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CLINICAL STUDY

Intracranial germ cells tumour: a single institution experience in Argentina

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Abstract

Background Intracranial germ cell tumor (iGCT) represents a rare and heterogeneous group, with variable incidence and diverse treatment strategies. Although multiagent chemotherapy with reduced radiotherapy strategy has been applied by several cooperative groups in North America and Western Europe, there is a paucity of data to understand if this combined regimen is suitable in low-middle income countries (LMIC).

Methods We evaluate the outcome in a cohort of iGCT treated by SIOP-CNS-GCT-96 strategy at hospital J.P Garrahan in Argentina over the last 20 years. Radiation field and dose included focal radiotherapy (FRT) before 2009 or focal radiotherapy plus whole ventricular radiotherapy (WVRT) after 2009 for localized germinoma and FRT or FRT plus WVRT or CSI for non germinomatous germ cell tumors (NGGCT)

Results Sixty iGCT were identified; 39 germinoma and 21 NGGCT. Median follow-up was 6.57 years (range 0.13–20.5). 5-year PFS and OS were 83.5% (95% CI [165.53–223.2]) and 88.7% (95% CI [169.84–223.2]) for the germinoma group, while for the NGGCT group were 75% (95% CI [133.27–219.96]) and 64.2% (95% CI [107.38–201.81]) respectively. The localized germinoma group showed poor results between 2000 and 2009 with 5-year PFS and OS of 69 and 75% respectively, and an excellent outcome between 2010 and 2019 with a 5-years PFS and OS of 92.8 and 100%. A univariable analysis identified this difference in survival as related to the field of radiotherapy, specifically whole ventricular radiotherapy. FRT increased the risk of recurrence in localized germinoma, involving not only ventricular relapses; but spinal cord and disseminated disease as well. There were no relapses of localized NGGCT after FRT and FRT plus WVRT.

Conclusion Herein we demonstrate that intensive chemotherapy followed by FRT plus WVRT for germinoma is a feasible and effective strategy, warranting further study in the developing world.

Keywords Germ-cell tumor · Germinoma · Non germinomatous · Brain tumor · Reduced radiation field

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Introduction

Intracranial germ cell tumor (iGCT) represents a rare and heterogeneous group, with variable incidence and diverse treatment strategies across the continents [1, 2]. Histologically, iGCT are classified into seven types by the 2016 World Health Organization guidelines: germinomas, embryonal carcinomas, yolk sac tumors, choriocarcinomas, teratomas, teratomas with malignant transformation, and mixed germ cell tumors [3]. However, the initial surgical management is based on the levels of specific tumor markers in serum and cerebrospinal fluid concentration (CSF). Historically, alpha-fetoprotein (AFP) and human chorionic gonadotropin-beta (hCGβ) classified iGCT in Europe and the Americas, in two groups: germinoma and non-germinomatous germ-cell

tumours (NGGCT). This classification system reflects the excellent overall survival for the first group, and the inferior survival for the second one. Most recently, concentration of AFP more than 1000 kU/l identified a high risk NGGCT subgroup with a poor outcome that may be benefited from intensification of therapy [4, 5].

Although some international consensus in the management of iGCT has been achieved, several challenges persist [6, 7]. Currently, the role of surgery at diagnosis is limited to surgical intervention for obstructive hydrocephalus or acute visual deterioration and/or biopsy in marker-negative cases. Radiotherapy is almost ubiquitously prescribed across all cases of germinoma and NGGCT in order to achieve satisfactory survival [8]. Despite efforts to substitute radiation with chemotherapy only, the high relapse rates of up to 50% and inferior outcome, suggested this is an unacceptable treatment approach for iGCT [9–11]. Being highly radiation sensitive, all patients with germinomas were historically treated with craniospinal irradiation (CSI) alone, which yielded a cure rate of more than 90% [12]. However, this approach results in severe long-term toxicities, such as neurocognitive impairment and endocrinopathies, which has led to studies on reduced radiotherapy dose and field to minimise the risk of late toxicities while maintaining excellent prognosis [13, 14]. On the other hand, historical series of NGGCT treated by radiotherapy alone reported 20–40% overall survival suggesting that a multimodal approach was required [15]. Chemotherapy has been used for the treatment of both germinoma and NGGCT, helping to reduce radiotherapy fields or doses, or both, during germinoma treatment while improving outcomes substantially for NGGCT.

