A multi-disciplinary Delphi method to identify consensus in the management of intracranial germ cell tumours

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Abstract

The management of intracranial germ cell tumours (ICGCT) is complex. It was agreed at the 2013 Third International ICGCT Symposium (Cambridge, UK) to undertake a multi-disciplinary Delphi process to identify consensus in their management. Seventy-seven delegates from the Symposium were selected as suitable experts and were invited to participate in the Delphi survey; 64 (83%) responded. Those invited represented multiple disciplines from the Far East, Australasia, Europe and America. Thirty-eight consensus statements, encompassing aspects of work-up, staging, treatment and follow-up, were prepared. To achieve consensus, statements required ≥70% agreement from ≥60% of respondents. Overall, 34/38 statements (89%) met consensus criteria. This international Delphi approach has defined key areas of consensus which will guide and streamline future management of ICGCT. In addition, it has identified areas of different understanding and practice internationally which should be the focus of future collaborative studies. Such efforts will likely translate into improved patient outcomes.

Keywords: consensus; Delphi; GCT; germ cell tumour; germinoma; intracranial; ICGCT; non-germinomatous germ cell tumour (NGGCT)

Background

Intracranial germ cell tumours (ICGCTs) represent a rare and histologically heterogeneous group of predominantly midline neoplasms. Incidence varies markedly across continents, with North American (SEER-CBTRUS) and international (IARC) data[1] showing overall incidence rates of 0.6/million in the United States (US), 1/million in Europe, to 2.7/million in Japan[2]. The classification systems and terminology used to describe ICGCTs is controversial. Histologically, these tumours are often segregated into three groups, namely pure germinoma, teratoma and 'non-germinomatous' germ cell tumours (the latter will subsequently be referred to as NGGCT throughout). NGGCT are often mixed tumours, and include those with yolk sac tumour (YST), embryonal carcinoma (EC) and/or choriocarcinoma (CHC) components[2]. Confusingly, NGGCT may also contain germinoma and/or teratoma which challenge some classification systems.

Diagnostic methods also vary, with some countries relying on surgical (histological) verification for diagnosis upfront, often with a gross total resection rather than biopsy[2]. Others diagnose GCTs without primary surgery based on tumour marker elevation in the presence of consistent radiological appearances. The tumour markers utilised for this purpose are alpha-fetoprotein (AFP; typically raised in the presence of YST) and human chorionic gonadotrophin (HCG; typically raised in the presence of CHC). Elevation of AFP or HCG above a defined threshold in either the serum or cerebrospinal fluid (CSF) is taken to indicate the presence of these specific malignant components and confirms the diagnosis of a 'secreting' NGGCT. It should be noted, however, that marker thresholds vary across continents, based on historical experience. Surgical biopsy is reserved for 'marker-negative' patients, where neither AFP nor HCG is raised beyond the threshold[2].

Classification systems for ICGCTs reflect the excellent overall survival (OS) for patients with germinoma and the inferior survival for those with NGGCTs. Three risk groups are identified in Japanese treatment stratifications, namely pure germinoma, intermediate-prognosis ICGCTs and poor-prognosis tumours, the latter two groups comprising mixed malignant NGGCTs[3]. Historically, in Europe and America, two risk groups were identified (germinoma and NGGCT). More recently, patients with diagnostic serum or CSF AFP level more than 1000 IU/L have been identified in Europe as a high-risk NGGCT group[4], for which the benefit of treatment intensification is currently being tested. Final results of the Children's Oncology Group NGGCT trial (ACNS 0122) including children from North America and Australia are due to be reported shortly[5].

Not surprisingly, given these differing diagnostic and classification approaches, the evolution of treatment by neurosurgeons, radiation oncologists, and medical or pediatric oncologists has resulted in diverse treatment strategies[2]. Principles of treatment include the necessity to deliver radiotherapy (RT) in all cases of germinoma and NGGCT in order to achieve good cure rates, except in infants and very young children where a chemotherapy only approach is often attempted in order to avoid the devastating long-term sequelae of RT. Given inferior survival in NGGCT, higher RT doses have been employed with less scope for the dose reductions that have been possible for pure germinoma[2]. Chemotherapy has been used for both germinoma and NGGCT; this has facilitated reductions in RT fields and/or doses in germinoma by some groups, with the aim of reducing or sparing late-effects of treatment[2]. Generally, the mainstay of treatment for teratoma without malignant transformation is surgery which is curative for the majority of patients if a gross total resection can be achieved[2].

