Intracranial germ cell tumors in Adolescents and Young Adults: European and North American consensus review, current management and future development.

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ABSTRACT

The incidence of intracranial germ cell tumors (iCGT) is much lower in European and North American (E&NA) than in Asian population. However, E&NA cooperative groups have successfully developed in parallel treatment strategies with specific attention paid to long-term sequelae. Neurological sequelae may be reduced by establishing a diagnosis with an endoscopic biopsy and/or CSF and/or serum analysis, deferring the need to perform a radical surgery. Depending on markers and/or histological characteristics, patients are treated either as germinoma, or as non-germinomatous germ cell tumors (NGGCT). Metastatic disease is defined by a positive CSF cytology and/or distant drops in cranio-spinal MRI. The combination of surgery and/or chemotherapy and radiation therapy is tailored according to grouping and staging. With more than 90% 5-year event-free survival (EFS), localized germinomas can be managed without aggressive surgery, and benefit from chemotherapy followed by whole ventricular irradiation with local boost. Bifocal germinomas are treated as non-metastatic entities. Metastatic germinomas may be cured with craniospinal irradiation.. With a 5-year EFS over 70%, NGGCT benefit from chemotherapy followed by delayed surgery in case of residual disease, and some form of radiotherapy. Future strategies will aim at decreasing long-term side effects while preserving high cure rates.

KEY WORDS: Brain tumors, Germ Cell Tumor, Germinoma, Non-germinomatous germ cell tumor, adolescent and young adult

Most publications on iGCT begin with an introduction that points out the five to eight-fold greater incidence between the Asian and non-Asian populations.. Other major differences particularly concern the management of this condition, which is primarily under the supervision of neurosurgical teams in Asian countries, whereas it is primarily coordinated by pediatric or medical oncologists in E&NA. This has contributed to differences in the risk classification and in the surgical management of iGCT. The aim of this review from Society for Neuro-Oncology (SNO), European Association for Neuro-Oncology (EANO) and EUropean reference network for Rare Adult solid CANcers (Euracan) is to describe how Western cooperative groups have developed a specific consensus on most aspects of the diagnosis and management of this complex entity.

Epidemiology and symptoms

iGCT are rare CNS neoplasms that mainly affect adolescents and young adults (AYA), with a peak incidence between 10 and 19 years. [1,2] In E&NA, iGCTs make up 1-3% of brain tumors, in contrast to 8-15% in East Asia[2]. High incidence persists in East Asiatic migrants, suggesting a genetic background.[3] No specific genetic origin has been identified in the E&NA populations. The incidence of iGCT is lower in the African-American population. The incidence of iGCT has significantly increased in the United States over the recent decades. Most iGCT arise in the midline pineal (40-60%) or suprasellar (30-40%) regions, simultaneously in both locations (bi-focal) (2-26%), and rarely in basal ganglia and other sites.[1,4] AYA iGCT predominate in males in whom the majority (50%) are germinomas in the pineal region, where the male:female ratio is roughly 13-15:1 while germinomas in the suprasellar region show a slight female predominance.[1,5]

Pathology and markers

According to 2016 WHO classification, iGCT include 5 subtypes: germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (mature and immature) (Table 1). iGCT are divided into germinoma (55-65%) and NGGCT (35-45%).[1] Mixed iGCTs are composed of two or more of the subtypes, including most often germinoma and teratoma[67] The immature teratomatous component may be graded following the Gonzalez-Crussi classification; however, its prognostic value remains unclear.[8] Residual masses after chemotherapy mostly show mature teratoma.[9]Teratomas with somatic-type malignancy are rare with the malignant components being mostly sarcomas.[10]

iGCT may secrete HCG (the beta subunit of Human Chorionic Gonadotrophin) and/or AFP (alpha-feto protein) in serum and/or cerebrospinal fluid (CSF): AFP is mainly produced by yolk sac tumors, though low levels may be detected from embryonal carcinomas and immature teratomas. HCG is secreted by choriocarcinoma (that contains both cyto- and syncytiotrophoblastic cells) and embryonal carcinomas. Germinoma through their syncytiotrophoblastic component can also secrete small amounts of HCG. In E&NA, there is no consensus regarding the cutoff of HCG value between germinoma and choriocarcinoma: patients with a similar HCG level may be treated as a germinoma in some protocols and as NGCCT in others. Levels of HCG tend to be higher in the CSF, especially in ventricular compared to lumbar samples, while AFP values tend to be more elevated in the serum..

Biology

iGCT may arise from primordial germ cells (PGCs) that did not migrate properly to the genital ridge in the first weeks of gestation due to altered expression of additional mediators.[11] Germinoma cells recapitulate the features of pluripotent human embryonic stem cells by upregulation of genes responsible for self-renewal such as *OCT4*, *NANOG* and *KLF4*. In contrast, NGGCT are characterized by expression of genes associated with neuronal differentiation, epithelial-mesenchymal transition or the Wnt/b-catenin pathway. The latter is important for PGC proliferation and differentiation of pluripotent embryonal carcinoma [11,12]. While chromosomal instability is a characteristic of all iGCT [13–15], global DNA hypomethylation is exclusively present in germinoma.[16] Somatic *KIT/RAS* [15,16] and *PI3K/AKT* [15–17] mutations have been described in all iGCT, but more frequently in germinoma. Germinomas are further characterized by abundant expression of genes linked to immune response such as *CCL18*, *CD72* and *IL6R*, consistent with lymphocyte infiltration[18,19]. Germinoma cells highly express PD-L1, whereas tumor infiltrating leukocytes show PD-1 expression,[19] which may suppress the antitumoral immune response and lead to subsequent tumor growth.

