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Clinical Study

Early response to chemotherapy as an indicator for the management of germinoma-like tumors of the pineal and/or suprasellar regions

Ryuta Saito [a], Toshihiro Kumabe [b,*], Masayuki Kanamori [a], Yukihiko Sonoda [a], Mika Watanabe [c], Shunji Mugikura [d], Shoki Takahashi [d], Teiji Tominaga [a]

[a] Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan
[b] Department of Neurosurgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
[c] Department of Pathology, Tohoku University Hospital, Sendai, Japan
[d] Department of Diagnostic Radiology, Tohoku University Graduate School of Medicine, Sendai, Japan

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ABSTRACT

Recent advances in diagnostic imaging and experience with germinomas may allow for the differentiation of central nervous system germinomas from other tumors based on clinical information, without histological verification. We retrospectively analyzed clinically diagnosed germinoma-like tumors of the pineal and/or suprasellar regions. This was done to evaluate the efficacy of our strategy of defining germinoma-compatible tumors based on good responses to initial chemotherapy. The responses to chemotherapy and survival of 34 consecutive patients with germinoma-like tumors who underwent initial treatment from July 2001 to October 2010 were analyzed. The minimum apparent diffusion coefficient (minADC) value and proton magnetic resonance spectroscopy (MRS) were evaluated in recent patients. Twelve patients with histologically verified germinomas and 18 with germinoma-compatible tumors showed early logarithmic decreases in tumor volume in response to initial chemotherapy, typical low minADC values and typical MRS characteristics, including increased choline/creatine ratios, decreased N-acetylasparate/creatine ratios, and large lipid peaks. These patients had good progression-free survival. The other four patients, with histologically verified non-germinomas, showed no response to chemotherapy, and one patient with a pineoblastoma showed a similar minADC value and MRS characteristics to those of patients with germinomas. The response to initial chemotherapy can be used to distinguish germinoma-compatible tumors from non-germinoma in patients with germinoma-like tumors of the pineal and/or suprasellar regions. The evaluation of minADC and proton MRS are useful for distinguishing germinomas from other tumors. However, a subset of non-germinomas may show similar characteristics to germinomas. The benefit of bypassing unnecessary surgical intervention can be achieved, at least in Asian populations with a high incidence of germinomas.

1. Introduction

Central nervous system germinomas generally occur in midline locations, with 80% or more arising in structures around the third ventricle. Most commonly, they arise in the region of the pineal gland, followed by the suprasellar region [1]. More than two decades ago, the pineal region was considered to be nearly inoperable and as such, the diagnosis of a germinoma was often inferred or based on the patient's response to radiotherapy [2]. Recent improvements in surgical techniques have rendered empirical radiotherapy of the pineal region tumors without histological diagnosis obsolete [3]. However, for both non-germinoma germ cell tumors and germinomas, no positive correlation between the extent of surgery and outcome has been found [4]. Moreover, a biopsy followed by chemo-radiation therapy is the standard treatment for germinomas, and extensive resection is considered to be unnecessary [4–7]. Therefore, surgery is avoidable, assuming that the diagnosis of germinoma is correct.

We have defined tumors that clinically resemble germinomas as germinoma-like tumors (for the detailed definition, see Section 2). We assumed that if the histological type of the germinoma-like tumor was a germinoma, but not any other tumor type, it would show a very good response to treatment, defined by a logarithmic reduction in tumor volume after initial chemotherapy. Based on this hypothesis, our current treatment strategy for germinoma-like tumors has been to attempt chemotherapy without histological verification, or so-called diagnostic treatment [8]. However, a subset of patients in our series were diagnosed histologically before initial treatment and registered in a national

* Corresponding author. Tel.: +81 42 778 8115; fax: +81 42 778 7788.
E-mail address: kuma@kitasato-u.ac.jp (T. Kumabe).

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survey or were referred to us after biopsy. Therefore, our series of patients with germinoma-like tumors can be divided into the three following groups: patients who received chemo-radiotherapy after histological verification of germinoma and showed good responses (germinoma group), patients who received chemo-radiotherapy without histological diagnosis and showed similarly good responses (germinoma-compatible tumor group), and patients with insufficient responses to the initial chemotherapy and who underwent subsequent surgery for histological diagnosis (non-germinoma group).

The present study examined the validity of our hypothesis and our treatment strategy of avoiding unnecessary surgical intervention. To this end, we analyzed the reduction in tumor volume after initial chemotherapy and patient survival in the three patient groups. We also evaluated the magnetic resonance spectroscopy (MRS) findings and the apparent diffusion coefficient (ADC) values in very recent patients to assess their diagnostic value for germinoma-like tumors [9–11].