As a consequence of these complexities, which include relative difficulty of surgical access, the lack of diagnostic markers for some cases, response to both chemotherapy and RT, and

the frequent presence of endocrine complications, optimal management of patients with ICGCTs necessitates the input of multiple disciplines and a collaborative approach to care[2].

In addition, the paucity of ICGCT specimens available for molecular analysis has hampered our understanding of the pathogenesis of ICGCTs. Recently, this has been addressed by the formation of consortia facilitating the publication of key biological findings[6,7]. In the future, the aim will be to incorporate molecular markers into clinical trials of this rare disease, in order to assist diagnosis and inform prognostic and treatment strategies[2].

As a result of these challenges, there have now been three international symposia focussing specifically on ICGCT management, with a fourth taking place in Tokyo in 2015. The First Symposium was held in Kyoto, Japan, in 2003, followed by the Second in Los Angeles, US in 2005[2]. A number of the key controversies in the management of ICGCTs were highlighted during these meetings. Outputs from these early symposia, for example, included the reporting of surgical management guidelines[8]. The aims of the Third Symposium, held in Cambridge in 2013, were to further increase our clinical and biological understanding of ICGCTs, to overcome differences where necessary and to reach consensus where possible[2]. In total, 117 delegates attended from 25 countries across five continents, representing the multidisciplinary specialities involved in the management of ICGCTs. From these initial discussions, a committee was formed (MJM, UB, RN, JF, MM, JCN) which developed Delphi consensus statements[9,10], covering wide-ranging aspects of ICGCT management. These were subsequently subjected to online voting by representative selected experts who attended the Third Symposium. The results of this multi-disciplinary Delphi method, and the challenges that remain, are described below.

Methods: Consensus process

There was a preliminary discussion of possible areas for international consensus at the Third International ICGCT Symposium held on the 17th - 20th of April 2013, in Cambridge, UK. In attendance were 117 delegates from five continents, including invited recognised experts in the field and those who had submitted abstracts. At the symposium, it was agreed that Delphi consensus statements[10] would subsequently be drafted. A representative committee of six individuals representing Asia, America and Europe was responsible for this process [MJM (UK), UB (Canada), RN (Japan), JF (US), MM (Japan), and JCN (UK)].

Figure 1 provides details of the consensus process. Of the 117 symposium delegates, 77 recognised experts in their respective national/international groups were invited to participate in the Delphi process. Thirty-one were from Europe (40%), 26 from Asia (34%) and 20 from America (26%). Sixty-four (83%) experts responded [25 Europe (39%); 23 Asia (36%); 16 America (25%)]; this figure was set as the initial denominator for subsequent Delphi voting. Thirty-eight consensus statements, encompassing various aspects of work-up, staging, treatment and follow-up, were prepared by the Delphi committee between December 2013 and June 2014, using Delphi consensus methodology[10]. Voting and responses were collated using a web-based survey tool (SurveyMonkey; www.surveymonkey.com). The statements were distributed for a first round of voting between October 2014 and November 2014. Participants were asked to rate each statement with four possible responses, as follows: 'I support the statement', 'I would support the statement with modification', 'I do not support the statement', as described[11] or, additionally, 'I do not have the experience in this area to be able to comment'. If respondents selected this last response, their vote did not count towards the denominator (i.e. the total number of responses recorded for that statement). In addition, a free text comments section was included below each statement to allow for suggested modifications. If a participant did not agree with the statement completely, they were strongly

encouraged to make comments to explain their rationale. If ≥70% of votes were in support of a statement from ≥60% of participants in each round of voting, it was accepted, as described[11]. Where <70% consensus occurred, statements were revised based on respondents' comments and re-distributed in a second and final round of voting between November 2014 and December 2014. Accepted statements are described below in the Results and Discussion sections. The themes and comments behind the rejection of unsuccessful statements are also summarised in the Discussion; these statements reflecting the current lack of consensus will help to focus future discussions and research.

