Growth Hormone Deficiency in Childhood Germ Cell Tumor Survivors

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Abstract

Background: Intracranial germ cell tumor (iGCT) survivors have multiple risk factors for growth hormone (GH) deficiency, a commonly reported late effect in childhood cancer survivors. The objective of this study is to examine the prevalence of GH deficiency among childhood iGCT survivors.

Methods: Participants were previously enrolled in the Germ Cell Tumor Epidemiology Study (GaMETES), a case-parent triad study by the Children's Oncology Group registries. A subset of these participants consented to this late effects follow-up study. Questionnaire responses or medical records were available for 129 participants.

Results: Forty-five percent had GH deficiency. Eighteen percent had GH deficiency predating the iGCT and 27% developed it within a median of 19 months. Younger age, suprasellar location, and higher radiation doses were associated with GH deficiency as a late effect.

*Conclusions***:** GH deficiency is highly prevalent as an early clinical sign for an iGCT and frequently arises as an early late effect.

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List of Abbreviations and Acronyms

AYA	Adolescent Young Adult
CCRN	Childhood Cancer Research Network
CCSS	Childhood Cancer Survivorship Study
CI	Confidence interval
COG	Children's Oncology Group
CSI	Craniospinal irradiation
GaMETES	Germ Cell Tumor Epidemiology Study
GCT	Germ cell tumor
GH	Growth hormone
GHD	Growth hormone deficiency
HIPAA	Health Insurance Portability and Accountability Act
HP	Hypothalamic-pituitary
iGCT	Intracranial germ cell tumor
NGGCT	Non-germinomatous germ cell tumor
NIH	National Institutes of Health
OR	Odds ratio
SJLIFE	St. Jude Lifetime Cohort Study

Introduction

Germ cell tumors (GCTs) are a rare heterogenous group of cancers arising from primordial germ cells. They often arise from gonadal sites but in children, 40-55% manifest at extragonadal sites along the midline, with intracranial locations being the most common.[1–3] It is hypothesized that the variation in tumor site is attributed to abnormal germ cell migration and apoptosis during gonadal development.[4] In addition to variable location, GCTs are comprised of cells of many different histological subtypes, reflecting variable stages of cell differentiation at the time of malignant transformation.

Germ cell tumors are rare, with an annual incidence of 3.9 cases per million in the United States. This accounts for 3% of all childhood cancers and 15% of all adolescent cancers.[5] They are most commonly diagnosed in early childhood (under age 1) or in adolescence (age 15-19 years).[6] With modern therapy, survival rates have significantly improved across the last several decades. For those diagnosed with a GCT between 1996-2000, 5-year overall survival rates approaches 90%.[6]

As of 2011, GCT survivors account for the 3rd largest group of childhood cancer survivors living greater than 5 years from diagnosis, and the largest group living beyond 20 years from diagnosis.[7] Despite this, late effects experienced by this large group of long-term survivors is poorly understood. Historically, they were excluded from the largest long-term follow up studies conducted by the Childhood Cancer Survivorship Study (CCSS).[7] Subsequent studies mostly focused on late effects by anatomic location rather than by histology. For

example, intracranial GCTs (iGCTs) are more frequently studied among childhood brain tumors rather than among GCTs as a group, and outcomes are extrapolated from studies of these heterogenous groups.[8–10] Therefore, there is an important gap in knowledge regarding late effects specific to GCT survivors.

Longitudinal studies of childhood cancer survivors demonstrated that up to 67% experienced at least one hormonal disorder, making endocrinopathies one of the leading treatment-related late effects. [8,11–15] The hypothalamic-pituitary (HP) deficiencies are common endocrinopathies that manifest as short term late effects, arising within 5 years after treatment exposure.[8,9] The most common of these is growth hormone (GH) deficiency.[8,10,11,16] According to the SJLIFE cohort study of childhood cancer survivors treated with cranial radiation, the prevalence for GH deficiency was 46.5%.[16]

There is a strong dose-dependent relationship between cranial radiation and subsequent development of GH deficiency, with higher cumulative doses associated with greater risk for GH deficiency.[8,10,11,16–19] Additional risk factors for treatment-related GH deficiency include younger age at exposure, longer follow-up time, suprasellar tumor location, and craniospinal irradiation (CSI).[8,13] GH deficiency left untreated can cause growth delay in children, metabolic issues in adulthood, and negatively impact quality of life.[20–23] Fortunately, GH deficiency can be treated with hormone replacement therapy.

