Vinblastine monotherapy induction prior to radiotherapy for patients with intracranial germinoma during the COVID-19 pandemic.

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Vinblastine monotherapy induction prior to radiotherapy for patients with intracranial germinoma during the COVID-19 pandemic.

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Abbreviations	
AFP	alpha-fetoprotein
AP	anterior-posterior
carboPEI	carboplatin/etoposide/ifosfamide chemotherapy
CCLG	Children's Cancer and Leukaemia Group
CSF	cerebrospinal fluid
CSI	craniospinal irradiation
CTCAE	Common Terminology Criteria for Adverse Events
DI	diabetes insipidus
FBC	full blood count
GCT	germ cell tumor
GCTNAP	Germ Cell Tumour National Advisory Panel
HCG	human chorionic gonadotropin
PPI	patient and public involvement
WVI	whole ventricular irradiation

Abstract

Background. Patients with localized intracranial germinoma have excellent survival. Reducing treatment burden and long-term sequelae is a priority. Intensive inpatient chemotherapy (e.g., carboPEI=carboplatin/etoposide/ifosfamide) has been effectively employed to reduce radiotherapy treatment volume/dose. Outpatient-based carboplatin monotherapy is associated with excellent outcomes in metastatic testicular seminoma (an identical pathology) and successful vinblastine monotherapy induction (with 77% tumor volume reduction after just two weekly vinblastine doses) has recently been reported in an intracranial germinoma patient.

Methods. Adapted UK guidelines for germ-cell-tumor management were distributed during the COVID-19 pandemic, including non-standard treatment options to reduce hospital visits and/or admissions. This included vinblastine monotherapy for intracranial germinoma (6 mg/m^2 intravenously, or 4 mg/m^2 for moderate count suppression, delivered weekly). We describe three such patients treated using this approach.

Results. A 30-year-old male with a pineal tumor received 12-week vinblastine induction, with >60% volume reduction, prior to definitive radiotherapy. A 12-year-old female with a metastatic suprasellar tumor and progression at all sites of disease whilst awaiting proton radiotherapy received two vinblastine doses with good early response, including 36% primary tumor volume reduction. The patients tolerated vinblastine well.

Conclusion. Patients with intracranial germinoma have excellent outcomes and reduction of late-effects remains a priority. The description of vinblastine monotherapy in these intracranial germinoma patients warrants further exploration.

Introduction

Intracranial germ cell tumors (GCTs) are rare and diagnosis and management is challenging due to their heterogeneity, e.g., regarding differing tumor sites, histological subtypes, and marker expression. For germinoma patients, which comprise the majority of intracranial GCT cases [1], the internationally agreed priority for future management is to maintain excellent overall survival whilst attempting to reduce treatment burden and minimize late-effects and sequelae of treatment [2]. Historically, craniospinal irradiation (CSI) was used to treat all intracranial germinoma patients, regardless of metastatic status [3,4], although the requirement for CSI in localized disease was questioned [5]. A chemotherapy-only approach for cure has also been attempted but was unsuccessful [6], and thus radiotherapy remains the definitive treatment. However, use of intensive inpatient induction chemotherapy, prior to radiotherapy, for localized intracranial germinoma patients has been effective in reducing radiotherapy treatment volume and/or dose whilst maintaining survival [7-9]. In Europe, 'carboPEI' (alternating courses of carboplatin/etoposide and ifosfamide/etoposide) has been used for this purpose [7,8]. CarboPEI involves prolonged inpatient stays and use of intravenous hydration. Given the common co-morbidity of central diabetes insipidus (DI) in patients with neurohypophyseal–suprasellar germinoma, use of a chemotherapy regimen without concomitant intravenous hydration would be a major advantage [10]. Of note, in a study of 32 patients with intracranial GCT receiving cisplatin- and/or ifosfamide-based chemotherapy, 21 (66%) had DI and, furthermore, six of these 21 patients (29%) experienced serious complications [10]. In addition to the challenges of managing DI, carboPEI chemotherapy is associated with short-term toxicities of myelosuppression, vomiting and/or diarrhoea, electrolyte disturbances which may lead to seizures, renal impairment and elevation of liver enzymes [8]. Long-term sequelae of these drugs include ototoxicity from cisplatin [11] and reduced fertility from alkylating agents (ifosfamide) [12,13]. Current

chemotherapy regimens also require the use of indwelling central venous access devices, which are associated with increased risk of infection [14] and thrombosis [15] and which may affect quality-of-life. In North America, the standard-of-care schedule to reduce radiotherapy treatment volume and/or dose is carboplatin-etoposide [9]. Similar to carboPEI, there is an associated, albeit small, second malignancy risk with etoposide [16].