The strategies employed by the various cooperative groups varied widely. Specifically, the European strategy has compared CSI to a chemotherapy and focal radiation approach in localized germinoma yielding a 5-year progression free survival of 97 and 88% respectively, North America (ACNS 0232/1123) has employed chemotherapy followed by whole ventricular radiotherapy (WVRT) and focal boost and the Japanese group a chemotherapy strategy consisting of carboplatin and etoposide followed by ventricular radiation; both strategies yielding a comparable survival. When analysing our cohort we found that previous to 2009, our treatment strategy was similar to European approach and after 2009 treatment was based on North American approach. On the other hand, the European strategy for NGGCT consists of a cisplatin-based chemotherapy, followed by surgical resection if residual disease is present and then focal radiotherapy, while North America (ACNS0122) has employed a carboplatin-based chemotherapy followed by craniospinal radiotherapy and focal boost, and the Japanese group employs concomitant chemoradiotherapy with ICE (Ifosfamide-Carboplatin-Etoposide) and radiotherapy to the tumour bed followed by CSI and ICE chemotherapy [8, 16, 17].

The European Société Internationale d'Oncologie Pédiatrique (SIOP) showed that chemotherapy followed by local field radiotherapy presented a good initial response in germinoma tumours, but this treatment was insufficient to control subependymal growth in the ventricular area suggesting the need to enlarge the radiation field to include the ventricles. Moreover, they did not identify the presence of residual lesions at the end of treatment as an adverse prognostic factor in germinoma showing an excellent survival for the total cohort [18]. On the other hand, SIOP-CNS-GCT-96 strategy showed that combination chemotherapy and radiotherapy for all intracranial NGGCT patients, with risk-adapted radiotherapy tailored according to initial dissemination (focal for those with localized disease and craniospinal plus focal boost for metastatic cases), is effective in producing long term durable treatment responses with a 5-year progression free survival of 72 and 68% for localized and metastatic disease, respectively. In contrast to the germinoma experience, they identified that survival for patients with intracranial malignant NGGCTs who had end-of-treatment residual disease (including after second-look surgery) was significantly worse [19].

Most reports on pediatric central nervous system tumors from LMIC describe the epidemiology of these tumors and rarely describe in detail treatment modalities and outcomes. Due to the limitation of health care resources, protocols in LMIC should not only consider survival, but also feasibility. The treatment of malignant childhood brain tumours remains a challenge in LMIC as it requires a multidisciplinary team that may not available worldwide, such as access to chemotherapy, surgical expertise, supportive care and radiation facilities. Although the SIOP-CNS-GCT-96 strategy is followed by many countries across the world, the viability and survival outcome in the LMIC setting is not well described. Despite small series [20–22], there is a paucity of data to understand if this combined regimen would be considered a possible and practicable strategy outside the developed world. Here, we evaluate the outcome of a cohort of iGCT treated using the SIOP-CNS-GCT-96 approach prior to 2009 followed by the adoption of the North American approach of whole ventricular radiotherapy after 2009 at hospital JP Garrahan in Buenos Aires.

Methods

Patients and treatment

This retrospective study was performed in accordance with the approval of the hospital JP Garrahan Research Ethics Board. The treatment strategy was used as a standard of care from 2000 to 2020 in hospital JP Garrahan. All patients had AFP and hCGβ level in serum and/or CSF as initial

management. ¨Secreting¨ or malignant NGGCT was defined as per SIOP regimen with serum or CSF elevation of AFP more than 25 ng/mL and/or serum CSF elevation of hCGβ more than 50UI/ml and /or biopsy demonstrating nongerminomatous elements (yolk sac tumor, embryonal carcinoma, choriocarcinoma, teratoma with malignant transformation, and mixed malignant germ cell tumour). All germinoma were diagnosed based on biopsy performed in the context of levels of the tumour markers AFP and hCGβ within the defined limits stated above. Patients were staged with craniospinal imaging and lumbar CSF cytology at baseline unless clinically contra-indicated. Positive CSF-cytology and/or positive imaging was defined as metastatic disease. Synchronous bifocal intracranial tumors (defined as masses in the pineal and suprasellar region only by magnetic resonance imaging) were considered non-metastatic disease and were treated in the same way as unifocal tumours. Although a European consensus has been reached that a biopsy is not mandatory in bifocal tumours with typical appearance, all of them had histological verification in our cohort. Except for 1 localized germinoma who received CSI alone, all patients received chemotherapy followed by radiotherapy. Neoadjuvant chemotherapy was based on SIOP-CNS-GCT 96 (2 courses of carboplatin/etoposide alternating with Ifosfamide/Etoposide for germinoma and 4 courses of Cisplatin/Etoposide/Ifosfamide for NGGCT) in 55 patients while 4 patients received 4 courses of Carboplatin/Etoposide (avoiding Ifosfamide) for better diabetes insipidus management. Radiation field and dose changed over the years and as per radiotherapist consideration, FRT was defined as radiation delivered to the tumor bed at the time of diagnosis, including any residual tumor present at the time of treatment planning. The WVRT encompassed the lateral, third, and fourth ventricles, including the suprasellar and pineal cisterns. In reporting radiotherapy fractionations, equivalent dose in 1.8-Gy (LQ model) was used with an alpha/beta ratio of 10 [23, 24]. Radiation fields and median radiotherapy doses are shown in supplementary Table 1.