Childhood iGCT survivors are of particular interest as this group has numerous risk factors for GH deficiency. Recall that GCT diagnosis has a bimodal age distribution with peaks in early childhood and in adolescence, critical

time periods for growth and pubertal development.[6] Intracranial GCTs can arise in various sites within the brain, with about one-quarter arising from a suprasellar location where the pituitary gland resides.[1,13,24] The majority of iGCT patients are treated with cranial radiation, consisting of whole ventricular irradiation with a boost to the primary site, and sometimes CSI. Contemporary treatment regimens have aimed at reducing radiation-related toxicities by lowering cumulative radiation doses based on tumor response to neoadjuvant chemotherapy, hyper-fractionating treatments, and reducing radiation volume. Treatment-related hormone deficits have been evaluated only among adolescents and young adults with iGCTs but not in younger children.[13]

The success of modern multimodal therapy for GCTs has resulted in an increasing number of survivors from childhood GCT. The improved survival rates do come at the cost of late effects. Thus, there is an urgent need to better understand treatment-related toxicities that can have lasting sequalae on the largest group of long-term childhood cancer survivors. To our knowledge, there are no studies evaluating GH deficiency among childhood iGCT survivors treated in the United States. Therefore, the primary objective of this study is to examine the prevalence of GH deficiency, the most common HP deficit, in childhood iGCT survivors. Our secondary objective is to identify the risk factors related to therapy-induced GH deficiency. Exploratory aims include defining the duration of time from GCT diagnosis to the development of GH deficiency and the time to initiation of hormone replacement therapy.

Methods

Study Population

This is a prospective cohort study utilizing the resources of the Germ Cell Tumor Epidemiology Study (GaMETES), which is a case parent triad study conducted using the Children's Oncology Group (COG) Childhood Cancer Research Network (CCRN).[25] A full description of the GaMETES study has been previously published.[26] Briefly, 866 individuals with a GCT diagnosed in any anatomic location at age of 0-19 years and between 2008-2015 were enrolled in the study. The majority of participants in the GaMETES study (95%) consented to be contacted for future research studies. To date, we have consented 369 individuals to participate in this late effects study. Of these individuals, 284 (77%) have completed an online questionnaire and medical records are available for 201 cases (54%). This study was approved by the Institutional Review Board at the University of Minnesota.

Questionnaire

Following consent, participants and/or their parents were provided with a secure link to a REDCap survey. Materials developed for the Childhood Cancer Survivor Study were adapted and used to collect information on current health status, medication use, physical measurements, health behaviors, quality of life and school/employment history. For cases who are under 18 years of age at contact, we asked the parent to complete the questionnaire and cases who have reached the age of 18 completed a self-administered version.

Medical Record Review

As part of the consent process, we obtained HIPAA authorization from participants to collect treatment records and updated health history information from the individual COG institutions as well as from institutions reported in the questionnaire. At the time of enrollment cases are asked to name all treating hospitals and clinics. Following release authorization for medical information, site-specific authorizations to obtain these records are prepared and then faxed to these facilities by study staff. For this project, medical records were reviewed for tumor characteristics, treatment exposures, and hormone deficiencies. Data was abstracted from the medical records by two individuals and discrepant data was adjudicated. Self-reported questionnaire responses were validated against the medical records.

Variables

The primary outcome of interest for this analysis was growth hormone deficiency. Growth hormone status was abstracted from the medical records and validated against questionnaire responses. GH deficiency was further divided into those with GH deficiency prior to GCT diagnosis and those who developed GH deficiency after GCT diagnosis.

Risk factors included patient, tumor, and treatment exposures. Patient characteristics were available for all participants. Tumor characteristics were available from pathology reports provided for all individuals as part of the CCRN

protocol. Treatment data was obtained from medical records and was available for 95 individuals.

For iGCTs, tumor histology was categorized as either germinoma or non-germinomatous GCT (NGGCT) following the standard groupings used to determine treatment.[24] Primary intracranial tumor site was divided into suprasellar region (suprasellar or bifocal) versus other (pineal, thalamic, spinal, other) since the hypothalamus and pituitary gland that regulate growth hormone reside within the suprasellar space. Cumulative radiation doses were grouped into low (<38 Gy), medium (38-51 Gy), and high (51+ Gy) dose categories. The cutoffs for each category were determined based around target radiation doses per COG response-stratified guidelines.[27,28]

Statistical Analysis

Statistical analysis was performed using SAS Studio software. Chi-squared analysis was used to identify patient, tumor, or treatment exposure variables that were associated with GH deficiency. Logistic regression models were conducted to estimate odds ratios for GH deficiency.