Of note, outpatient-based single-agent carboplatin chemotherapy is associated with excellent outcomes in metastatic testicular seminoma [17,18], an identical pathology to intracranial germinoma (and ovarian dysgerminoma). Carboplatin monotherapy, at modest dosing, has also been successfully utilized in intracranial germinoma to allow a reduction in subsequent radiotherapy doses [19]. Furthermore, we recently reported successful vinblastine monotherapy induction, prior to radiotherapy, in a patient with intracranial germinoma [20]. The patient presented with complete loss of vision and imaging demonstrated a suprasellar lesion, measuring 36 x 28 x 23 mm. The initial working diagnosis was low-grade glioma and accordingly, weekly vinblastine monotherapy was commenced. Vision returned within four days of starting vinblastine and after further review, the diagnosis was revised to germinoma. After dramatic radiological reduction in tumor size after just two vinblastine doses (to 21 x 19 x 12 mm; a 77% volume reduction), a twelve-week induction course was delivered, with excellent response, prior to radiotherapy [20]. Importantly, both carboplatin and vinblastine schedules can be successfully delivered peripherally without recourse to placement of a central venous access device.

Due to the COVID-19 pandemic, adapted UK guidelines for GCT patient management were distributed to clinicians, including potential non-standard treatment options that would reduce

hospital visits and/or admissions. This included vinblastine monotherapy as an option for intracranial germinoma, based on our case report [20] and practical/pragmatic considerations. We describe two patients successfully treated using this approach. The experience of vinblastine monotherapy in these patients warrants further exploration.

Case Reports

Case 1.

A 30-year-old male patient presented with intermittent dizziness, headache, and blurred vision. MRI scan revealed a large, predominantly solid mass in the pineal region, with some cystic elements (Figure 1A). The solid enhancing component measured 28 x 27 (axial dimensions) x 32 mm anterior-posterior (AP) on sagittal images (enhancing tumor volume 12.7 cm^3). The rest of the neuroaxis showed no evidence of dissemination on imaging. Serum and cerebrospinal fluid (CSF) alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) levels were normal. CSF cytology showed no malignant cells. Morphological and immunohistochemical features of the biopsy were those of a germinoma. The patient required no treatment with steroids.

At the time of the diagnosis, the UK was at the height of the first wave of the COVID-19 pandemic (April 2020). Options for treatment for this patient with intracranial localized germinoma included CSI or induction chemotherapy followed by reduced field radiotherapy (focal and whole ventricular irradiation; WVI). However, the patient was very geographically distanced from the treating hospital and wished to minimize hospital admissions and/or visits. Daily travel was not feasible due to the distance from the patient's residence to the treating hospital. CSI or intensive prolonged inpatient chemotherapy would have required a protracted hospital stay at a time when the impact of COVID-19 in hospital and intensive care capacity was uncertain and both would have implied a risk of unplanned admissions with febrile neutropenia. These concerns were discussed with the treating clinician so alternative treatment options, or treatment deferral, were explored. After extensive discussion through

the Children's Cancer and Leukaemia Group (CCLG) Germ Cell Tumour National Advisory Panel (GCTNAP; https://www.cclg.org.uk/NAP/GCT), and with our recent report of successful intracranial germinoma treatment with vinblastine [20], the joint decision was made with the patient to commence weekly peripheral vinblastine induction, with dosing and modifications as for low-grade glioma [21,22]. Typically, if the weekly full blood count (FBC) showed a neutrophil count of $\geq 0.75 \times 10^9$/l and platelet count $\geq 75 \times 10^9$/l, dosing was continued at 6 mg/m^2. If the neutrophil count was $<0.75 \times 10^9$/l but $\geq 0.5 \times 10^9$/l and/or platelet count $<75 \times 10^9$/l but $\geq 50 \times 10^9$/l, the dose was reduced to 66% (4 mg/m^2). Finally, if the neutrophil count was $<0.5 \times 10^9$/l and/or platelet count $<50 \times 10^9$/l, vinblastine was held until count recovery. Adequate renal and liver function was checked by monthly blood testing.

Appropriate consent for non-standard treatment was obtained. Due to the older age of the patient (30 years) and anticipated reduction in tolerance vinblastine was commenced at 4 mg/m^2 dosing. This was well tolerated and therefore the dose for week 2 was increased to the standard 6 mg/m^2 dose [21,22]. However, this resulted in neutropenia (0.5×10^9/l) and a further repeat level three days later confirmed ongoing neutropenia (0.4×10^9/l) and thus the week 3 dose was completely omitted. Subsequent doses were all therefore delivered at 4 mg/m^2 and well tolerated, with only minor Common Terminology Criteria for Adverse Events (CTCAE) grade 1 fatigue reported in the final three weeks of therapy (weeks 10-12). Median neutrophil count was 1.3×10^9/l (range 0.5-1.9) and platelet count 348×10^9/l (range 255-373) during treatment.