Methods: Search Strategy and Selection Criteria

References for this article were identified through searches of PubMed relevant to the Delphi statements, particularly where areas of non-consensus were highlighted. Articles were also identified through searches of the authors' own files. In particular, where published full manuscripts were lacking in a certain area, published abstracts were considered. Only manuscripts and abstracts published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of the Delphi consensus process.

Results: Consensus statements

Fifty-seven participants (89%) voted in the first round and 29/38 statements (76%) met consensus criteria. Nine statements were revised based on participants' comments and re-distributed for voting. This included one statement that was initially accepted, but which was rewritten for greater clarity (Statement 15) and two others that were revised into a single statement (Statement 30). Forty-nine participants (77%) voted in the second round, and six of the revised statements were passed. In all, 34 statements met consensus criteria from the original 38 statements (89%) and are listed below.

- ***Description of intracranial germ cell tumours (ICGCTs)***

Statement 1. A new name(s) to describe 'non-germinomatous' ICGCTs is required.

- ***Overall therapeutic purpose***

Statement 2. The current overall aim of management in intracranial germinoma is to maintain excellent OS whilst attempting to minimise the late-effects of treatment.

Statement 3. The current overall aim of management in intracranial GCT (ICGCT) with non-germinomatous malignant components [yolk sac tumour (YST), embryonal carcinoma (EC), and choriocarcinoma (CHC)] is to improve OS.

Statement 4. All patients with ICGCT should be treated in a center with experience of managing these rare and complex tumours.

Statement 5. Multi-disciplinary team discussion involving core members (including neuroradiologists, neuropathologists, neurosurgeons, oncologists and radiation oncologists) should be the basis for all diagnostic and management decisions for patients with ICGCT.

- ***Radiological staging work-up***

Statement 6. Where MRI is available, patients with suspected ICGCT should have MRI head with at least pre- and post-contrast enhanced T1 weighted images, and sagittal MRI spine post-contrast, at the time of diagnostic work-up and subsequently during treatment and follow-up.

- ***Cytological staging work-up***

Statement 7. Where treatment protocol decisions are based on the result of CSF cytology, then CSF cytology examination at ICGCT diagnosis, once acute hydrocephalus is under control, and before treatment commences, is essential.

Statement 8: In ICGCT patients where CSF cytology is performed, lumbar CSF is preferred to ventricular CSF.

- ***Biochemical work-up***

Statement 9. All patients with possible ICGCT (based on imaging and presentation) should have serum AFP and HCG markers measured at diagnosis.

Statement 10: All patients with possible ICGCT (based on imaging and presentation) should have CSF AFP and HCG markers measured at diagnosis, unless medically contra-indicated.

Statement 11. CSF AFP and HCG markers should preferably be measured at the same time as serum markers in patients with suspected ICGCT.

Statement 12. The site from which the CSF sample was obtained for markers and cytology (lumbar/ventricular) should be clearly documented in patients with suspected ICGCT.

- ***Management of symptomatic obstructive hydrocephalus***

Statement 13. The initial surgical management of obstructive hydrocephalus in patients with presumed ICGCT is CSF diversion, regardless of the provisional tumour type or markers.

Statement 14. If CSF diversion is necessary in ICGCT patients, CSF should be taken for tumour markers (AFP, HCG) first.

Statement 15: For patients with ICGCTs, an endoscopic third ventriculostomy (ETV), where feasible, is the favoured surgical intervention for obstructive hydrocephalus.

Statement 16: For patients with ICGCTs, if ETV is not possible, then placement of an external ventricular drain (EVD), where feasible, is favoured over a permanent ventricular shunt.

- ***Diagnosis - the role of surgery***

Statement 17. Patients with AFP and/or HCG levels (serum and/or CSF) below national protocol thresholds require surgical biopsy for ICGCT diagnosis, regardless of imaging findings.