Results

To date, 284 participants have completed the late effects study questionnaire. One-hundred and fourteen responses were from survivors of intracranial, 48 from extragonadal, 48 from testicular, and 74 from ovarian GCTs. Only one survivor with an extragonadal GCT reported having GH deficiency and none of the survivors of testicular or ovarian GCTs reported GH deficiency. Hence, all (except for 1) who self-reported GH deficiency had an intracranial GCT (Figure 1).

We received a total of 201 medical records, including 95 from intracranial GCTs and 106 from extracranial GCTs. Because GH deficiency was observed almost exclusively in the iGCT cases, we have restricted the remaining analyses to this group. In total, this analysis includes 129 iGCT survivors with either questionnaire data (n=114) and/or medical record data (n=95). Eighty of these belonged to participants who responded to the questionnaire and for which records were available; therefore, results could be validated between the two sources (Figure 2). Thirty-four had questionnaire responses only, and 15 had medical record data only.

Patient and tumor characteristics for the 129 participants are shown in Table 1. Thirty-two (24.8%) were diagnosed with an iGCT under the age of 10 years and 97 (75.2%) were diagnosed over age 10. There was a male predominance (n=92, 71.3%) and the majority were of Non-Hispanic White ethnicity (n=92, 71.3%). Eighty-two (68.3%) of these tumors were germinomas and 38 (31.7%) were NGGCTs. Thirty-nine (41.9%) tumors were from the

suprasellar region (suprasellar or bifocal) and 54 (58.1%) were from other intracranial sites (pineal, thalamic, spinal, and other). Eleven (13.4%) had metastatic disease at the time of primary tumor diagnosis.

Treatment exposures are shown in Table 2. Nearly all participants underwent a surgery but of variable extent; some received biopsies only, others subtotal resection, and some gross total resections. Seventy-three (81.1%) participants received upfront chemotherapy and 17 (18.9%) did not. Most participants with germinomas were treated with 2-4 cycles of neoadjuvant chemotherapy with a platinum agent and Etoposide, and those with NGGCTs were treated with 6 cycles of Ifosfamide/Etoposide alternating with cycles of a platinum and Etoposide. All but 5 received radiation therapy consisting of whole ventricular radiation with a boost to the primary site with or without CSI. Twenty-four (66.7%) participants received conventional radiation and 12 (33.3%) received proton beam radiation. Thirty-one participants received low doses of cumulative radiation, 16 received medium, and 20 received high doses. A small subset of participants received additional chemotherapy as a part of a preparative regimen for autologous stem cell transplant or for salvage therapy (n=8).

Growth hormone deficiency was the primary outcome of interest. Growth hormone status was obtained from the medical records and validated against questionnaire responses resulting in 87 evaluable cases. Of these, 43 (49.4%) had GH deficiency and 44 (50.6%) did not.

Of the 43 cases with GH deficiency, dates for GH diagnosis were available for 35. GH deficiency predated GCT diagnosis in 14 of 35 (40.0%) and 21 (60.0%) developed GH deficiency after GCT diagnosis (Figure 3). Analysis was done separately for those with GH deficiency before and after GCT diagnosis.

GH deficiency predating GCT diagnosis

Chi-square analysis was conducted comparing cases with GH deficiency before GCT diagnosis to cases that developed GH deficiency after GCT diagnosis and those with intact GH regulation. (Table 3). Males and those who would develop tumors in the suprasellar region were more likely to have GH deficiency prior to being diagnosed with the GCT ($p=0.05$ and $p=<0.0001$, respectively). GH deficiency was diagnosed within a median of 4.5 months prior to diagnosis of the GCT in this group.

GH deficiency after GCT diagnosis

Logistic regression analysis was performed to estimate the odds for GH deficiency after cancer diagnosis. Variables included in the model were selected based on statistically significant p-values from the contingency table analysis or previous associations reported in the literature, and included age, primary tumor site, and radiation dose. After adjusting for each of these variables, suprasellar tumor location (OR 33.25, 95% CI 3.41-323.76) and age younger than 10 years (OR 20.10, 95% CI 1.30-310.09) were found to be strongly associated with GH deficiency. The odds ratio for GH deficiency was also higher among those

treated with medium doses of radiation compared to low dose (OR 14.25, 95%CI 1.11-182.46), and for high compared to low dose (OR 6.14, 95% CI 0.46-82.60) but these did not reach levels of statistical significance. The median time from GCT diagnosis to GH deficiency detection was 19.0 months. Seventeen were treated with GH replacement this was initiated within a median of 2.0 months. None of the participants treated with GH replacement have developed a secondary malignancy at the time of this evaluation (median follow up of 6.7 years). One had recurrence of the primary NGGCT after initiation of GH replacement. This individual was started on GH therapy 29 months after the primary NGGCT, and later developed recurrent disease after another 50 months. GH therapy was subsequently discontinued, and this individual underwent numerous courses of salvage therapy for ultimately multiply recurrent disease.