Early evaluation MRI scan after six weeks' vinblastine (five doses; four at 4 mg/m^2) showed response of the solid enhancing aspect of the pineal lesion (Figure 1B) to 25 x 18 (axial) x 26 mm (AP) dimensions. Although the cystic areas were of similar size, this corresponded to a >50% volume reduction in the solid enhancing component to 6.1 cm^3. MRI evaluation after 12 weeks' therapy showed a further modest response (Figure 1C), with the solid enhancing component now 20 x 20 (axial) x 23 mm (AP), corresponding to a >60% overall volume reduction to 4.8 cms^3. Cystic areas of the tumor were still prominent. To exclude any teratoma component given the continued solid and cystic nature of the residual disease, and given non-standard induction chemotherapy, following careful consideration and discussion, maximal safe resection of the residual pineal mass prior to radiotherapy was advocated and deemed to be feasible neurosurgically. This revealed residual germinoma. Repeat post-operative imaging confirmed complete resection and no other sites of disease. Following recovery from surgery, the patient proceeded safely to radiotherapy (24Gy CSI with 16Gy boost; European standard-of-care dosing) at a time when hospital admissions from COVID-19 were at a nadir. The rationale for CSI was that this was the original plan at diagnosis and only deferred due to the COVID-19 pandemic. Furthermore, following an incomplete response to non-standard vinblastine induction chemotherapy, it was felt prudent, after GCTNAP discussion, to retain this approach. The patient remains well in uneventful clinical follow-up and most recent imaging, six months following completion of treatment, reveals only a small ill-defined focus of T1 and T2 hyperintensity with minor associated contrast enhancement centred on the site of previous resection, consistent with further subtle regression of presumed postsurgical changes (Figure 1D). T2/FLAIR sequences (Supplementary Figure S1) did not provide additional information to that obtained with T1 sequences with contrast.

Case 2.

A 12-year-old female was referred to the pediatric endocrine service for growth failure over a two-year period, with initially normal IGF-1 levels. During investigation DI evolved, and thus an MRI head was undertaken. This was performed during the COVID-19 pandemic and showed a primary neurohypophyseal-suprasellar tumor with contiguous extension involving areas including the cavum septum pellucidum, as well as separate metastatic foci in the anterior horns of the lateral ventricles. Serum and CSF AFP and HCG estimation were normal. MRI spine was normal and CSF cytology was clear. Stereotactic biopsy of the neurohypophyseal-suprasellar lesion, which was undertaken five weeks later, confirmed germinoma. A stress dose of hydrocortisone was electively commenced the day prior to surgery due to a low random cortisol level (285 nmol/l) and continued for 48 hours post-operatively, before reducing to maintenance hydrocortisone treatment (which was continued and then stopped after a satisfactory synacthen test at the end-of-treatment). Referral for proton radiotherapy (CSI) was made shortly after biopsy (August 2020), for which there was an eight-week delay to start due to the COVID-19 pandemic. Three weeks after proton radiotherapy referral, and five weeks following biopsy, a further MRI was performed, which showed evidence of progressive disease at all sites, both primary and metastatic. For example, the primary neurohypophyseal-suprasellar lesion had increased to 20 x 19 x 21 mm diameter (4.2 cm^3) compared with 19 x 17 x 14 mm (2.4 cm^3) nine weeks earlier (Figure 2A). Additional sites of disease progression involved the right anterior septal leaflet at the right foramen of Munro, measuring 7 mm transversely, previously 5 mm. The more midline deposits involving the cavum septum pellucidum had increased in size measuring up to 10 mm, previously 8 mm. The ependymal deposits lining the anterior horns had also increased in size compared with previous. Given the delay from diagnosis to starting CSI for metastatic intracranial germinoma, and to prevent the onset of new co-morbidities or hydrocephalus, the

local multidisciplinary team felt that intervention with chemotherapy treatment prior to CSI was required. The patient did not have central access and due to concerns that myelosuppression from carboPEI chemotherapy may delay radiation planning and delivery, vinblastine was suggested based on our earlier report [20]. The case was discussed at the CCLG GCNAP and it was agreed that it was reasonable to proceed with weekly vinblastine whilst awaiting the start of proton radiotherapy. Accordingly, two doses at 6mg/m^2 were delivered peripherally, well tolerated and allowed cessation with good blood counts in time for protons. The patient developed no new co-morbidities during this time. A further MRI scan performed just four weeks later, prior to proton radiotherapy, showed a clear response to treatment at all sites, both primary and metastatic. For example, the primary neurohypophyseal-suprasellar lesion had reduced in size to 17 x 16 x 19 mm (2.7 cm^3) from 4.2 cm^3 previously (a 36% volume decrease) (Figure 2B). Disease involving the cavum septum pellucidum measured 7 mm in diameter, previously 10 mm, and other metastatic disease was similarly reported as much less bulky and not easily measurable, with reduced enhancement. The patient proceeded to proton radiotherapy (24Gy CSI with 16Gy boost) and remains well in follow-up, with imaging at the end-of-treatment showing a further reduction in size of the primary neurohypophyseal-suprasellar lesion to 7 x 10 x 8 mm (0.29 cm^3) and cavum septum pellucidum disease to a diameter of 6 mm (Figure 2C), with barely discernible/non-measurable other sites of metastatic disease. Further imaging four months later remained stable (Figure 2D). T2/FLAIR sequences (Supplementary Figure S2) did not provide additional information to that obtained with T1 sequences with contrast.