Clinical presentation and Imaging

Most pineal iGCTs present with obstructive hydrocephalus, increased intracranial pressure and/or Parinaud syndrome.[5,20] Suprasellar iGCT present with hypothalamic-pituitary axis insufficiency and/or decreased visual acuity and/or bi-temporal field deficits from compression or involvement of the optic chiasm. Diabetes insipidus (DI) is especially common, and other pituitary hormone deficits occur in 40-60% of cases[21,22]. HCG secreting tumors may present with precocious puberty and gynecomastia. Basal ganglia iGCT often present with gradual hemiparesis and cognitive decline. They are exceptional in the Western population..[23]

Standard craniospinal MRI is the primary imaging method for evaluating iGCTs (Table 2).

iGCTs are iso- or hypointense on T1- and T2- weighted sequences, with moderate to marked enhancement, with multiple small cyst-like areas without necrosis and with a drop in apparent diffusion coefficient. Teratomas may be suggested when the three components (parenchymal, fat, and calcifications) are present. Basal ganglia germinomas show ipsilateral atrophy of the cerebral peduncle and/ or basal ganglia and/ or cerebral hemisphere; Contrast enhancement is inconstant and patchy.

Among additional sequences, heavily T2-weighted sequences [driven equilibrium (DRIVE), constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA) sequences] can be useful in cases of suprasellar involvement [24]. A T2*-based MR sequence [conventional T2* gradient echo (GRE) or Susceptibility Weighted Imaging (SWI)] is very sensitive for the detection of basal ganglia involvement [25]. Magnetic Resonance Spectroscopy (MRS) typically shows a prominent lipid peak [26] .

Disappearance of the spontaneously bright spot of the posterior pituitary on T1 is correlated to DI. Diabetes insipidus with isolated pituitary stalk thickening can precede the diagnosis of iGCT by years.. Algorithms have been suggested for the monitoring of these patients.[27]

The assessment of response is not homogeneous in E&NA protocols [volumetric vs bi-dimensional tumor measurements, volumetric changes defining response or progression, evaluation of complete response]. Several E&NA protocols are proposing a response-based radiation strategy, real time central review is becoming part of many trials. A consensus is highly desirable to facilitate data comparability.

Initial staging

The diagnosis of iGCT is based on clinical signs, neuroimaging, markers inserum and CSF and by histology when required (Figure 1) . In the International Society of Pediatric Oncology (SIOP) trials, serum and/or CSF AFP 25ng/ml or higher and/or HCG $\geq$ 50IU/L define a secreting NGGCT whereas the cut-offs in Children's Oncology Group (COG) studies is 10ng/ml for AFP and 100IU/L for HCG.[28] [29] SIOP have suggested an inferior outcome for patients whose AFP>1000 ng/ml[30]. But this have not been replicated in two COG protocols. In E&NA grouping systems, similarly to other paediatric brain tumors, metastases (M+) are defined by a positive CSF cytology and/or drop metastasis: around 20% of iGCT have metastatic disease at diagnosis. However, interpretation of CSF cytology is still a matter of debate in E&NA. If CSF sample obtained from the 3rd ventricle prior to biopsy shows tumor cells, a lumbar CSF cytology is advised with a 2 weeks delay: if negative, the tumor is considered localized. Deposits found on the walls of the ventricle during endoscopic procedure do not qualify the patient to have metastatic disease, unless they are visible on MRI. Bifocal lesions defined as lesions occurring within the pineal and suprasellar region are considered non-disseminated[31]. Bifocal lesions and negative tumor markers are considered by consensus as germinomas and treated as such if imaging features are compatible. Loco-regional extension may not portend an inferior prognosis.[32]

Surgery

In E&NA countries, surgery has a limited role at the time of diagnosis. The benefit/risk of a systematic documentation argues in favour of selective indications for biopsy at time of diagnosis though this will prevent development of biological studies. A biopsy restricted to those who relapse may guide targeted therapy. Only marker-negative tumors should be biopsied with a preference for endoscopic techniques (Figure 2). Preferred management for pineal tumors and obstructive hydrocephalus is endoscopic third ventriculostomy (ETV) with or without tumor biopsy. If unsuitable, externalized ventricular drainage is an acceptable alternative. Ventriculoperitoneal shunt (VPS) should be avoided in most cases. For large supra or parasellar masses causing compartmentalized hydrocephalus simultaneous VPS with septal fenestration is favoured. Sampling for cytology and markers is recommended in any form of CSF diversion prior to any biopsy.