Tumor markers were performed before each cycle of chemotherapy, after radiation therapy and every 4 months after treatment. Neuroimaging was performed after two initial cycles and after finishing chemotherapy, 4–6 weeks after the end of radiotherapy, every 4–6 months for 3 years and yearly after that.

Statistical analysis

Descriptive statistics were used to report baseline patient, tumor and treatment characteristics. Progression free survival (PFS) was defined as the time between diagnosis and either relapse or last follow up contact for patients who did not experience a recurrence. Overall survival (OS) was defined as the time between diagnosis and death from any cause or last follow up contact for patients who were alive. PFS and OS were calculated using the Kaplan–Meier method and reported at 5 years. Survival curves were compared using the log-rank test. All statistical analyses were performed in graph pad prism 8. For the analysis, FRT and FRT plus WVRT were considered reduced-volume radiotherapy.

Results

Demographics of the entire cohort

Sixty consecutive patients with iGCT at our institution were treated between September 2000 and October 2019 (28 between 2000 and 2009; 32 between 2010 and 2019). Median time of follow-up was 6.57 years (range 0.13–20.5). Demographic and disease characteristics of the entire cohort (39 germinomas and 21 NGGCT) are summarized in Table 1. Initial surgery was conducted in 49 patients, 39 were biopsies (32 = endoscopic, 3 = Stereotactic, open surgery = 4), 8 partial resections and 2 gross total resections. No patient died due to surgical complications and the median time between diagnosis and the first course of chemotherapy was 49 days (range 9–79). Residual tumor was described in 19 patients after completing chemotherapy (germinoma = 7; NGGCT = 12) and 9 after radiotherapy (germinoma = 3; NGGCT = 6); two of them had a second look surgery as part of the treatment strategy (germinoma = 1, NGGCT = 1).

Germinoma and NGGCT specific outcome

Five-year PFS and OS for the total cohort were 80% (95% CI [164.52–213.44]) and 80.5% (95% CI [158.43–207.78]) respectively. 5-year PFS and OS were 83.5% (95% CI [165.53–223.2]) and 88.7% (95% CI [169.84–223.2]) for the germinoma group (Fig. 1a), being 78% (95% CI [155.18–207]) and 88% (95% CI [156.18–210.03]) for the localized subgroup (excluding the only patient who received CSI without chemotherapy) (Fig. 1c) and 100% for the metastatic subgroup. Localized germinoma group showed poor results between 2000 and 2009 but excellent outcome between 2010 and 2019, having a 5-year PFS of 69% in the first cohort and 92.8% in the second cohort (Fig. 1d; p = 0.17 h 3.3 95% CI [0.6786–13.59]) and a 5-year OS of 75% in the first cohort and 100% in the second cohort (Fig. 1e; p = 0.10 h 4.7 95% CI [0.734–31.06]). 5-year PFS for localized germinoma who received FRT was 63% while for the subgroup who received FRT plus WVRT was 94% (Fig. 1f; p = 0.07 h 4.8 95% CI [0.96–24.31]).