Discussion

Patients with intracranial germinoma have excellent outcomes, but reducing treatment effects remain a priority [2]. In Europe, carboPEI [7,8] is delivered with large volumes of intravenous hydration, can exacerbate pre-existing DI, particularly where no thirst mechanism is present, and is associated with prolonged inpatient admissions [20]. Such chemotherapy schedules are also associated with short- [8] and long-term [11-13,16] toxicities, and, moreover, require central venous access devices for delivery, with associated infection and thrombosis risk [14,15]. A further UK intracranial germinoma case, in addition to the two formally described here, received two vinblastine doses to complete induction as a 'bridge' to radiotherapy with stable radiological appearances; this patient developed ifosfamide encephalopathy [23] during standard-of-care carboPEI chemotherapy and experienced a fall and subdural hematoma. Even the standard-of-care schedule in North America (carboplatin-etoposide) [9] is associated with the additional long-term toxicities of etoposide, which include second malignancy [16].

Regarding definitive radiotherapy, currently patients with metastatic intracranial germinoma receive 24Gy CSI with boost of 16Gy to 40Gy for macroscopic disease. Although patients are eligible for proton beam therapy, due to the logistical challenges of travel to a distant centre, patients and parents may choose to have photon treatment more locally. In addition, during the COVID-19 pandemic, there were delays in starting timely radiotherapy, which necessitated a 'bridging' strategy to prevent further tumor growth (Case 2). During this time, tumors may grow and cause additional co-morbidities such as visual loss, hormone dysfunction and/or hydrocephalus; consequently there is interest in using gentle 'window'

chemotherapy to bridge individuals to radiotherapy. If successful, this may also facilitate a reduction in radiotherapy treatment volume for macroscopic disease at diagnosis.

The malignant GCT subtype germinoma, and its extracranial testicular counterpart seminoma, are indistinguishable pathologically, with biological evidence suggesting that these tumors share a common molecular pathogenesis [24]. Germinoma/seminoma are known to be exquisitely chemosensitive, in addition to their radiosensitivity. Carboplatin monotherapy has been successfully employed for metastatic testicular seminoma with excellent outcomes [17,18] and at modest dosing has been utilized in intracranial germinoma permitting radiotherapy dose reductions [19]. Vinblastine has also been used within multi-agent regimens to treat intracranial germinoma [25], and the induction response to vinblastine monotherapy [20] is noteworthy. Weekly vinblastine monotherapy is well tolerated with minimal side-effects for treatment of other central nervous system conditions such as low-grade glioma and Langerhans Cell Histiocytosis [21,22,26]. It can also be delivered peripherally as an intravenous bolus in an outpatient setting in some treatment centers [20]. Further potential advantages of monotherapy induction for intracranial germinoma include patient and carer benefit, consistent with recent patient and public involvement (PPI) work [27] and benefit for lower- and middle-income countries (Supplementary Discussion),

Our case series has a number of limitations. The numbers of patients described is very small and only one of the two patients received a ‘full’ induction course. However, the cases described here during the COVID-19 pandemic, along with a previously described case [20], suggest that further investigation is warranted to assess the role for induction monotherapy, prior to definitive radiotherapy, more formally in the context of a clinical trial. This should

include study of complete remission rates after induction, as in future this may allow omission of radiotherapy boosts. In addition, it should be noted that any potential reduction in therapy for cancer could be associated with a theoretical increase in relapse risk. Consequently, prior to implementation, it is important to understand how effective any treatment for potential relapse is. Due to the effectiveness of existing therapies, relapsed intracranial germinoma is rare and data is relatively sparse. However, evidence to date shows that patients with relapsed germinoma can be successfully cured, even following the intensity of current first-line therapy [28-30].

In summary, patients with intracranial germinoma have excellent outcomes and reduction of treatment-effects remains a priority. The chemosensitivity of germinoma and description of vinblastine monotherapy in these two cases, along with our previous report [20], warrant further exploration.