Statement 18. Patients with consistent radiological imaging and AFP and/or HCG elevation (serum and/or CSF) above nationally defined protocol thresholds do not require surgical biopsy for ICGCT diagnosis, but instead treatment may be initiated, based on the diagnosis suggested by the markers.

- ***Diagnosis - the role of histopathology***

Statement 19. The World Health Organization (WHO) classification of tumours of the Central Nervous System should be used as the current international standard for pathological classification of ICGCTs.

Statement 20. The minimum immunohistochemical panel for ICGCT diagnostic work-up should include all of the following: i) CD117/KIT (for germinoma) ii) POU5F1 (OCT3/4) (germinoma), iii) PLAP (germinoma), iv) AFP (yolk sac tumour), v) CD30 (embryonal carcinoma) and vi) HCG (CHC or syncytiotrophoblast within germinoma).

- ***Treatment for teratoma***

Statement 21. Complete surgical resection, where feasible, is the treatment of choice for intracranial mature and immature teratomas without malignant transformation.

- ***Treatment for pure germinoma***

Statement 22. Based on current knowledge, patients with intracranial germinoma should receive RT to maximise their chance of cure.

Statement 23. For localised germinoma, focal RT fields alone are insufficient, and therefore, RT should also include at least the ventricles (i.e. at least whole ventricular RT).

Statement 24. Chemotherapy is an effective strategy to reduce the dose of RT for localised germinoma.

- ***Treatment for malignant ICGCTs with non-germinomatous components***

Statement 25. All patients with ICGCTs containing malignant non-germinomatous components (i.e. NGGCTs) should receive a combination of chemotherapy and RT, to maximise their chance of cure.

Statement 26. For patients with metastatic ICGCTs containing malignant non-germinomatous components (i.e. NGGCTs), craniospinal RT should be included in the treatment plan.

Statement 27. For patients with ICGCTs containing malignant non-germinomatous components, residual disease should be surgically resected, if feasible, prior to completion of therapy.

- ***Follow-up***

Statement 28. Serum tumour markers should be monitored during treatment and follow-up for ICGCTs, even if initially negative.

- ***Management of relapsed ICGCTs following optimal first line treatment***

Statement 29. All patients with symptomatic, radiological or marker detected ICGCT relapse should be fully re-staged and assessed, prior to considering management options.

Statement 30. Relapsed germinoma patients are salvageable with variable, but not yet standardised, treatment regimens.

Statement 31. For patients with relapsed ICGCTs containing malignant non-germinomatous components (i.e. NGGCTs), who are to be treated with curative intent, high-dose chemotherapy with haematopoietic stem cell rescue should be employed, with surgery and additional RT where feasible.

- ***Banking of tissue/material for biological research***

Statement 32. Where national provision for tumour banking is available, and after appropriate ethical consents, the banking and storage of ICGCT tissue, where available (ideally fresh frozen but formalin fixed paraffin embedded if not), serum, CSF and constitutional DNA should be undertaken.

- ***Late-effects and Quality of Life (QoL) studies***

Statement 33. QoL questionnaires should be mandated in future ICGCT clinical trials.

Statement 34. Assessments for late-effects related to the tumour itself, associated hydrocephalus, surgery, chemotherapy and RT are essential components of long-term follow-up for patients with ICGCT.

Discussion

Overview. There are no previously published reports of consensus in the field of intracranial germ cell tumours (ICGCTs), a rare and heterogeneous cancer type. International discussions and collaboration, facilitated through three international ICGCT symposia, have allowed the initiation of the described consensus process using Delphi methodology[2]. The 77 delegates from the Third Symposium who were invited to take part (and the 64 who responded) were recognised experts in the field, from multiple disciplines and many different countries and continents. This ensured that the varied clinical practice observed internationally was represented equitably. Preset thresholds for the voting process also ensured that agreement was measurable and representative, lending credence and robustness to the process and reported outcomes[10]. The results, namely 34 agreed statements encompassing wide-ranging aspects of ICGCT management, including diagnostic work-up, staging, treatment and follow-up, represent a contemporary opinion by international leaders in the field and are a key foundation for further advancing ICGCT management. Key aspects of these statements are highlighted further below.