5-year PFS and OS were 75% (95% CI [133.27–219.96]) and 64.2% (95% CI [107.38–201.81]) NGGCT group, being 61 and 62.8% for the localized NGGCT subgroup and

Table 1 Demographic characteristics of the NGGCT and GCT cohort

	NGGCT n = 21	Germinomas N = 39
Age		
Median (years)	12.1 (IQR 8.78–14.46)	12.1 (IQR 8.92–14.31)
Less than 6 years	3	1
+ 6 years	18	38
Gender		
Female	5	12
Male	16	27
Localization		
Pineal Gland	8	15
Bifocal	1	7
Sellar/Suprasellar region	5	9
Thalamus and Basal Ganglia	2	2
Disseminated	2	5
Spinal Cord	1	0
Intraventricular	1	0
Others	1	1
Metastatic status		
M0	*19*	*34*
M+	*2*	*5*
Cranial (2 or more foci, no bifocal)	2	5
Spinal	0	0
CSF cytometry	0	0
Initial surgery		
Biopsy	7	32
Partial resection	2	6
Complete resection	1	1
Without surgery	11	0
Residual tumor after chemo		
Yes	12	7
No	8	31
N/A	1	1
Residual tumour after radiotherapy		
Yes	6	3
No	11	35
N/A	4	1
Relapse		
	5	7
Pattern of relapse		
Local	3	1
Intracranial metastasis	0	1
Intraventricular	0	2
Isolated spinal cord	0	1
Isolated serum/CSF biomarquers level	2	0
Combination (local and Spinal Cord)	0	2
Biomarquers at relapse		
Serum/CSF AFP	3	1
Serum/CSF BHCG	1	1
Both tumor markers	0	1

NGGCT non germinomatous germ cell tumour, *GCT* germinoma, *CSF* Craniospinal fluid