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393 **Legends to Figures.**

394

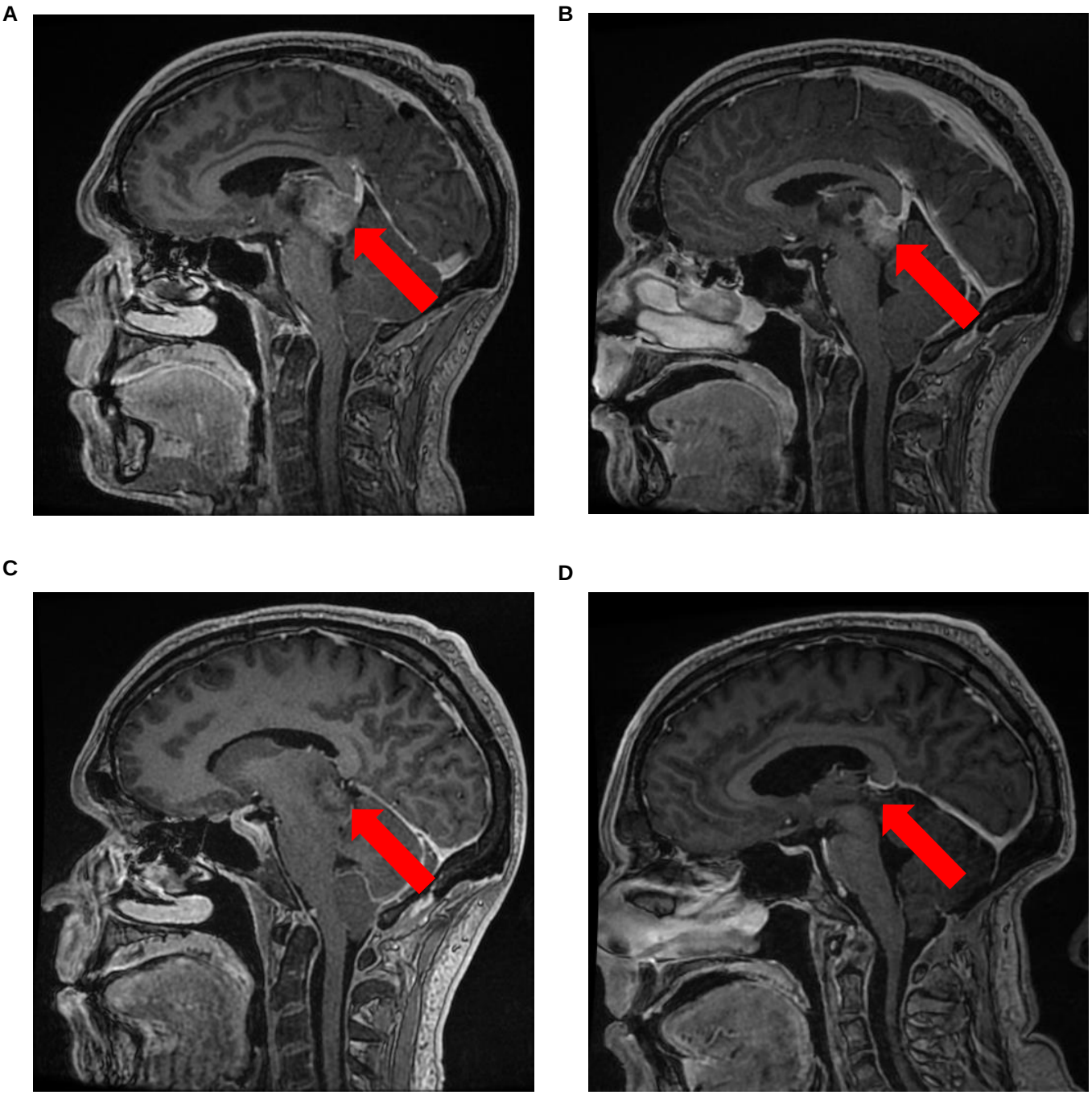
395 **Figure 1.** Representative sagittal T1-weighted MRI head images with contrast for Case 1
396 (localized pineal germinoma) showing response to treatment. A) At diagnosis, revealing a
397 large, predominantly solid pineal lesion (arrow); B) after six weeks' of induction vinblastine
398 monotherapy showing reduction in size of the pineal lesion (arrow); C) after 12 weeks'
399 vinblastine revealing further modest response to treatment (arrow); and D) six months after
400 the end-of-treatment with definitive radiotherapy, showing a small ill-defined focus of
401 minimally enhancing T1 hyperintensity centred on the site of previous resection (arrow),
402 consistent with further subtle regression of presumed postsurgical changes.

403

404 **Figure 2.** Representative sagittal T1-weighted MRI head images with contrast for Case 2
405 (metastatic suprasellar germinoma) showing response to treatment. A) At initial progression
406 following diagnosis, whilst awaiting proton craniospinal irradiation. Top arrow highlights
407 representative disease of the cavum septum pellucidum and the lower arrow the primary
408 suprasellar lesion; B) after two doses of vinblastine, revealing a response at both the primary
409 and metastatic sites (arrows); C) after completion of proton radiotherapy, showing continued
410 response (arrows); and D) five months after the end-of-treatment showing stable residual
411 (arrows).