Surgery of the residual mass is highly recommended in NGGCT [30](Figure 3). In germinoma, surgery is recommended when an associated teratoma component is suspected based on failure of the tumor to shrink during chemotherapy. The intent of second look surgery is a safe maximal resection. When tumor progression occurs *during* induction chemotherapy while markers are decreasing, this usually represents growing teratoma syndrome unresponsive to chemo/radiation therapy [33]. It warrants a surgical excision The prognosis of these patients is usually excellent.[34]

Radiotherapy

Radiotherapy is an integral component in the curative treatment of iGCT. A major aim of modern treatment technologies (Volumetric modulated arc therapy(VMAT), Intensity-modulated radiotherapy (IMRT), proton beam radiation therapy (PBRT)) is to reduce the risk for long-term sequelae, in particular neurocognitive dysfunction.[35,36] Chemo-radiotherapy approaches for adults are essentially based on data from retrospective and prospective paediatric and adolescent series[37]. Treatment volumes can comprise craniospinal irradiation (CSI), whole brain irradiation (WBI), whole ventricular irradiation (WVI) or radiotherapy of tumor site (IF-RT). Selection of treatment volumes and dose prescriptions are tailored according to histological subtypes, extent of disease, the combination with and the response to chemotherapy. Pre-irradiation chemotherapy has allowed reduction of treatment volumes (e.g. from CSI to WVI in germinoma) and dose prescriptions to tumor site and/or adjuvant regions. Given the heterogeneity of data, it is difficult to define a standard (Table3).[29,38,39] Increasingly, PBRT is being used[38,] allowing a dose reduction to the non-target brain.

Because of their rarity and histological heterogeneity no detailed recommendations can be given for teratoma: After incomplete resection IF-RT with 54Gy dose is an option [40];The role of radiosurgery remains unclear.[41]

Chemotherapy

The chemosensitivity of iGCT is well recognized. Cisplatin or carboplatin have become the backbone of E&NA protocols, which have also included etoposide plus either cyclophosphamide or ifosfamide in most regimens[30].[,39,42] The use of bleomycin has been progressively abandoned.[43] There is no clear demonstration of survival benefit of cisplatin compared to carboplatin in iGCT. Rather, there is some evidence that cisplatin and other agents such as ifosfamide that require hyperhydration are associated with a higher risk of toxicity (renal and/or neurological) among patients with DI[44]. High dose, marrow-ablative chemotherapy (HDC) regimens are used for poor responders or patients with recurrence. Most high-dose regimens include high-dose Thiotepa combined with etoposide and/or carboplatin [45,46]. Newer chemotherapeutic agents such as the combination of gemcitabine, oxaliplatin or paclitaxel (GemPOx) and topotecan-containing regimens are currently being assessed in the recurrent setting.[47]

Strategy for germinomas

Survival rates over 90%, are reported in both E&NA trials. Current strategies have focused on treatment reduction to minimize long term sequelae of treatment. The standard treatment comprises of combination of chemotherapy and radiotherapy, with surgery playing a limited role. Germinomas can be successfully treated with less chemotherapy and radiotherapy than NGGCT.

Since the 1950s, germinomas have been treated successfully with radiotherapy. Modern radiotherapy-only regimens can achieve high cure rates.[48] CSI, followed by a tumor bed boost, was

considered the gold standard treatment until the 1990s. It resulted in a 97% 5 year EFS in the SIOP CNS GCT 96 trial, but this may amount to over-treatment for localized cases,[49] The introduction of chemotherapy into treatment regimens aimed to reduce both the dose and volume of radiotherapy. Attempts to treat germinoma with chemotherapy alone resulted in less than 50% of cases being cured[50]. Adjuvant chemotherapy followed by reduced dose and field radiotherapy, even following complete response to chemotherapy, is now considered standard of care, at least for localized germinoma.[4]

The focus over the last 30 years has been to identify the optimum combination of chemotherapy and radiotherapy. Early studies in the 1980s demonstrated excellent radiological responses to single agent cyclophosphamide or carboplatin, with reduction of tumor bed boost from 50Gy to 30Gy without affecting overall survival for localized germinoma.[51,52] International prospective trials in the late 1990s from SIOP and COG evaluated combinations of chemotherapy followed by IF radiotherapy for localized germinoma. The COG trial used a combination of cisplatin, etoposide, cyclophosphamide and vincristine followed by 30.4Gy focal radiotherapy and achieved a 3-year EFS of 92 ± 8% in 12 evaluable patients.[53] The SIOP CNS GCT 96 trial compared 24Gy CSI plus 16 Gy tumor bed boost with a combined approach using alternating courses of carboplatin-etoposide with ifosfamide-etoposide ('CarboPEI') followed by 40Gy IF radiotherapy. At 5 years, the EFS in the combined treatment group (n=65) was 88 ± 4%.[42] An excess of recurrences in the ventricles was identified.[42,44,54] Thus WVI was adopted in place of IF-RT. The SIOP group utilized chemotherapy followed by 24Gy WVI with 16Gy boost to the tumor bed as the standard arm in their recently closed SIOP CNS GCT II trial, with the boost dose omitted for those with complete response (CR) to 'CarboPEI.' Other groups have successfully employed only carboplatin and etoposide prior to radiotherapy, thus avoiding the need for hyper-hydration ; these regimens have been followed successfully with WVI to a total of 24Gy without boost.[55] The COG conducted a response-based trial with a WVI dose of 18Gy and 12Gy tumor bed boost for patients with localized germinoma achieving CR after 4 courses of carboplatin-etoposide. Of 137 patients enrolled, 74 achieved a CR with an estimated 3-year PFS of 94.4 ±2.7%.[56]