Discussion

Our study sample was representative of the broader GaMETES cohort. The age, sex, and histology distribution for iGCTs was very similar between our smaller sample and the full cohort. There is an over-representation of Non-Hispanic Whites and under-representation of Hispanic and other/mixed races in our sample compared to the full cohort. This may reflect the differences in groups who consented for future contact as well as delayed incorporation of Spanish-translated consent forms.

The overall prevalence for GH deficiency in our study of iGCTs was 45.3% (43 of 95). This approximates the estimated point prevalence for GH deficiency reported as 47.5% among adult survivors of childhood cancers treated with cranial radiation >18Gy in the SJLIFE cohort.[16] A large percentage of the iGCT survivors with GH deficiency were diagnosed prior to the tumor diagnosis (17.7%), suggesting that GH deficiency can be caused by the disease process. Risk factors for developing GH deficiency after diagnosis of iGCT included younger age at diagnosis, tumor location in the suprasellar region and higher doses of radiation therapy, although risk estimates were imprecise due to small sample sizes.

We found that 17.7% of the iGCT survivors had GH deficiency prior to detection of the tumor. Thus, GH deficiency was not a late effect of treatment in these cases but rather likely an early sign of disease. Our finding was very similar to the 16% reported in a study of adolescents/young adults (AYA), between 15 and 39 years old, with iGCTs treated between 1975-2015.[13] This

suggests that age is not significantly associated with pre-treatment GH deficiency. Other studies reported endocrinopathies as a common manifestation for suprasellar intracranial tumors.[29,30] We redemonstrate this with our finding that the suprasellar tumor site was most strongly associated with early manifestation of GH deficiency. This brings to the forefront the importance of completing a thorough evaluation for a brain tumor in children who present with growth failure and GH deficiency. GH deficiency was diagnosed within a median of 4.5 months (range 0-28 months) prior to diagnosis of the GCT in this group. Another study showed that growth deceleration predated radiologic GCT detection by as long as 1.1 years, though this included only 12 iGCTs.[31] While growth hormone deficiency can rarely be a presenting sign for an intracranial neoplasm, other endocrinopathies are more common, especially diabetes insipidus (DI).[30,31] DI was not specifically investigated in this study as it is not considered a late effect, but at least 15 cases had DI preceding iGCT diagnosis, 6 of whom had both DI and GH deficiency and 9 with DI but no GH deficiency before tumor detection. This highlights the need for ongoing close follow up with attention to cancer in children with endocrinopathies even if there was no evidence for a tumor at the time of the initial evaluation.

Our prevalence rate for GH deficiency as a late effect was 26.6% (21 out of the evaluable 79). This is higher than the 12.5% reported among childhood brain tumor survivors who were treated with >30 Gy radiation.[8] This might be attributed to a different distribution of radiation treatment doses that was used for the heterogenous group of brain tumors in that study compared to the more

uniform population in our study. Our prevalence was also higher than the 1% reported among AYAs with iGCTs.[13] This further supports our finding that younger age at exposure is significantly associated with higher odds for GH deficiency. We additionally found that suprasellar tumor location was very strongly associated with GH deficiency after adjusting for radiation. This may be attributed to the local destruction of the pituitary gland by the tumor itself compounded by radiation targeted at this site. Our findings are consistent with other studies that have shown that younger age and suprasellar tumor location to be major risk factors for GH deficiency as a late effect.[8,11,12,16,17,32]