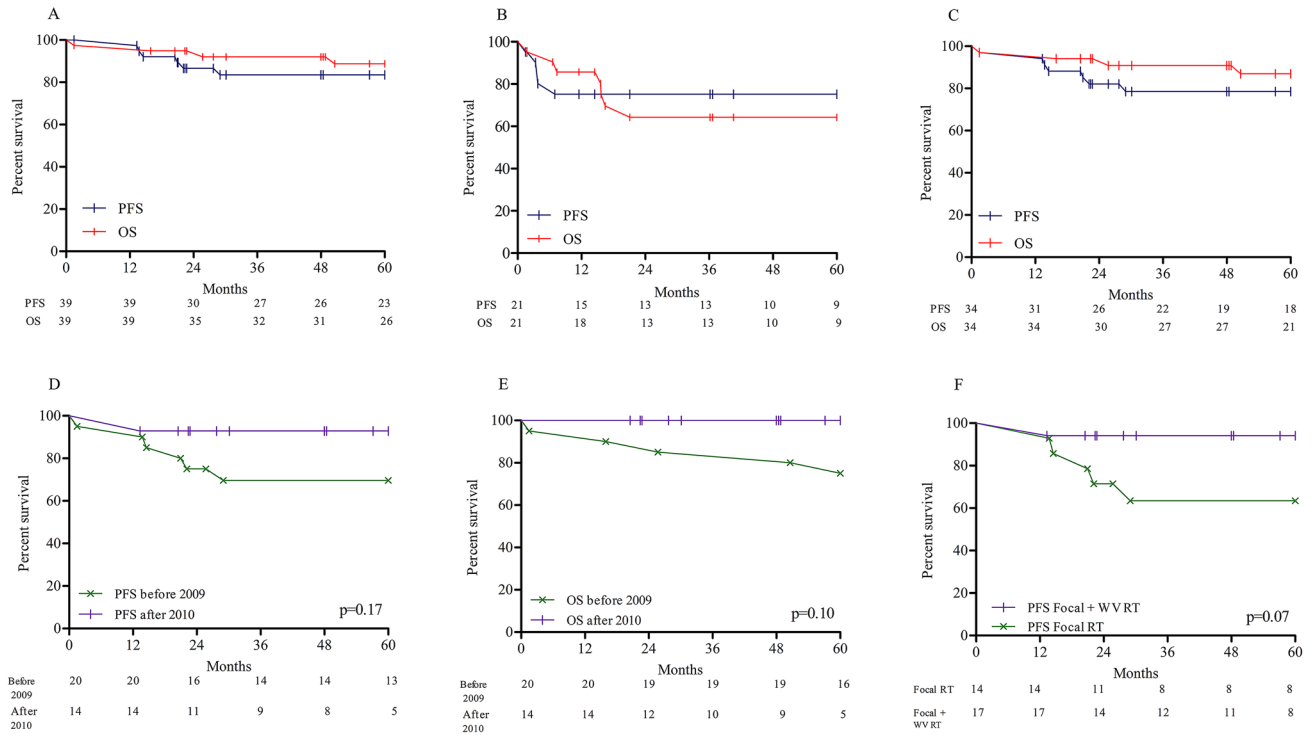

Fig. 1 Outcome of iGCT (germinoma and NGGCT). **a** Kaplan–Meier estimates of PFS and OS for germinoma and **b** NGGCT. **c** Kaplan–Meier estimates of PFS and OS for localized germinoma treated with multiagent chemotherapy followed by reduced-volume radiation field (including FRT and FRT plus WVRT subgroup). **d** Kaplan–Meier estimates of PFS and **e** OS for localized germinoma treated with multiagent chemotherapy followed by reduced-volume radiation field (including FRT and FRT plus WVRT) between 2000–2009 and 2010–2019. **f** Kaplan–Meier estimates of PFS for localized germinoma treated with multiagent chemotherapy followed by FRT and localized germinoma treated with multiagent chemotherapy followed by FRT plus WVRT. P-values are determined using the log-rank method.

100% for the metastatic subgroup. Localized NGGCT group showed similar results between 2000–2009 and 2010–2019, having a 5-year PFS of 60% in the first cohort and 67.5% in the second cohort (p = 0.9 h 1.17 95% CI [0.21–6.54]). There were no relapses of localized NGGCT after reduced-volume radiotherapy treatment (FRT and FRT plus WVRT).

Relapses

Our relapsed germinoma cohort represents a relatively small and heterogeneous group, in terms of type of relapse (marker-negative vs. marker-positive) and relapse treatments delivered (standard dose chemotherapy vs HD-SCR; re-irradiation vs. none). During the first 24 months after diagnosis, 5 patients with localized Germinoma (bifocal = 2, sellar/suprasellar = 2, pineal = 1) experienced relapse at a median time of 20.9 months. Late relapse (by definition at ≥ 2 years after successful treatment) was observed in two localized germinoma (bifocal = 1, sellar/suprasellar = 1) at 108 and 145 months. No biopsy was performed at relapse. Three relapses had high tumor markers levels at recurrence, but none of them at initial diagnosis (Tables 1, 2). While five of the seven relapses had received FRT as initial management, 2 had received FRT plus WVRT. Two patients had isolated intraventricular relapse; both had received FRT upfront. Three patients had spinal lesions at recurrence (isolated = 1, in combination with others supratentorial lesions = 2); all of them had received reduced-volume radiation at diagnosis (FRT = 1, FRT plus WVRT = 2) (Table 2). The majority of relapsed germinomas treated with curative intention received re-induction chemotherapy with a platinum-based (cisplatin–carboplatin) strategy followed by CSI as 1st line salvage therapy (N = 5). One marker positive relapsed germinoma received four cycles of Gemcitabine-Paclitaxel-Oxaliplatin (GEMPOX) followed by high dose chemotherapy and stem cell rescue as a second line salvage treatment with tumor remission for 30 months after second recurrence. Four of the germinoma´s relapse patients died, 3 due to tumor progression and 1 associated with a second tumor (Table 2).

Four patients with localized NGGCT (pineal = 2, thalamus = 1, intraventricular = 1) progressed during multi-agent chemotherapy treatment (SIOP strategy) and 1 (pineal) immediately after end of treatment. No late