There is general consensus that bifocal germinomas can be safely treated as localized tumors (at two sites) rather than as metastatic tumors,[57] although the need for a biopsy in radiologically typical cases is a subject of ongoing debate,[4] particularly given the report of non-secreting bifocal tumors that were confirmed as NGGCT.[31,58,59]

Successful treatment of metastatic germinoma requires CSI. Whilst the European standard of care is 24Gy CSI with 16Gy boost to primary and metastatic sites, without additional chemotherapy,[42] there is evidence supporting treatment without boost if chemotherapy is delivered prior to radiotherapy.[55]

Residual of germinoma following a good response to treatment can be left without negative impact on outcome.[42]The presence of teratoma in cases initially treated as germinoma may only become apparent later, when reassessment imaging demonstrates less than expected response to chemotherapy; In such cases, where imaging indicates stable disease or poor response, surgical removal of residual tumor should be attempted before radiotherapy.

Strategy for NGGCT

One major specific change over the past decade in the E&NA experience is the reliance on tumor markers in serum and CSF alone for diagnosis, thereby avoiding the need for a biopsy or the risks associated with surgical debulking. Multi-modality treatment includes a timely combination of chemotherapy, radiation therapy, and selected neurosurgical resection. The optimum goal is to obtain a CR prior to initiating RT. Four to six courses of multi-agent chemotherapy are usually administered. For patients not experiencing CR, additional radical surgery or HDC is considered followed by some form of RT. Although there is some consistency and overlap in chemotherapy regimens used by E&NA cooperative groups, the doses and volumes of RT have been variable, with a persistent trend to consider CSI as the standard of care in North America, while the European approach was to deliver IF-RT to localized tumors and CSI to patients with metastatic disease only. As the diagnostic criteria for NGGCT are becoming more reliant on tumor markers in serum +/- CSF, it is challenging to compare current outcomes to prior historical and cooperative group experiences where diagnosis was histologically based.

In the SIOP CNS GCT-96, patients received four courses of chemotherapy with cisplatin, ifosfamide and etoposide followed by IF-RT to 54Gy in case of localized disease (n=116) or CSI to 30Gy along with a boost to a total dose of 54Gy to the primary and metastatic sites (n=37). The 5-year PFS was 72±4% and OS was 82±4% for patients with localized disease and 68±9% and 75±8%, respectively, for patients with metastatic disease. AFP ≥1,000ng/mL in serum and/or CSF (n=19) and presence of residual disease at the end of treatment (n=52) were adverse prognostic factors (5-year PFS of 32±12% and 48±7%, respectively)[30.] The SIOP study CNS GCTII now recommends up front HDC in patients with AFP>1000 ng/ml and advises surgical resection in case of residual disease following completion of chemotherapy.

COG ACNS0122 utilized full-dose CSI (36Gy) along with a 18Gy tumor bed boost following six alternating cycles of carboplatin and etoposide with ifosfamide and etoposide. The 5-year EFS and OS for 102 eligible patients was 84%±4% and 93%±3%, respectively. There was no impact of serum or CSF elevations of HCG ≥1000mIU/mL on survival; However, there was a trend towards inferior survival for patients with AFP elevations in serum and/or CSF (AFP≥10 ng/L, p=0.063). The 3-year PFS and OS for patients with CR+PR was 92% and 98%, respectively.[39] In the successor COG study ACNS1123, only patients with localized NGGCT were included. The same induction chemotherapy regimen was used, but for patients with CR/PR the dose was reduced to 30.6Gy WVI along with a boost to a total dose of 54Gy to the tumor bed. Of 107 eligible/enrolled patients on study, the 4-year PFS and OS for 66 patients with CR/PR to induction was 88%±4% and 92%±3%, respectively.[29] Twenty-four patients underwent second-look surgery, of whom 17 had mature teratoma or fibrosis/scar tissue and continued to receive reduced-radiation, illustrating the fact that second-look surgery has a significant impact on treatment and should be strongly considered for patients with radiographic residual post-induction. The 3-year PFS and OS rates (+/- SD) for the 41 patients who did not qualify for CR/PR were 60.2% +/- 7.8% and 81.7% +/- 6.4%, respectively. There was no significant difference in survival for NGGCT patients with localized disease and CR/PR to induction chemotherapy in the two COG studies ACNS0122 and ACNS1123. However, the predominant site of relapse for patients in ACNS1123 was outside the WVI field, that is, in the spine (Table 4). Although it is tempting to speculate that the increase in spinal relapses was secondary to elimination of spinal