The dose dependent effect of cranial radiation on GH deficiency has been repeatedly demonstrated in the literature. GH deficiency has been reported as a late effect for patients who received as little as 18 Gy of craniospinal radiation[16,33] and risk increases in a dose-dependent manner.[10,11,13,17–19,32] However, variable dose cutoffs have been used to determine low versus high doses for radiation. In this study, the radiation dosing categories were grouped around target radiation doses per COG guidelines. According to the most common treatment regimens during the study period, radiation doses were selected based on tumor response to neoadjuvant chemotherapy and the use of CSI was minimized. Therefore, germinoma treatment included either 30, 36, or 45 Gy of cranial radiation (per ACNS0232 and ACNS1123)[27] and NGGCT treatment consisted of either 45 or 54 Gy of cranial radiation (per ACNS0122 and ACNS1123).[28] The dosing ranges we selected were expanded to capture those who received slightly above or below those targets. We also demonstrated a dose dependent response with

higher odds for GH deficiency among those treated with higher doses compared to those treated with lower doses. Our analysis showed a stronger association for GH deficiency when comparing cases treated with medium versus low dose rather than for those treated with high versus low dose. This inverse association is likely insignificant due to the small sample sizes in these groups.

Like other studies of childhood brain tumor survivors who were treated with cranial radiation, the median time from cancer to GH deficiency was short.[8,9] In our study, the median time to GH deficiency was only 19 months. However, this timeframe may be over-estimated as it is dependent upon when providers chose to evaluate for GH deficiency. From the review of medical records, we observed that many providers did not initiate evaluation for GH deficiency until the patient had completed their cancer-directed therapy, which spanned anywhere from 2-6 months or longer. Therefore, it is possible that GH deficiency could have been present sooner but went undetected and untreated. Regardless, the current expert recommendation for when it is safe to initiate GH therapy remains controversial. Previous studies suggested an association between GH replacement and secondary neoplasms; however, this association was not demonstrated in more recent studies of childhood cancer survivors.[20,34,35] We further contribute to this evidence as none of the participants treated with GH replacement in our study developed a secondary malignancy within our median follow up period of 6.7 years. Only 1 had recurrence of the primary tumor.

Despite this, the general practice is still to delay GH replacement therapy until a patient is at least 12 months past completion of cancer-directed

therapy.[36,37] Consistent with these standard practices, many of the participants in our study were not evaluated for GH deficiency until they completed cancer treatment, and those who were diagnosed prior to 12 months off therapy delayed initiation of GH replacement until that point. The median time from GH deficiency until treatment initiation was 2 months, but the range spanned across 4 to 82 months. Further studies are needed to define the relationship between current generations of GH replacement agents and the risk for secondary malignancies as childhood cancer survivors could benefit from earlier initiation of GH replacement.

Limitations to this study

There were several limitations to this study. We did not have sufficient data or expertise among the study team to detect the impact of varying modalities of radiation delivery. Our analysis of treatment exposures was restricted to the number of participants for which we had the available data. Our sample size for those who developed GH deficiency as a late effect was small after excluding those with insufficient data on GH status and those who developed GH deficiency predating cancer. Dates for end of radiation therapy were missing for a subset of the participants, restricting our ability to attribute GH deficiency to radiation rather than to all cancer-directed therapies. This also limited our ability to describe the time from end of radiation to start of GH deficiency. Lastly, our analysis is restricted by the short follow up time of 6.7 years.

Conclusions

In conclusion, 45.3% of evaluable iGCT survivors had GH deficiency but 17.7% already had GH deficiency at the time of their GCT diagnosis. Odds for GH deficiency among this group was highest for those with a tumor located in the suprasellar region, suggesting that local damage to the hypothalamus and pituitary gland by the tumor is the main source for GH deficiency. For the subgroup that developed GH deficiency after GCT diagnosis, age, suprasellar tumor location, and dose dependent radiation were strongly associated with GH deficiency and GH deficiency developed within a median of 19 months from cancer diagnosis. Therefore, the prevalence for GH deficiency as a late effect among childhood iGCTs is 26.6% and is diagnosed soon after cancer diagnosis. Additional investigation is needed to address earlier detection and treatment for this highly prevalent late effect in iGCT survivors.

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Figure 1: Distribution of questionnaire responses