Areas of consensus. Despite varied approaches across continents in the management of these tumours, substantial areas of agreement were reached. Firstly, although it was agreed that a new term to describe 'non-germinomatous' ICGCTs was required (Statement 1), as many of these are mixed tumours and some include germinoma with other non-germinomatous components, there was no agreement on what that term might be. Participants were cognizant that suggestions such as 'mixed malignant' ICGCTs would miss pure malignant tumours, and that terms such as 'secreting' would miss embryonal carcinoma components. Pragmatically, it was suggested that it may be easier in the future to attempt to align classification systems internationally to identify a 'common language', rather than attempt to define a single term for these tumours. Participants agreed that ICGCTs are complex neoplasms (Statement 4)

requiring specialist and multi-disciplinary input and team-working through MDTs (Statement 5). There was a strong acknowledgement that due to the excellent OS for germinoma, strategies should focus on reducing the late-effects of treatment (Statement 2), whereas for ICGCTs with non-germinomatous malignant components (i.e. NGGCTs), the aim should primarily be to improve OS (Statement 3).

In diagnostic work-up, MRI is the investigation of choice for neuroimaging (Statement 6), rather than the less sensitive modality of CT scanning. While treatment is recommended in centres of excellence with access to MRI, the statement however acknowledges that in some resource-poor countries, MRI may be difficult to achieve. In addition, at diagnosis, all patients should have serum (Statement 9) and CSF (Statement 10) AFP and HCG markers measured, the only exception to the latter being if medically contra-indicated, and ideally at the same time (Statement 11). It was also agreed that CSF cytology should be performed where treatment protocol decisions are based on the results (Statement 7). The importance of clearly documenting the site from which CSF was obtained was highlighted (Statement 12), particularly as most participants preferred lumbar CSF to ventricular CSF for cytological examination (Statement 8). Whilst lumbar CSF, usually taken 10-14 days post-operatively, is considered gold standard for staging malignant brain tumours by many neurooncologists, some argue that the evidence for this approach is not strong enough. A prospective institutional trial documented diagnostic superiority of CSF cytology obtained via lumbar tap over ventricular aspiration for identifying disseminated disease; however, only three of 52 patients included in this study had germinoma[12]. The majority of cases described were medulloblastoma, located in the posterior fossa/4th ventricular region[12], where the distribution of metastases may be very different from more centrally located ICGCTs. For marker estimation, recent publications suggest that lumbar CSF is more sensitive for detecting HCG than either ventricular CSF[13] or serum[14]. In contrast, as intra-ventricular lepto-meningeal

spread of malignant cells is more common than spread to the spine in germinoma, some groups believe that ventricular CSF is superior for detecting disease in this patient group, whereas lumbar CSF should be reserved for NGGCT cases. Others would argue that ventricular CSF may result in the over-staging of only regionally disseminated germinoma patients, committing them to craniospinal irradiation, when more focal RT fields, at least including the whole ventricles, may well be sufficient for cure. Careful documentation of site of CSF sampling (Statement 8) in future clinical trials may help to answer these outstanding questions.

Participants agreed that the initial surgical management of obstructive hydrocephalus is CSF diversion (Statement 13) and that in such circumstances, CSF should be sent for AFP/HCG estimation first, at the time of surgery, but prior to tumour manipulation (Statement 14). Endoscopic third ventriculostomy (ETV), where feasible, is the favoured surgical CSF diversion procedure (Statement 15) and if not, an external ventricular drain (EVD), where feasible, is favoured over a permanent ventricular shunt (Statement 16). This statement reflects an experience shared by many experts in the field that chemotherapy, especially in the context of chemosensitive germinoma, results in rapid tumour shrinkage and re-opening of the CSF pathways within days. Hence a permanent shunt, with its inherent potential complications, can be avoided.

