG +	PEI	yes	Focal-40	No	CR		Alive (171)
NG10	M 6	pineal	AFP and HCG	TGM TC 90-92	partial	6	none	1 y	distant	HCG +	PEI	no	CSI-? Boost-45	Yes	PD		DOD (4)
NG11	M 12	pineal	HCG ++	TGM TC 90-92	no	12	none	2.1 y	combined	HCG ++	CarboPEI	yes	CSI-37 Boost-57	No	CR		Alive (249)
NG12	M 10	pineal	AFP and HCG	TGM TC 90-92	second look	12	none	2.3 y	combined	AFP	PEI	yes	CSI-35 Boost-55	Yes	CR		Alive (109)
NG13	M 18	pineal	AFP	TGM TC 90-92	second look	12	focal	1.3 y	distant	AFP	PEI	yes	CSI-36	No	relapse (9 m)		DOD (11)
NG14	F 6	SS	AFP and HCG	GCT 96	no	5	focal	1,1 y	focal	HCG +	PEI	yes	no	No	PD		DOD (5)
NG15	F 6	SS	HCG ++	GCT 96	partial	4	focal	1.8 y	combined	none	PEI	yes	no	No	relapse (2 y)		DOD (20)
NG16	M 17	pineal	AFP and HCG	TGM TC 90-92	second look	12	none	1.8 y	combined	none	PEI, VP16-CPM	yes	no	No	mature teratoma (8 y)		Alive (317)
NG17	F 11	SS	HCG ++	GCT 96	no	4	focal	8 y	combined	HCG +	PEI	yes	no	No	CR		Alive (70)
NG18	M 13	bifocal	HCG ++	GCT 96	no	4	bifocal	6.8 y	combined	AFP and HCG	PEI	yes	CSI-24	No	CR		Alive (105)
NG19	F 7	SS	NA	GCT 96	total	4	focal	6 y	combined	NA	PEI	no	no	Yes	relapse (2 y)	yes	DOD (78)
NG20	M 8	pineal	AFP	GCT 96	total	4	focal	1.4 y	Focal	none	PEI, CarboPEI	yes	CSI-18	Yes	relapse (1 y)		DOD (15)
NG21	M 12	V3	AFP	GCT 96	total	4	focal	0,6 y	distant	AFP and HCG	PEI, CarboPEI	no	CSI-? Boost 45	Yes	PR		Alive (168)

NG22	M 5	pineal	AFP and HCG	TGM TC 90-92	partial	6	focal	0.6 y	combine d	AFP	PEI	yes	CSI-36 Boost-?	No	CR	Alive (180)
NG23	M 11	pineal	AFP and HCG	GCT 96	partial	4	focal	4.9 y	combine d	HCG ++	PEI, CarboPEI	no	CSI-?	No	2 relapses	yes DOD (53)
NG24	F 6	SS	HCG ++	GCT 96	no	4	focal	1.1 y	combine d	AFP and HCG	Gemox	yes	CSI-? Boost-?	No	CR	Alive (77)
NG25	F 15	SS	HCG ++	GCT 96	partial	4	focal	3.4 y	focal	none	CarboPEI	yes	no	No	CR	Alive (31)

AFP was defined as elevated when the level was >25 ng/ml; The HCG level was designated (++) when > 50 IU/L and (+) when positive but <50 IU/l.. NA: not available; CPM= cyclophosphamide, CR: complete response; CSI: cerebrospinal irradiation; CT: chemotherapy; DOD: dead of disease; F: female; HDC: high-dose chemotherapy; M: male; m: months; NA: not available; PD: progressive disease; PR: partial response; SS: suprasellar; RT: radiotherapy; y=year; VBP= vinblastine, bleomycin, cisplatinium, V3: third ventricle

Table III: Series reporting relapsing IGCT

Reference	Initial diagnosis	Nb of pt	Treatment at 1 st relapse				Post-relapse outcome	Key message regarding salvage therapy
			HDC+RT (alive)	HDC (alive)	RT (alive)	No HDC no RT (alive)		
Murray [8]	germinoma	11	-	4 (2) -1 toxic death	6 (3) -1 toxic death	1 (1)	5-y OS 55%	RT or HDC are valid options
	NGGCT	32	9 (2)	7(1)	10 (0)	6 (0)	5-y OS 9%	Both HDCand RT are required for cure
Kubota [9]	germinoma	6	2 (2)	4 (3)	-	-	5/6 alive with NED	RT can be omitted if CR can be obtained before HDC
Modak [10]	germinoma	11	5 (4)	6 (5) -1 toxic death	-	-	4-y OS 58%	HDC is effective with or without RT
	NGGCT	10	5 (2)	5(1)	-	-		
Baek [11]	germinoma	9	3 (2)	5 (5) -4 salvaged with further RT	-	1 (0)	3-y OS 88.9%	Post-HDC relapse may be salvaged with RT
	NGGCT	11	5 (4)	3 (1)	2 (0)	1 (0)	3-y OS 36.4%	
Current series	germinoma	14	8 (6)	3 (2)	3 (3)	-	5-y OS 86%	
	NGGCT	25	10 (8)	8 (5)	4 (1)	3 (0)	5-y OS 60%	

HDC+RT: patients received both high-dose chemotherapy and radiotherapy; HDC: patients received high-dose chemotherapy without radiotherapy; RT: patients received radiotherapy but not high-dose chemotherapy; No HDC no RT: patients received neither high-dose chemotherapy nor radiotherapy