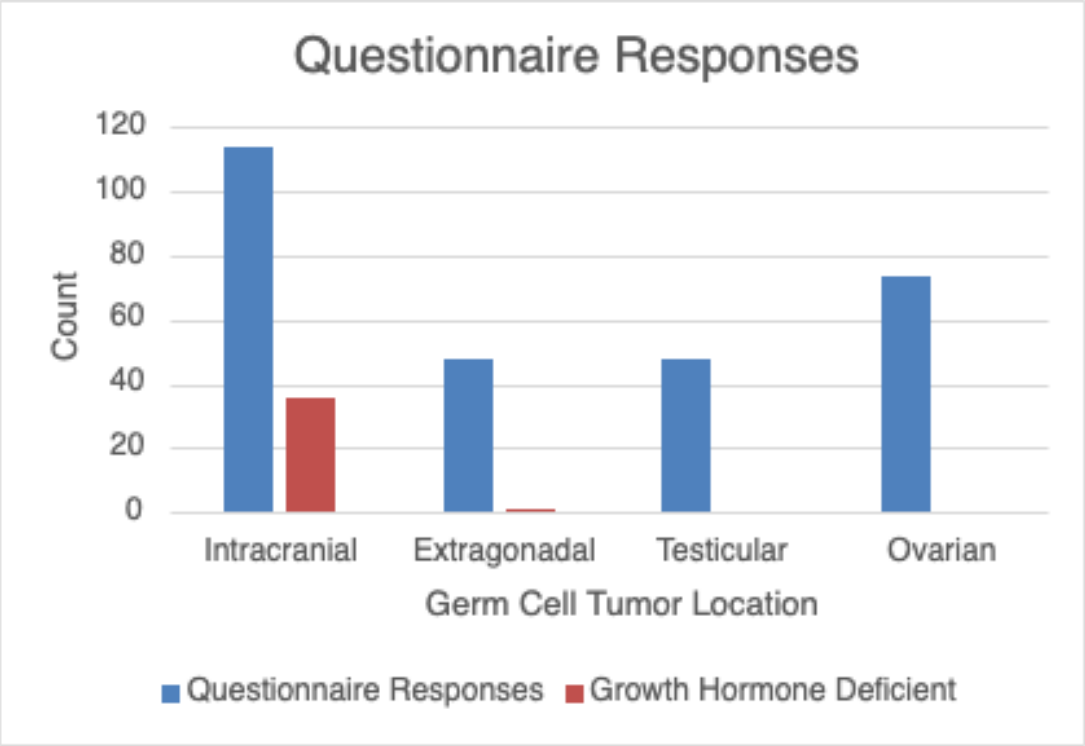

Figure 2: CONSORT diagram for study population

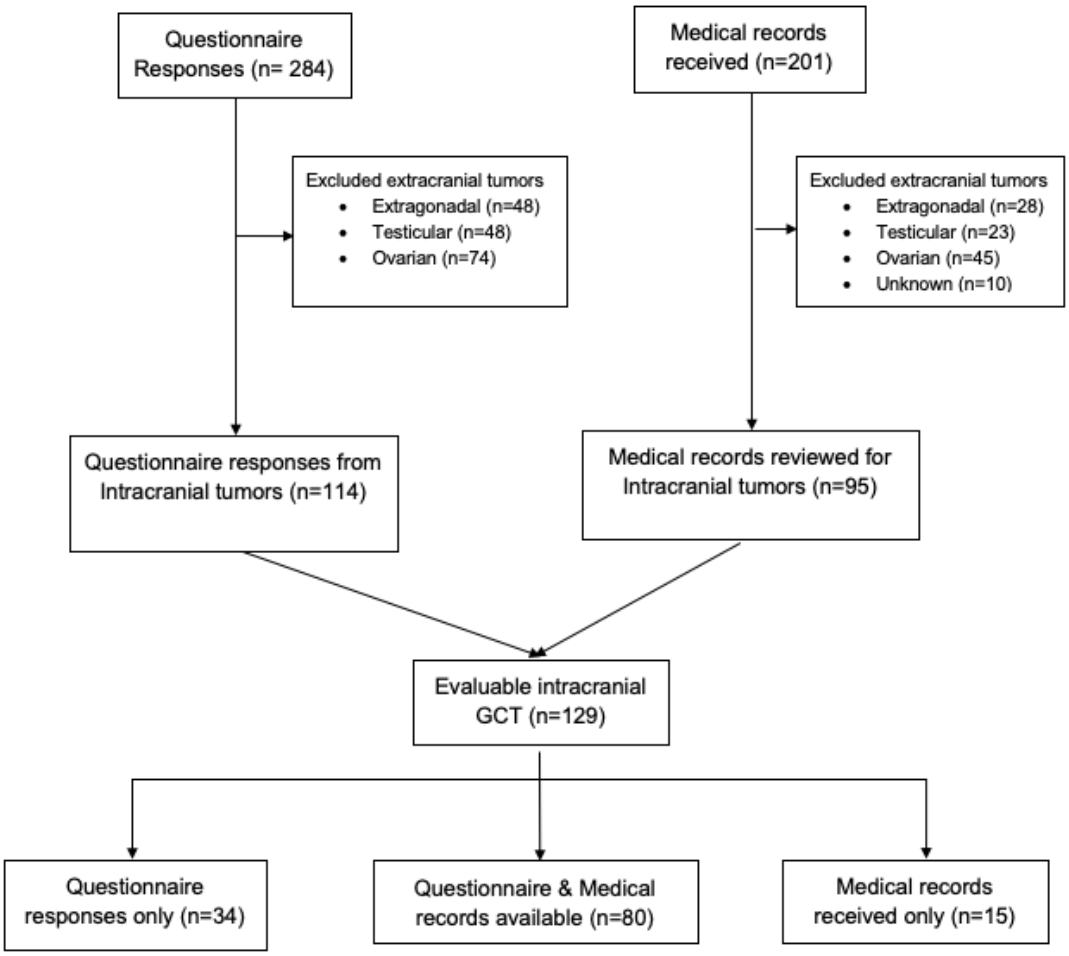

Table 1: Characteristics of the iGCT Study Population

	Frequency (%)
Age at diagnosis	
<10 yrs	32 (24.8)
10 + yrs	97 (75.2)
Median age	13.3 years
Sex	
Male	92 (71.3)
Female	37 (26.7)
Race/Ethnicity	
Non-Hispanic White	92 (71.3)
Black	4 (3.1)
Hispanic	10 (7.8)
Asian/Pacific Islander	9 (7.0)
Other/Mixed	14 (10.9)
Histology*	
Germinoma	82 (68.3)
NGGCT	38 (31.7)
Primary tumor site *	
Suprasellar	39 (41.9)
Other	54 (58.1%)
Metastatic disease at diagnosis*	
Yes	11 (13.4)
No	71 (86.6)
Total	129

These characteristics are reported on full study population (n=129) except where denoted due to missing information. The missing data was only available for the subset with available medical records.

*Tumor histology missing for n=9, primary tumor site missing for n=36, metastatic disease status missing for n=47.

Table 2: Treatment exposures

	Frequency (%)
Surgery*	
Yes	89 (96.7)
No	3 (3.3)
Chemotherapy**	
Yes	73 (81.1)
No	17(18.9)
Radiation therapy***	
Yes	85 (94.4)
No	5 (5.6)
Autologous stem cell transplant (ASCT)****	
Yes	8 (8.6)
No	85 (91.4)
Total	95

Treatment exposures were reported on the subset of participants with medical records available (n=95). Some data was missing as they were not reported in the medical records we received.
*Surgery missing for n=3, chemotherapy missing for n=5, radiation therapy missing for n=5, ASCT missing for n=2