irradiation, it is difficult to reconcile this observation when a similar trend was not observed on SIOP CNS 96. Based on the results of ACNS1123, COG recently launched a phase II trial of chemotherapy followed by WVI and spinal irradiation, with the aim of reducing the incidence of spinal relapses. In future studies, it may be reasonable to continue to validate the safety of dose and/or volume of radiotherapy reductions in patients experiencing a CR to pre-radiotherapy chemotherapy. The optimum RT treatment plan, however, is yet to be defined. There is an emerging consensus about the value of second-look surgery for persistent residual disease, post induction chemotherapy, in the absence of tumor marker positivity. One of the confounding challenges when comparing outcomes is the recent reliance on tumor markers alone for diagnosis and enrolment on clinical trials in E&NA. Variation in observed levels of ß-HCG may arise from differences in the timing (pre vs. post-op) and anatomic site of CSF acquisition (ventricular vs. lumbar) in the E&NA studies, as the timing and site of fluid acquisition is not always apparent.

RELAPSES

Available data in the literature are limited due to the paucity of these events, and most derive from E&NA experience. The median delay to relapse is longer in germinoma than in NGGCT. As some patients with positive markers may relapse without markers and vice versa, palliative situations excluded, complete staging should be performed prior to initiation of relapse treatment. Second-line treatments for relapse comprise chemotherapy, surgery and re-irradiation.[45,60–62] A prominent role of HDC for chemosensitive tumors has been suggested [45,63], with etoposide-thiotepa (with or without carboplatin) conditioning being the most commonly used regimen;[45,64] however, exact indications still remain to be defined. These outcomes are far better in germinoma , with post relapse 5-year OS ranging from 55 to 88.9 % [60,61] versus 9 to 60% in NGGCT.[46,604] Pure teratomas require exclusive surgical treatment. Other patients should be rechallenged with standard-dose chemotherapy (SDC) containing platinum-salt compounds, such as oxaliplatin, carboplatin or cisplatin. In germinoma HDC or reirradiation are both valid options [60] after SDC. Their combination may represent overtreatment with significant risk of toxicity. In NGCCT, both HDC and irradiation should be used after SDC in patients with at least good partial responses,[4,60] Whether single or tandem transplants are superior in this setting remains unproven, but the former is likely ineffective in the absence of complete response to reinduction. In refractory/relapsed disease, molecular profiling is encouraged and may identify therapeutic targets. This is particularly important as most relapsed patients are those with NGGCTs rather than germinomas, and by definition, many would not have an upfront biopsy as they will have had serum and/or CSF AFP and HCG marker levels above the thresholds required for biopsy at original diagnosis. Check point inhibitors [65] and brentuximab vedotin [66] warrant study for PDL1 and CD30-positive non-chemo sensitive tumors respectively.

Side effects and long-term patient care

Due to their primary locations, iGCT can cause early neurological and endocrine symptoms, [67]. Given the favourable prognosis of iGCT [2230], long-term tumor or treatment-related toxicities are therefore especially relevant [39].

Radiotherapy plays a central role in the development of long-term sequelae such as second malignant neoplasms (SMN), strokes, neurocognitive deficits and decline of health-related quality of life [55,68,69]. Chemotherapy has long-term toxicity, mainly related to platinum agents such as permanent kidney impairment, hearing loss or peripheral neuropathy, hypogonadism and infertility [70].

Endocrine deficiencies occur in roughly half of the patients [71]. Although there is always a risk of endocrine deficit associated with aggressive surgery and/or radiotherapy to the hypothalamic/pituitary region, endocrinoathies in iGCTs are generally related to the tumor itself rather than its management. Diabetes insipidus , central hypothyroidism, central hypoadrenalism, growth hormone deficiency (GHD), hypogonadism and hypothalamic obesity (HO) are the main endocrine complications[72]. management of these deficits require specific attention: ACTH deficiency requires adequate hydrocortisone replacement and stress dose cover when needed. GH treatment should be initiated usually more than 1 year after completion of therapy [73]. In hypogonadic patients, replacement therapy is needed. Patients should be referred for fertility preservation prior to treatment and later on for assisted reproductive technologies. Annual monitoring of thyroid and adrenal function and search for thyroid nodules is required. HO is one of the most challenging sequelae. Lifestyle intervention and psychological support should be initiated early as they have a limited success once HO is established[74]. The cumulative incidence for SMN at 25 years is 6.1% in germinoma and 4.1% in NGGCT. The most common non-cancer related cause of death is stroke [69]. A recent report on 499 long term survivors of iGCT from the SEER database identified a 59-fold increase in the risk of death from stroke at 25 years.[68] Neurocognitive impairment is related to tumor site, age at diagnosis, fields and doses of irradiation. Irradiation may negatively impact intellectual functions, concept crystallization, executive function, working memory, quality of life and adaptive skills, particularly in psychosocial domains. Patients treated with WVI had better outcomes than those with whole brain radiotherapy or with CSI [75]. Patients with pineal tumors showed early and stable deficits, whereas patients with suprasellar and bifocal tumors showed more protracted declines from initial average functioning.