From a surgical perspective, all patients with AFP and/or HCG levels below national protocol thresholds require surgical biopsy (Statement 17) and conversely, those with consistent radiological imaging and AFP and/or HCG elevation above national thresholds do not require surgical biopsy for ICGCT diagnosis (Statement 18), but instead treatment may be initiated, based on the diagnosis suggested by the markers. An area for future consensus will be to try and define common marker thresholds, as it is acknowledged that these vary across continents. It was agreed that the WHO classification of CNS tumours should be used as the

current international standard for pathological classification of ICGCTs (Statement 19), although it was hoped that in the future molecular markers may contribute to a revised classification. A minimum immunohistochemical panel for ICGCT diagnostic work-up was also defined (Statement 20). However, there was no agreement for a routine second pathological review, with participants stating that with current infrastructure this should only take place where diagnostic uncertainty existed or where mandated by clinical trials.

Regarding treatment, complete surgical resection, where safely feasible, is recommended for intracranial teratomas and curative for the majority of those teratomas without malignant transformation (Statement 21). For intracranial germinoma, it was agreed that all patients should receive RT to maximise their chance of cure (Statement 22), except in infants and very young children due to the devastating neuropsychological sequelae encountered when irradiating the developing brain. Age thresholds for dismissing whole brain radiation as part of brain tumour treatment vary from <3 to <5 years, depending on institutions and countries. It was recognised that for patients with localised germinoma, at least whole ventricular RT should be used (Statement 23) and chemotherapy may be utilised to reduce the RT dose (Statement 24)[15], questions also currently being studied in ongoing trials such as the European SIOP CNS GCT II trial and the North American ACNS 1123 trial. Patients with NGGCTs should receive a combination of chemotherapy and RT, to maximise their chance of cure (Statement 25), again except for very young children. For patients with metastatic NGGCTs craniospinal RT should be included in the treatment plan (Statement 26). For NGGCT, residual disease should be surgically resected, if feasible, prior to completion of therapy (Statement 27), as residuals are associated with a worse outcome[4] and/or may represent the phenomenon of growing teratoma syndrome. The exact timing depends on treatment protocols. In Europe and America, this would most commonly occur post-chemotherapy but prior to RT, whereas in Japan this would be at the completion of both

chemotherapy and RT. In contrast, the SIOP CNS germinoma trial did not find any evidence that residual germinoma at the end of treatment is associated with inferior outcomes[16].

For relapse, all patients should be fully re-staged and assessed, prior to considering management options (Statement 29), to allow delivery of the most appropriate treatment. It was agreed that relapsed germinoma patients are salvageable with variable, but not yet standardised, treatment regimens (Statement 30), but with no clear consensus as to whether standard or high-dose chemotherapy regimens offered the best outcomes. This uncertainty, at least in part, reflects the excellent outcomes from first line germinoma treatment and the rarity of relapse. This is in alignment with a European retrospective review of treatment regimens utilised for a small cohort of relapsed germinoma patients treated within SIOP CNS GCT 96 trial at initial diagnosis[17]. Good salvage rates were seen using various standard and high-dose chemotherapeutic regimes, with no clear indication to support one approach over another[17]. In the future, as a first step, it would be beneficial to agree appropriate and homogeneous data collection, to facilitate comparison of survival and late-effects outcomes, in order to develop recommendations or even guidelines on the optimal relapse strategy. It was agreed that for patients with relapsed NGGCTs, who are to be treated with curative intent, high-dose chemotherapy with haematopoietic stem cell rescue should be employed (Statement 31)[18], although a minority of participants highlighted that the evidence base for this statement was weak. More published series of such relapsed cases are required to help inform such decisions.

Banking of tumours and associated samples was strongly recommended (Statement 32), to support molecular studies of ICGCTs and facilitate recent progress[6,7]. We acknowledge that tumour banking *per se* may be ethically difficult to undertake in certain settings, especially as a biopsy is considered unnecessary for diagnostic purposes in the presence of raised AFP/HCG markers above national thresholds. However, the collection of associated samples

such as serum/plasma, CSF and constitutional DNA is of critical importance, as in the future these specimens may provide a relatively non-invasive method for identifying molecular changes that are representative of those in the tumours, thereby assisting diagnosis and risk stratification. For example, specific short non-protein-coding RNAs, termed microRNAs, are known to be dysregulated in all malignant GCTs[22] and the same microRNAs have been shown to be elevated at diagnosis in serum[23,24] and CSF[25] from patients with extracranial and intracranial malignant GCTs, respectively. The importance of embedding quality of life (QoL) and late-effects assessments in clinical trials (Statements 33 and 34, respectively) was also highlighted.