Figure 3: Growth hormone deficiency flow chart

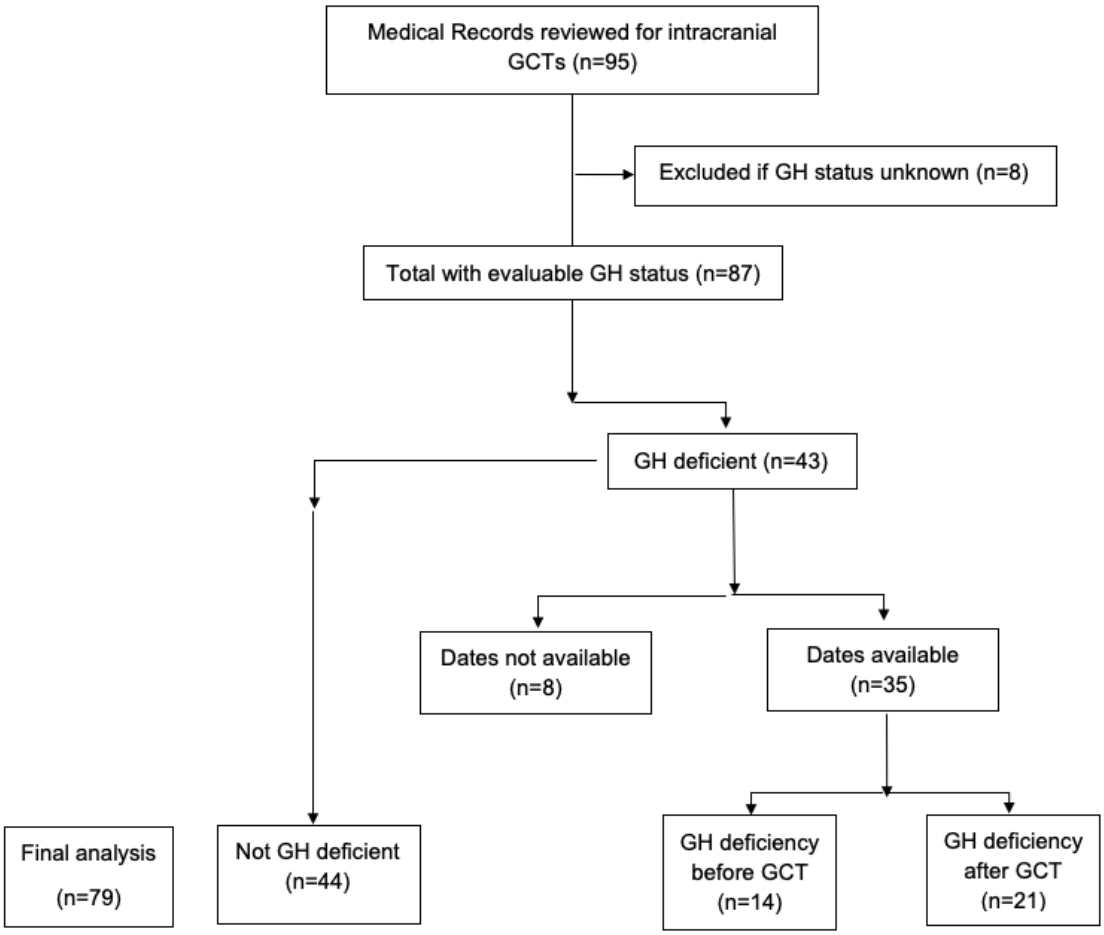

Table 3: GH deficiency before and after GCT diagnosis

	No GHD (%)	Pre GHD (%)	Post GHD (%)	Chi sq p-value Pre vs No GHD	Chi sq p-value Post vs No GHD
Total	44 (55.7)	14 (17.7)	21 (26.6)		
Age at diagnosis				0.12	0.08
<10 yrs	5	4	6		
10+ yrs	39	10	15		
Sex				**0.05**	0.36
Male	34	7	14		
Female	10	7	7		
Race/Ethnicity				0.78	0.55
Non-Hispanic White	33	10	17		
Black	1	0	1		
Hispanic	3	2	0		
Asian/Pacific Islander	5	2	1		
Other/Mixed	2	0	2		
Primary tumor site				**<0.0001**	**<0.0001**
Suprasellar	5	13	15		
Other	38	1	6		
Histology				0.09	0.75
Germinoma	29	12	13		
NGGCT	13	1	7		
Surgery				N/C	**0.04**
Yes	43	13	19		
No	0	1	2		
Chemotherapy				N/C	0.63
Yes	36	11	17		
No	6	3	4		
Radiation				N/C	0.14
Yes	37	14	21		
No	4	0	0		
Radiation modality				N/C	0.88
Proton	6	3	2		
Conventional	14	4	4		
Cumulative Radiation Dose				N/C	0.13
Low dose <38 Gy	16	8	5		
Medium dose 38-51 Gy	4	4	6		
High dose 51+ Gy	9	0	7		
ASCT				N/C	0.14
Yes	3	0	4		
No	41	14	17		

Pre GHD = GHD diagnosed before iGCT, Post GHD = GHD diagnosis after iGCT
Analysis completed on n=79, N/C = not calculated

Table 4: Odds Ratios for GH deficiency after GCT dx

Risk Factors	Post GHD	No GHD	Unadjusted odds ratio (95% CI)	Chi Sq p-value	Adjusted odds ratio (95% CI)	Chi Sq p-value
Age at diagnosis			10.77 (1.14,101.72)	0.04	20.10 (1.30, 310.09)	**0.03**
<10 yrs	6	5				
10+ yrs	15	39				
Tumor Site			9.60 (2.43, 37.94)	0.001	33.25 (3.41, 323.76)	**0.003**
Suprasellar	15	5				
Other	6	38				
Radiation Dose High vs Low			2.49 (0.61,10.18)	0.84	6.14 (0.46,82.60)	0.66
Low <38 Gy	5	16				
High 51+ Gy	7	9				
Radiation Dose Med vs Low			4.80 (0.95, 24.14)	0.13	14.25 (1.11, 182.46)	0.10
Low <38 Gy	5	16				
Med 38-51 Gy	6	4				

*Surgery was removed from the adjusted and unadjusted models as it was too unstable of a variable with all but 2 having surgery.