Younger patients are at increased risk for psychosocial and physical problems. Quality of Life at follow up was better for patients $\geq$ 19 years (average range) than for those $\leq$ 18 years (low average-borderline).

Perspectives and future directions in diagnostics and therapy

Five International CNS GCT Symposia have been held, from 2003 to 2017 in Japan, US and Europe. Since the third one [20] , a formal international consensus process was undertaken, and many similar areas of practice identified [4]. Future directions in diagnostics include working towards a common AFP/HCG marker threshold definition. Consensus on which cases require diagnostic biopsy is also required. In future iGCT trials, incorporation of prospective biological studies is critical. Reports of

the mutational landscape of these tumors [13 15 76] have improved our molecular understanding. However, limited tissue specimens are available to study, particularly for NGGCT cases [30 29]. If high-risk groups can be identified upfront, then biopsy with molecular interrogation would become an attractive option. Future collection of biospecimens such as CSF and serum/plasma may allow minimally-invasive diagnosis and disease-monitoring using microRNA expression levels [77] and also identification of the presence of tumor mutations through circulating-tumor DNA analysis[78], which may inform prognosis and/or novel treatment strategies. It will be important to successfully exploit dysregulated molecular pathways. Mutually exclusive KIT/KRAS mutations occur in germinomas [15], similar to their testicular counterparts, but only rarely in NGGCT [15]. However, when tyrosine kinase inhibitors have been employed in germinoma to target KIT, e.g. imatinib [79] or dasatinib [80], no partial/complete remissions were reported due to the predominance of exon 17 mutations present in germinoma which are less sensitive to early generations of KIT inhibitors. mTOR pathway alterations have also been described in iGCT [17], but monotherapy with the mTOR-inhibitor everolimus had minimal success for testicular disease. Combinations of novel targeted agents will be required to overcome treatment resistance in such tumors, such as erlotinib and rapamycin which target EGFR and mTOR pathways, respectively[81]. Unfortunately, poor accrual resulted in early closure of a trial that was testing erlotinib and sirolimus for this purpose. Brentuximab-vedotin was successfully used in a patient with embryonal carcinoma and Down syndrome [82] as was palbociclib in a patient with unresectable growing teratoma syndrome [83]Other potential novel treatment options include exploring BMP/SMAD pathway dysregulation, targeting CD30 (expressed by embryonal carcinoma) and/or altering immune regulation [84]. In the future, the role for immunotherapy in treatment of iGCT is another avenue to be explored.

SUMMARY

Though much less frequent in E&NA as compared to Eastern Asia, the success story of iGCT management over the last 50 years is a paradigm. Both E&NA cooperative groups have successfully developed large networks and conducted clinical trials with a significant impact on clinical practice. Avoiding initial surgery when CSF and/or serum markers are positive, and using CSF cytology with spinal MRI to define metastatic disease are a hallmark of these trials. The combination of surgery, chemotherapy and radiation therapy is tailored accordingly. With more than 90% 5 year EFS, most patients with localized or bifocal germinomas avoid aggressive surgery, and benefit from chemotherapy followed by WVI with/without local boost. Only metastatic germinomas patients are treated with CSI. NGGCT are essentially diagnosed by positive markers and less often by pathology. With a 5-year EFS over 70%, they benefit from chemotherapy followed by aggressive surgery in case of residue. There are still ongoing debates regarding the optimal radiation management. Future strategies will aim at decreasing long-term side effects while preserving these high cure rates.

AKNOWLEDGEMENT to Kathy Oliver for reviewing the manuscript.

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Table 1: **Histopathology and immunohistochemistry of iGCT**

Table 2: Brain and spine MRI protocol

Table 3: Radiotherapy for iGCT

Table 4: Strategy for NGGCT.

Figure Legends

Figure Legends

1. Flow chart of management.
2. Sagittal post-contrast MRI of the brain demonstrating a hypothalamic and infundibular mass in a 10-year old female presenting with diabetes insipidus. Given normal serum and CSF tumor markers a right frontal endoscopic tumor biopsy was performed which confirmed pure germinoma. Endoscopic view of the third ventricle (inset) revealing the exophytic tumor mass (a), 1 mm endoscopic biopsy forceps (b), and the bilateral hypothalami (c).
3. This adolescent male presenting with obstructive hydrocephalus underwent an endoscopic third ventriculostomy (ETV) with simultaneous CSF sampling that confirmed a nongerminomatous germ cell tumor (NGGCT). Sagittal post-contrast MRI scans at diagnosis (left), after induction chemotherapy with normalization of tumor markers (center), and after 2nd look surgery via a supracerebellar infratentorial approach.