412

413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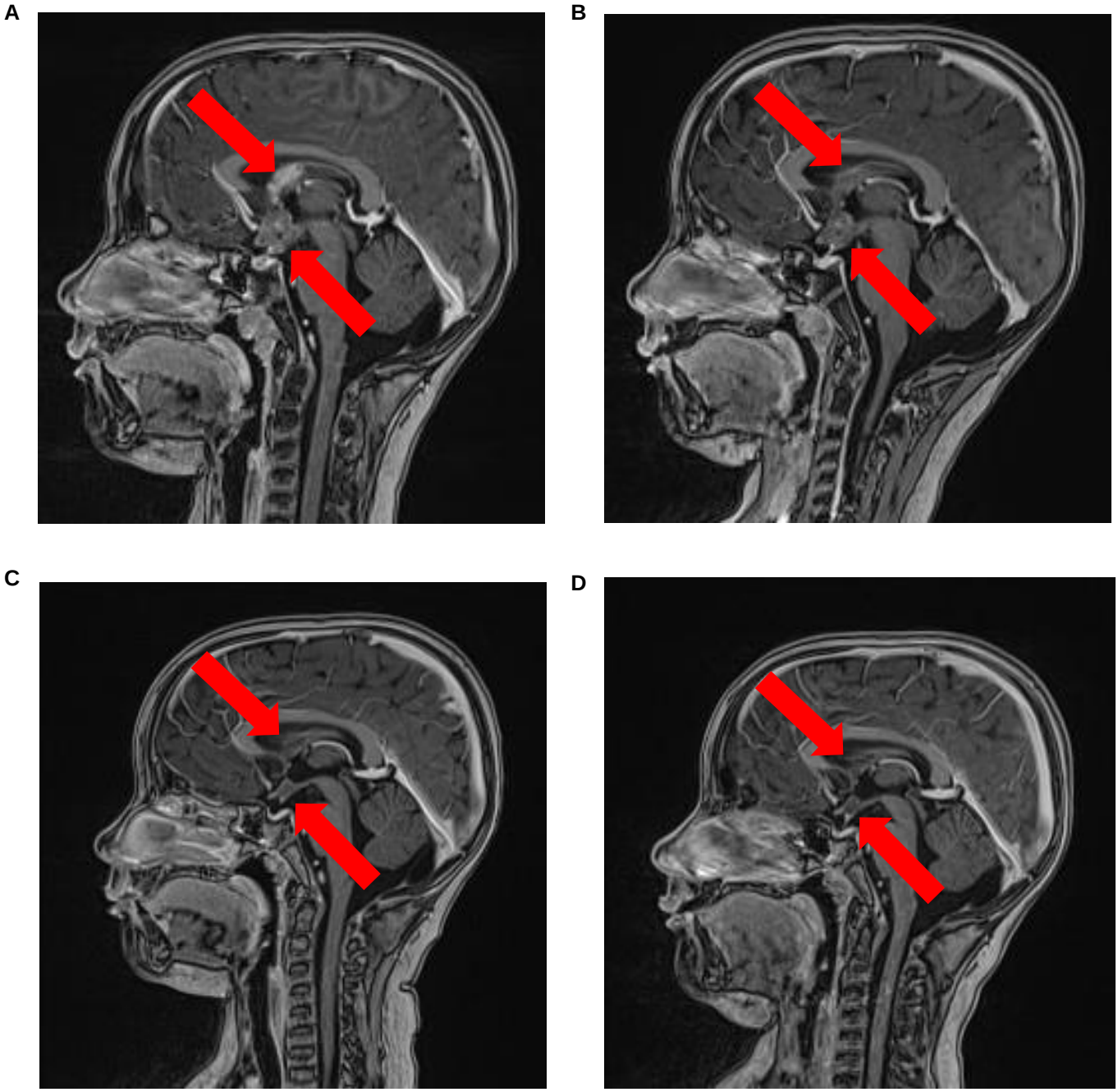
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Supplementary Information

Supplementary Discussion

Further potential advantages of monotherapy induction (carboplatin or vinblastine) for intracranial germinoma include patient and carer benefit and benefit for lower- and middle-income countries. For patients/carers, this could mean reduced time in hospital admissions/outpatients and reduced short-term side effects. For example, whilst carboPEI chemotherapy is inpatient based, the carboplatin-etoposide schedule used in North America is three days of outpatient-based chemotherapy every three weeks. Vinblastine monotherapy would also be three outpatient visits every three weeks, although the visit times would be expected to be shorter. Furthermore, the potential carboplatin monotherapy option could provide the opportunity to be in clinic for just a single visit every three weeks. Such approaches will facilitate attendance at school, college, university or employment for the patient and parents/carers continuing to work. This is consistent with recently undertaken patient and public involvement (PPI) work, which has highlighted the top research priorities for patients living with and beyond cancer [1]. Research priority #2 (‘*how can patients and carers be appropriately informed of cancer diagnosis, treatment, prognosis, long-term side-effects and late effects of treatments, and how does this affect their treatment choices?*’) and research priority #6 (‘*how can the short-term, long-term and late effects of cancer treatments be (a) prevented, and/or (b) best treated/ managed?*’) are both addressed by future exploration of monotherapy induction for patients with intracranial germinoma. Clearly, an approach to reduce the burden of treatment for such patients is shared by both clinicians [2] and PPI representatives [1] alike. Furthermore, in addition to the primary potential benefits for patients, healthcare systems are also likely to receive secondary benefit from cost savings of delivering

such schedules. Moreover, there may be particular benefit for lower- and middle-income countries where healthcare/infrastructure resources are limited, and where a monotherapy induction option would be easier to deliver than existing induction schedules used in Europe and North America. This may facilitate a move away from delivery of CSI to all intracranial germinoma patients in such settings, regardless of metastatic status.