Table 2 Patients with Germinoma who relapsed

ID	1	31	38	39	42	45	49
Year of Diagnosis	2016	2008	2005	2001	2002	2002	2000
Age	12.2	10.05	15.5	12.1	14.4	14.5	10.4
Gender	Male	Female	Male	Male	Male	Female	Male
Primary site	Bifocal	Sellar/Suprasellar	Pineal	Bifocal	Sellar/Suprasellar	Bifocal	Sellar/Suprasellar
Pretreatment biopsy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum BHCG (IU/L) at diagnosis	30	37.8	N	N	N	N	N
Serum AFP (ng/ml) at diagnosis	N	3	N	N	N	N	N
CSF BHCG (IU/L) at diagnosis	N	UK	UK	N	11	N	N
CSF AFP (ng/ml) at diagnosis	N	UK	UK	N	N	N	N
CFS Cytology	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Baseline spinal imaging	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Initial Chemo	SIOP	SIOP	SIOP	SIOP	SIOP	SIOP	SIOP
Time (m) from diagnosis to chemotherapy	1.3	0.4	0.4	1	1.4	0.3	1
Initial RT volume	WV + TB	TB	TB	WV + TB	TB	TB	TB
Initial RT dose (Gy)	24/40	45	45	30.6/45	45	41.4	45
Time (m) from diagnosis to RT	5.5	5.5	3.6	4.2	4.6	3.7	4.2
Site of relapse	Sellar/Suprasellar + Spinal Cord	Intraventricular	Intracranial	Spinal Cord	Sellar/Suprasellar	Intraventricular	Intracranial + Spinal cord
Serum BHCG (IU/L) at relapse	537	N	N	N	23	N	589
Serum AFP (ng/ml) at relapse	5	N	N	N	324	N	77
CSF BHCG (IU/L) at relapse	N	N	N	N	N	N	2057
CSF AFP (ng/ml) at relapse	N	N	N	N	N	N	205
Biopsy at relapse	Negative	Negative	Negative	Negative	Negative	Negative	Negative
PFS1(m)	13.3	10.69	22.1	108.7	21	29	13.7
Salvage treatment 1	PEI + CSI 30.6/TB 45	None	ICE + CSI 36	PR + CSI	PEI + CSI 36	PEI + CSI 36	PEI + CSI 36
PFS2(m)	5.5	n/a	n/a	n/a	n/a	15.7	
Salvage treatment 2	GemPox + HDC and ASCT	n/a	n/a	n/a	n/a	Etoposide	
OS (m)	48.8	15.9	186.2	115.6	222.8	51	131.5
Outcome	No evidence of disease	Dead of disease	No evidence of disease	Dead of disease	No evidence of disease	Dead of disease	Dead not tumor related

UK unknown, *N* normal, *TB* tumor bed, *WVRT* whole ventricular irradiation, *CSI* craniospinal irradiation, *m* months, *HDC* high dose chemotherapy, *ASCT* autologous stem cell transplant, *PEI* cisplatin–etoposide–ifosfamide, *GemPox* gemcitabine–paclitaxel–oxaliplatin, *ICE* ifosfamide–carboplatin–etoposide, *Pos* positive, *CS* craniospinal fluid

relapses were observed in this group. Three patients had high risk serum AFP levels (> 1000 ng/ mL) at diagnosis and 1 had evidence of residual disease after chemotherapy. Two patients with NGGCT recurrence received GEMPOX regimen and showed an initial response but a rapid progression after 3–4 cycles. Although different approaches had been used, all NGGCT patients died after relapse showing the poor prognosis of this particular group (Table 3).

Table 3 Patients with NGGCT with progressive disease or relapsed

ID	2	12	23	47	50
Year of Diagnosis	2013	2018	2005	2018	2007
Age	0.8	7.9	11.1	15.4	13.4
Gender	Male	Male	Male	Male	Male
Primary site	Pineal	Thalamus	Intraventricular	Pineal	Pineal
Pretreatment biopsy	Yes	No	Yes	No	Yes
Serum BHCG (IU/L) at diagnosis	N	N	N	5670	108
Serum AFP (ng/ml) at diagnosis	118	11,351	7389	N	3857
CSF BHCG (IU/L) at diagnosis	UK	N	N	UK	53.2
CSF AFP (ng/ml) at diagnosis	UK	4760	274	UK	4906
CSF Cytology	Negative	Negative	Negative	Negative	Negative
Baseline spinal imaging	Negative	Negative	Negative	Negative	Negative
Initial Chemotherapy	SIOP	SIOP	SIOP	SIOP	SIOP
Time (m) from diagnosis to chemotherapy	0.39	0.42	0.98	0.26	0.29
Initial RT volume	None	None	None	None	CSI + TB
Initial RT dose (Gy)	0	0	0	0	30.6/50.4
Time (m) from diagnosis to RT	n/a	n/a	n/a	n/a	3.7
Site of relapse	Pineal	TM	TM	Pineal	Pineal
Serum BHCG (IU/L) at relapse	N	N	N	N	N
Serum AFP (ng/ml) at relapse	28.5	10,574.1	388	N	266
CSF BHCG (IU/L) at relapse	5	1.3	N	5765	N
CSF AFP (ng/ml) at relapse	N	4768.5	N	N	N
PFS1(m)	3.78	1.45	3.78	3.36	6.97
Salvage treatment 1	GemPox	HDC and ASCT	CSI 36 + TB 55.8	TB 54	VP16
PFS2(m)	n/a	n/a	3.75	2.43	n/a
Salvage treatment 2	n/a	n/a	PR	GemPox	n/a
OS (m)	6.58	7.91	15.69	16.45	15.59
Outcome	Dead of disease	Dead of disease	Dead of disease	Dead of disease	Dead of disease