Table 1: Histopathological and immunohistochemical features of germ cell tumors in the central nervous system

	Main histopathological features	Typical pattern of immunoreactivity
Germinoma	- Large monomorphous round cells with PAS (Periodic Acid Schiff)-positive clear cytoplasm - Atypical vesicular nuclei with prominent nucleolus - Association with an inflammatory population of lymphocytes (T cells>B cells) - Prominent granulomatous reaction may be observed and should not be misinterpreted as sarcoidosis or tuberculosis - Isolated syncytiotrophoblastic cells may be found and should not lead to the diagnosis of choriocarcinoma. It explains why low level (<50IU/L) of ß-HCG may be detected in serum or CSF	SALL4+; OCT3/4+; CD30- CD117+ (membranous +++ and golgian) D2-40 (membranous)
Embryonal carcinoma	- Poorly differentiated epithelial cells arranged in solid sheets, glandular structures and/or papillae - Marked nuclear atypia - High mitotic activity - Necrosis	SALL4+ ; OCT3/4+ ; CD30+ Cytokeratins+
Yolk sac tumor	- Neoplasm composed of atypical epithelial cells arranged in various architectural patterns - *Reticular pattern:* the most common, consisting in an anastomosing network of vacuolated tumoral cells lying in a myxoid stroma and delineating microcysts - *Endodermal sinus pattern:* the most typical, characterized by Schiller-Duval bodies (fibrovascular core surrounded by cuboidal to columnar neoplastic cells, the whole structure lying in a cystic space) - PAS-positive hyaline globules (especially found in hepatoid areas) - AFP may be detected in serum and/or CSF	SALL4+; OCT3/4-; CD30- Cytokeratins+; Alpha-fetoprotein+; Glypican 3+

Choriocarcinoma	- Neoplastic mononucleated cytotrophoblastic cells and neoplastic multinucleated syncytiotrophoblastic cells - Large blood lakes - Necrotic and hemorrhagic areas - High level ≥ 50IU/L of BHCG may be found in serum and/or CSF	SALL4 ± (cytotrophoblast); OCT3/4-; CD30- Cytokeratins+; Beta-HCG+
Teratoma	- *Mature:* admixture of adult-type tissue derived from the three main embryonic layers (ectoderm, endoderm, mesoderm) - *Immature:* admixture of fetal/embryonic tissues derived from the three main embryonic layers	Immunophenotype according to the tissue SALL4 immunopositivity may be focally observed in some tissues (*e.g.* primitive neuroepithelial tissue, mature-appearing enteric-type glands)

Table 2: Brain and spine MRI protocol

Essential MRI study			
Sequence	**Slice thickness (mm)**	**Gap**	**Comment**
Pre-contrast brain sequences			
Axial DWI (b = 0,1000) with ADC	≤4	≤0.4	Or axial DTI
Axial T2 TSE/FSE	≤4	≤0.4	
Axial T1 SE/TSE/FSE	≤4	≤0.4	Or 3D T1 (≤1 mm slice thickness)
Axial 2D FLAIR [or post-contrast]	≤4	≤0.4	Or 3D FLAIR
Post-contrast brain sequences			
Axial T1 SE/TSE/FSE	≤4	≤0.4	Or 3D T1 (≤1 mm slice thickness)
Coronal T1 SE/TSE/FSE	≤4	≤0.4	
Sagittal T1 SE/TSE/FSE	≤3	≤0.3	

Spine sequences			
Post-contrast sagittal T1 SE (whole thecal sac)	3	≤0.3	If necessary, add post-contrast axial T1
Complementary brain sequences			
Axial SWI			Or Axial T2* GRE (4 mm slice thickness)
Sagittal CISS, FIESTA or DRIVE	≤0.6		
Single voxel MRS			TE = 135-144ms at 1.5T; TE = 288ms at 3T (due to j-coupling at 135-144ms)

Abbreviations: DWI= Diffusion Weighted Imaging; ADC= Apparent Diffusion Coefficient; DTI= Diffusion Tensor Imaging, TSE= Turbo Spin Echo; FSE= Fast Spin Echo; SE= Spin Echo, FLAIR= Fluid Attenuated Inversion recovery; SWI= Susceptibility Weighted Imaging; GRE= Gradient Echo; CISS= Constructive Interference in Steady State; FIESTA= Fast Imaging Employing Steady-state Acquisition; DRIVE= Driven Equilibrium, MRS= Magnetic Resonance Spectroscopy, TE= Echo Time

Table 3: European and North-American concepts for radiotherapy

	Europe (SIOP)	North America (COG)
Pure germinoma	M0 Chx, WVI 24Gy, F-RT/boost 16 Gy; (if CR no boost (currently under evaluation) M+ RT CSI alone 24 Gy, IF-RT/boost 16 Gy ([53], [42])	M0 ACNS 1123: Chx WVI 18 Gy, IF-RT/boost 12 Gy for CR; WVI 24 Gy, IF-RT/boost 12 Gy if no CR is currently under evaluation
NGGCT	M0 Chx, IF-RT 54 Gy (surgery if not CR before RT) M+ Chx, CSI 30 Gy, IF-RT/boost 24 Gy ([29])	M0 ACNS 0122: Chx, CSI 36 Gy, boost 18 Gy ACNS 1123: Chx, WVI / 30,6 Gy, boost 23.4 Gy M+ ACNS 0122: CSI 36 Gy, boost 18 Gy ([28], [39])
Teratoma	No detailed recommendations (register)	No detailed recommendations