Supplementary References

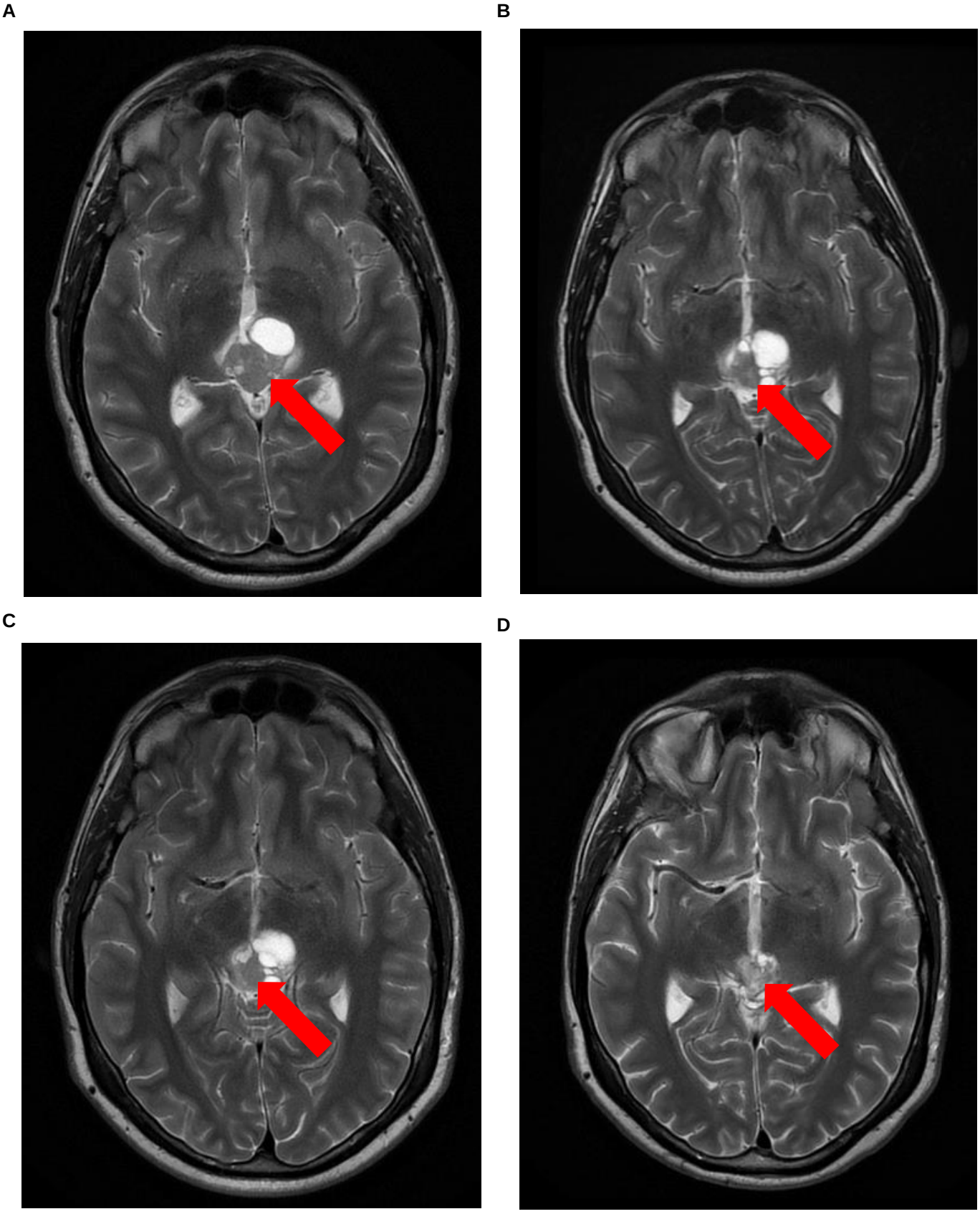
1. National Cancer Research Institute. (NCRI). *The UK top research priorities for living with and beyond cancer*. 2019 [cited 2021 17th May 2021]; Available from: https://www.ncri.org.uk/the-uk-top-10-research-priorities-for-living-with-and-beyond-cancer/.

2. Murray, M.J., et al., *Consensus on the management of intracranial germ-cell tumours.* Lancet Oncol, 2015. **16**(9): p. e470-e477.

Legends to Supplementary Figures.

Supplementary Figure S1. Representative axial T2-weighted MRI head images for Case 1 (localized pineal germinoma) showing response to treatment (arrows). A) At diagnosis, revealing the solid and cystic pineal lesion; B) after six weeks of induction vinblastine monotherapy showing reduction in size of the solid component of the pineal lesion; C) after 12 weeks of vinblastine monotherapy; and D) six months after the end-of-treatment with definitive radiotherapy, showing presumed postsurgical changes only.