UK unknown, *N* normal, *TB* tumor bed, *CSI* craniospinal irradiation, *m* months, *TM* tumor marker, *HDC* high dose chemotherapy, *ASCT* autologous stem cell transplant, *PEI* cisplatin–etoposide–ifosfamide, *GemPox* gemcitabine–paclitaxel–oxaliplatin, *ICE* ifosfamide–carboplatin–etoposide, *CSF* craniospinal fluid

Causes of death

Two patients (germinoma = 1, NGGCT = 1) died after the first cycle of chemotherapy (carboplatin-Etoposide) due to a systemic infection disease at 1.4 and 1.7 months from diagnosis. One patient with localized NGGCT with panhypopituitarism since diagnosis and poor treatment adherence, died regarding a diabetes insipidus disorder at 21 months without tumor recurrence. Three patients with germinoma (localized = 2, metastatic = 1) developed a second tumor; 1 acute myeloid leukemia M5 and 2 posterior fossa tumors (1 medulloblastoma and 1 malignant tumor no specify). These last two patients received CSI; 1 as part of the metastatic treatment regimen, and 1 as part of the first salvage strategy. No family history of cancer predisposition syndrome was found (Table 4).

Discussion

Herein we report the outcome of localized germinoma and NGGCT treated with multi-agent chemotherapy (carboplatin-based chemotherapy and cisplatin-based chemotherapy respectively), followed by reduced-volume radiation during 20 years in one center in Argentina. In addition, treatment results involving differences in radiation field prior to 2009 and after that date are described. We show that whole ventricular radiotherapy is required to achieve high survival rates in germinoma, and focal radiotherapy alone is insufficient for this group. Our study also confirms the feasibility of treating a subset of NGGCT with craniospinal irradiation sparing protocols in the developing world, suggesting this is as a global option to balance survival with acceptable quality of life.

Table 4 Patients with Germinoma and NGGCT with not disease related death

ID	16	40	49	51	60	28
Year of Diagnosis	2007	2005	2000	2004	2010	2016
Age	16.2	7.07	10.4	12.9	12.5	9.4
Gender	Male	Female	Male	Male	Male	Female
Primary site	Disseminated disease	Suprasellar	Sellar/ Suprasellar	Sellar/ Suprasellar	Pineal	Sellar/ Suprasellar
Diagnosis	Germinoma	Germinoma	Germinoma	Germinoma	NGGCT	NGGCT
Serum BHCG (IU/L)	N	N	N	5	73.3	123
Serum AFP (ng/ml)	N	N	N	N	N	N
CSF BHCG (IU/L)	N	N	N	9	504	577
CSF AFP (ng/ml)	N	N	N	N	N	N
Baseline spinal imaging	Positive	Negative	Negative	Negative	Negative	Negative
Initial Chemo	SIOP	SIOP	SIOP	SIOP	COG	SIOP
Initial Surgery	Biopsy	Biopsy	Partial Resection	Biopsy	Biopsy	None
Initial RT volume	CSI / TB	TB	TB	None	None	WV + TB
Initial RT dose (Gy)	30.6/50.4	45	45	0	0	24/45
Salvage treatment	None	None	PEI + CSI	None	None	None
PFS (m)	74.2	25.7	13.7	1.4	1.7	21.09
OS (m)	74.2	25.7	131.3	1.4	1.7	21.09
Reason of death	Second tumor	Second tumor	Second tumor	Infectious disease	Infectious disease	Diabetes insipidus disorder
Details	Unknown	Acute myeloid leukemia	Medulloblastoma			

CSF craniospinal fluid, *RT* radiotherapy, *CSI* craniospinal irradiation, *WV* whole ventricular, *TB* tumor bed, *PFS* progression free survival, *OS* overall survival, *m* months, *N* normal, *UK* unknown