Abbreviations

NGGCT: non-germinomatous germ cell tumors

CSI: craniospinal irradiation

WVI, whole ventricular irradiation, F-RT: focal irradiation

Chx: chemotherapy

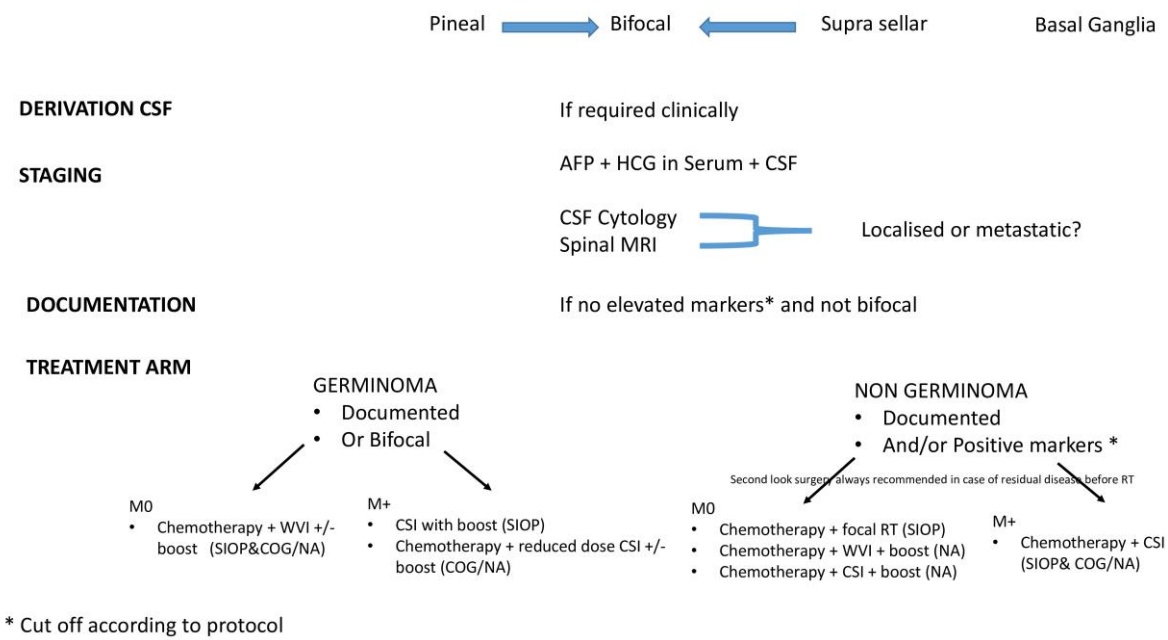
Table 4: Strategy for non-germinomatous intracranial germ cell tumors

				Patterns of Relapse			
Study	Treatment	PFS (5-Year)	OS (5-Year)	Local	Distant	Combined	Markers Alone
ACNS0122 (N=48)	Induction (6 cycles) Carboplatin/Etoposide alternating with ifosfamide/Etoposide Followed by CSI (36 Gy) Plus Tumor Bed Boost (54 Gy)	92%	98%	9	4	0	2
SIOP'96 (N=116)	Induction (4 cycles) With Cisplatin, Etoposide, and Ifosfamide Followed by IF RT (54 Gy)	72%	82%	14	9	6	0
ACNS1123 (N=66 CR/PR)	Induction (6 cycles) Carboplatin/Etoposide alternating with ifosfamide/Etoposide Followed by WVI (30.6 Gy) Plus Tumor Bed Boost (54 Gy)	88% (4-Year)	92% (4-Year)	0	7	1	0

M0, localized disease; CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival; CSI, craniospinal irradiation; IF, involved field; WVI, whole ventricular irradiation

*CR/PR data not captured/available for M0 patients post-induction;

Figure 1



* Cut off according to protocol

Figure 2

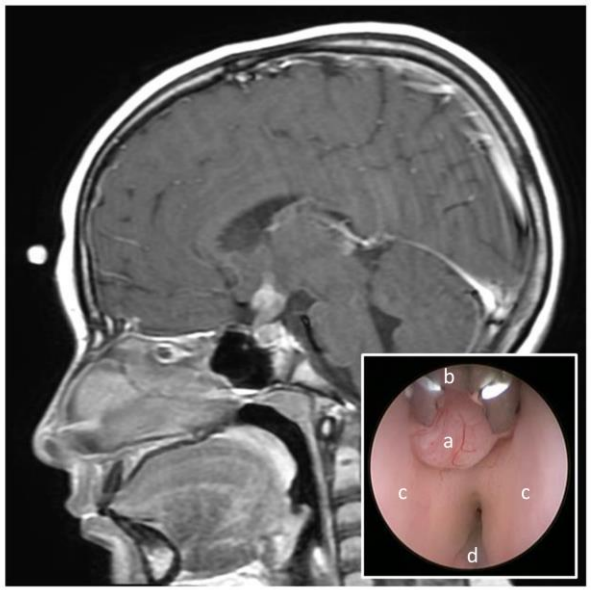


Figure 3