Supplementary Figure S2. Representative axial T2-weighted MRI head images for Case 2 (metastatic suprasellar germinoma) showing response to treatment at the primary hypophyseal-suprasellar site (arrows). A) At initial diagnosis; B) after initial progression following diagnosis, whilst awaiting proton craniospinal irradiation; C) after two doses of vinblastine, revealing response at the primary site; D) after completion of proton radiotherapy, showing continued response.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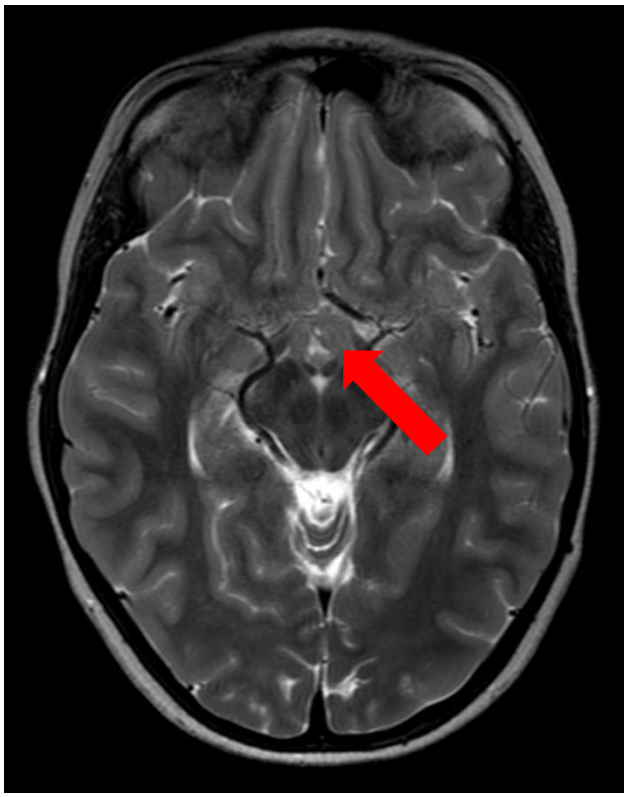

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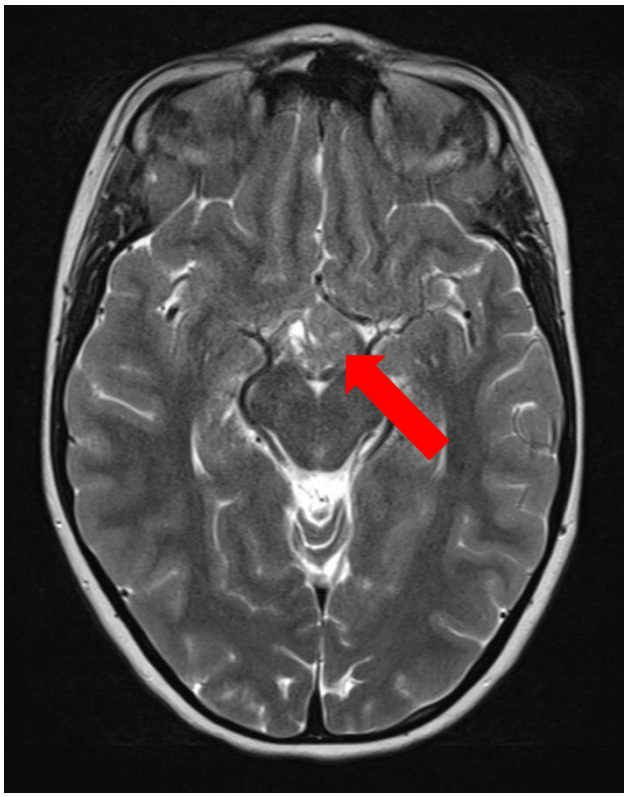

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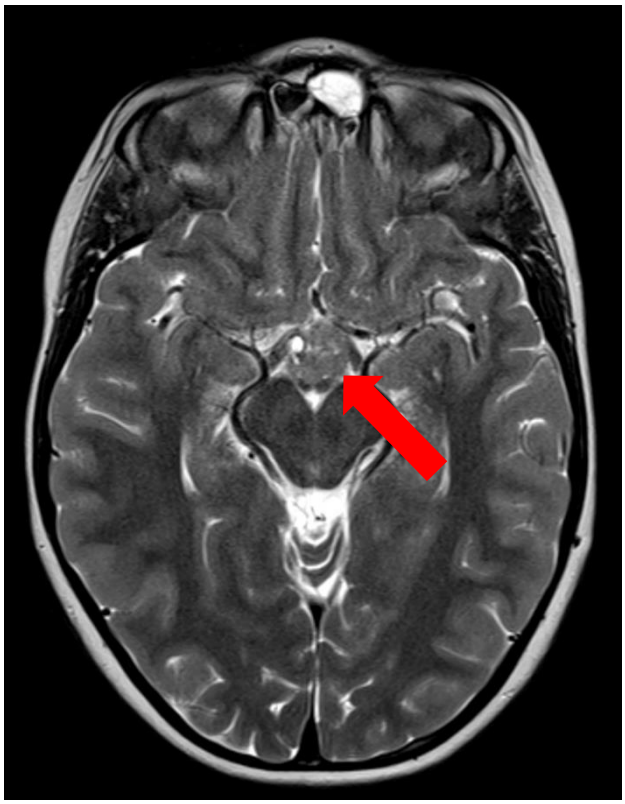

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