In order to preserve quality of survival highly curable disease like localized CNS germinoma, we employed a chemotherapy strategy followed by reduced-volume radiotherapy, reserving craniospinal radiation for cases with metastatic dissemination [18]. This strategy was previously described by several cooperative groups in Europe and Japan with excellent survival [5]. While the cohort between 2000 and 2009 showed an inferior PFS and OS outcome, the cohort between 2010 and 2019 demonstrated a similar favourable survival data to SIOP experience. Although chemotherapy was based on carboplatin in both cohorts, radiotherapy fields differed. When radiation fields were compared, we found that focal radiation alone increased the risk of recurrence, involving not only ventricle relapses; but spinal cord and disseminated disease as well. In our cohort WRTV following chemotherapy is likely to be a safe treatment to control subclinical disease, consistent with previous reports where a local field radiotherapy has shown to be insufficient to control subependymal growth in the ventricular area and increased the risk of ventricular relapse [25–27].

In our experience, NGGCT recurred on chemotherapy or immediately after the end of treatment. All recurrences had been locally and/or with high tumor markers levels. In contrast with ACNS0123 trial results [28], where the preponderance of distant relapse had been concerning; we did not find any distant relapse (including the subgroup who received FRT or FRT plus WVRT upfront), showing that craniospinal radiotherapy might be avoided without increased relapses outside the radiotherapy field. Consistent with previous SIOP-CNS-GCT-96 trial results [19], serum/CSF AFP level > 1000 ng/mL at diagnosis was associated with a negative prognostic impact in our cohort, confirming this as a marker of poor prognosis ($p = 0.009$ HR 22 95% CI [2.13–228]).

Our study has the classic limitations of a retrospective study, where there are missing observations, including isolated cases where staging was incomplete. Specifically, there were two relapsed germinoma's where CSF tumor markers at diagnosis were not performed due to concerns around lumbar CSF examinations, and as such we cannot completely dismiss the possibility that these were misdiagnosed NGGCT. Nevertheless, our overall trend that the radiation field is a predictor of outcome is highly significant, and our study confirms the feasibility of a craniospinal irradiation

avoiding approach for NGGCT. However, as a single centre consecutive cohort, our follow up was uniform, and as such, our study further confirms that the SIOP-CNS-GCT 96 approach results in excellent outcome in the developing world. A second limitation is a lack of uniform neurocognitive outcomes in our cohort, which is a crucial determinant moving forward to justify de-escalations of therapy—and more importantly a lack of uniform neurocognitive outcomes collected by the cooperative group trials.

Another important consideration are the three late deaths in the germinoma group after a second malignancy without evidence of germ cell tumor recurrence. Secondary leukemia after treatment with a conventional dose of etoposide has been well described, but the low incidence in patients who receive lower doses ($\leq 2gr/m^2$) does not alter the risk-to-benefit ratio of etoposide-based chemotherapy in germ cell cancer [29]. Topoisomerase II inhibitor-related secondary leukemias are generally diagnosed 2 to 3 years following treatment, most commonly exhibit M4 or M5 phenotype and have a poor prognosis [30]. On the other hand, both with solid second neoplasm received radiotherapy in that area; 1 as part of the primary treatment disease and 1 as part of the salvage treatment. Despite no obvious family history of cancer and the paucity of literature on germline mutations and germ cell tumors treated with radiation, we cannot exclude the possibility that these second tumors could have been related an underlying cancer predisposition.

Managing iGCT in LMIC poses a unique set of challenges including access to tumor markers screening, stage at presentation, adequacy of management and availability of therapeutic interventions. Optimal chemotherapy therapy was administered in all iGCT patients without delay. While proton therapy is not available in Argentina, intensity modulated radiotherapy and 3D-conformal radiotherapy are the two techniques most frequently used since 2015 at our institution. On the other hand, abandonment treatment rates seem to be higher in LMIC however, all iGCT´s patients were able to complete therapy without delays [31]. Implementing a patient-tracking system, monitoring missed appointments, and providing resources to help families during treatment prevented unnecessary treatment interruption.

Despite the limitations of analysing historical series, this study fills a gap in the literature on iGCT outcome and treatment patterns at a single institution in the developing world. Our experience suggests that adjuvant chemotherapy followed by focal radiotherapy results in inferior survival compared to whole ventricular radiotherapy, and confirms the feasibility of this approach in a low-middle income setting. Future collaborative studies in low-middle income countries might contribute to define better standards of care in our setting and help improve quality of life for this group of highly curable central nervous system malignancies.

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