Areas of non-consensus. A number of statements did not reach consensus, even after revision. The current ongoing trials in North America (ACNS 1123) and Europe (SIOP CNS GCT II) consider synchronous lesions occurring in both the neurohypophyseal/suprasellar and pineal region with typical imaging characteristics, and with negative serum and CSF AFP markers, consistent with a diagnosis of bifocal germinoma, and trial enrolment is possible without surgical biopsy. This clinical scenario was included as one of the original 38 Delphi statements but was rejected. Based on participants' comments, it was revised and the presence of diabetes insipidus was included; however, in the second round of voting, this was still clearly rejected, receiving only 49% support. Participants commented that a proportion of these cases can be NGGCT (e.g. EC with negative markers)[19,20], or even a non-ICGCT diagnosis (e.g. primitive neuroectodermal tumour;[21]). Concern was expressed that without biopsy, the risk would be under-treating some of these patients using germinoma protocols, when more aggressive malignant components may be present. This is an area where expert opinion was clearly divided and it is hoped that future study results may help to resolve this area of controversy.

Another statement where a consensus was not reached was for metastatic germinoma documented on craniospinal imaging. One of the original statements listed that craniospinal irradiation alone is a sufficient treatment in this situation. This statement was rejected (48% agreement); although participants felt that historically this had been the standard of care, many thought that by accepting it, it would preclude further attempts to use chemotherapy in order to reduce the RT dose and thus long-term morbidity. The statement was therefore revised to reflect these views, adding that craniospinal irradiation alone is sufficient treatment to secure excellent overall survival, but the use of pre-radiation chemotherapy may allow for a reduction in RT dose. This revised statement was narrowly defeated (64% agreement); a minority of participants then commented that there was currently no evidence for this statement.

Future challenges. The last decade has seen some international convergence of approaches in the management of ICGCTs[2], and the Delphi process has managed to identify substantial areas of agreement that will facilitate future collaboration. However, a number of recognised challenges remain, some of which were not addressed in this initial Delphi process, as the primary aim in this initial consensus was to find and document the areas where agreement could be reached. These challenges will need further discussion, and include the following: the timing and extent of surgery, particularly at the time of diagnosis; the need to attempt to align the disparate classification systems used internationally for germinoma and NGGCT; potentially coining a new term for NGGCT, evaluation of reduced RT doses to cure localised germinoma without increasing relapse rates; the need for further evidence for the management of relapsed disease; how new molecular markers may be incorporated into future clinical trials; and the specific identification of strategies to reduce long-term side effects of treatment.

Application to other areas of oncology. We believe that the Delphi process could be applied to draw together experts in other areas of oncology, particularly areas of paediatric neuro-oncology, which are relatively small subspecialties, in order to similarly identify areas of consensus. In doing so, it will be important to engage recognised experts from multiple disciplines and continents, to ensure equitable representation of observed variations in clinical practice. In turn, this will ensure the most robust statements are agreed, which will maximise the chance of positively impacting upon subsequent patient outcomes.

Conclusion. The Delphi consensus statements reported here are a contemporary representative opinion by international leaders in the field and a key foundation for further advancement in ICGCT management. In addition, the process has identified areas of contrasting practices and understanding which should be the focus for future collaborative studies. Such efforts will likely facilitate international cooperation and translate into improved patient outcomes.

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Legends to Figures

Figure 1. Schematic of the Delphi consensus process for the management of intracranial germ cell tumours.

Contributors' Statement

MJM - original idea, literature search, figure, study design, data collection, data analysis, data interpretation, extensive manuscript writing. UB - original idea, literature search, study design, data collection, data analysis, data interpretation, extensive manuscript writing. RN - original idea, literature search, study design, data collection, data analysis, data interpretation, manuscript writing. JF – original idea, literature search, study design, data collection, data analysis, data interpretation, manuscript writing. MM - original idea, study design, data interpretation, manuscript writing. JCN - original idea, literature search, study design, data collection, data analysis, data interpretation, extensive manuscript writing.

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