2. Patients and methods

2.1. Diagnosis of germinoma-like tumors

This study included patients with tumors located in the suprasellar and/or pineal regions. The clinical diagnosis of germinoma-like tumor was based on age, neurological imaging findings, and serum/cerebrospinal fluid tumor marker measurements. Approximately 80–90% of central nervous system germ cell tumors occur in patients aged less than 25 years, with the incidence peaking at 10–14 years [1]. The great majority of pineal germinomas occur in boys, while more suprasellar germinomas are encountered in girls [1]. A germinoma appears as a variably high density area on CT scans [12]. On MRI it appears as a solid mass that is isointense or hyperintense relative to gray matter, with prominent enhancement or heterogeneous enhancement if cysts are present [1,7]. Tandem lesions affecting both the suprasellar and pineal regions are highly indicative of germinomas. However, a suprasellar tumor with a large cyst and/or calcification may be a different tumor type, particularly a craniopharyngioma. Tumors with broad attachments to the meninges are more likely to be a meningioma.

Germinomas are generally associated with normal levels of the serum tumor markers, alpha-fetoprotein (AFP) <20 ng/mL (normal, <10 ng/mL), human chorionic gonadotropin (hCG) <1.0 mIU/mL (normal, <3.0 mIU/mL) and β-hCG <0.1 ng/mL (normal, 0 ng/mL), although certain patients have slightly elevated levels of hCG <50 mIU/mL or β-hCG <5 ng/mL without elevated levels of AFP. The symptoms of diabetes insipidus are also indicative of germinomas. Masked diabetes insipidus needs to be carefully diagnosed, but nearly all patients with suprasellar germinomas suffer from diabetes insipidus [13]. We defined tumors that fulfill these characteristics as clinically diagnosed germinoma-like tumors.

2.2. Patients

The medical records and radiographical data of 34 consecutive patients with germinoma-like tumors who underwent initial treatment at our institute from July 2001 to October 2010 were retrospectively analyzed. A histological diagnosis was obtained in 16 patients. These included four patients with non-germinomas, consisting of two patients with pineoblastomas, one patient with a glioblastoma, and one patient with a mixed germ cell tumor, which was a germinoma plus a teratoma. No histological diagnosis was available for the other 18 patients (Table 1).

2.3. Management of germinoma-like tumors

Chemotherapy using carboplatin and etoposide (CARE) or ifosfamide, cisplatin and etoposide (ICE) without histological verification was our strategy for the initial treatment of patients with germinoma-like tumors. The CARE regimen consisted of carboplatin (150 mg/m^2 on days 1–3) and etoposide (150 mg/m^2 on days 1–3), and the ICE regimen consisted of ifosfamide (900 mg/m^2 on days 1–5), cisplatin (20 mg/m^2 on days 1–5), and etoposide (60 mg/m^2 on days 1–5). If a drastic reduction in tumor volume was observed in response to the chemotherapy, two further courses of chemotherapy were added. After three courses of chemotherapy, the patient received 24 Gy of radiation to the whole ventricle, or to the whole brain if disseminated lesions were detected. If the patient had spinal dissemination or if the cytology of the cerebrospinal fluid was positive, whole neuraxis radiation was delivered. If a drastic response to the initial chemotherapy was not detected, the surgical removal of the tumor mass was performed for histological diagnosis and/or the complete resection of the lesion.

2.4. Volumetric tumor analysis

The tumor volumes were calculated from the T1-weighted MRI with gadolinium at each time point. The tumor volume was considered to be the enhancing area. The regions of interest (ROI) delineating the enhanced regions were generated manually and the volumes were calculated using the open-source OsiriX imaging software version 3.9.1 (OsiriX Foundation, Geneva, Switzerland).

2.5. MRI examination

MRI was performed with a 1.5 T machine (Signa; General Electric Medical Systems, Milwaukee, WI, USA) or one of two 3 T MRI machines (Intera Achieva Quasar Dual; Philips Electronics Japan, Tokyo, Japan, or Magnetom Trio, A Tim System; Siemens-Asahi Medical Technologies, Tokyo, Japan). The MRI for all 34 patients included axial spin echo T1-weighted, axial fast spin echo T2-weighted, and axial and sagittal T1-weighted sequences with gadolinium.

In 13 patients, diffusion-weighted imaging was performed using fat suppressed spin-echo type echo-planar imaging with three orthogonal directional motion probing gradients (MPG) (b = 1000 s/mm^2), followed by the automatic generation of isotropic diffusion-weighted images (Table 2). Images without MPG (b0 images) were obtained simultaneously. ADC maps were calculated from the isotropic diffusion-weighted images and b0 images.

In 11 patients, single or multivoxel proton MRS was performed (Table 2). Single voxel point-resolved spectroscopy was performed with either a 3 T machine (Patient 10, 11, 21 and 29) using 2.0 kHz spectral band width, 1024 data points, a 2000 ms repetition time, a 144 ms echo time, and averaging over 128 acquisitions, or a 1.5 T machine (Patient 22, 23, 24 and 27) using 2.5 kHz spectral band width, 2048 data points, a 1500 ms repetition time, a 135 ms echo time, and averaging over 128 acquisitions. The voxel of interest (VOI) varied from 12 × 12 × 16 mm to 20 × 20 × 20 mm, depending on the lesion size. The VOI was carefully adjusted to include a representative part of the lesion. If the lesion was enhancing with contrast medium, the VOI was drawn on the enhancing area. Multivoxel proton chemical shift imaging was performed with a 3 T scanner (Patient 28, 30, and 33) using 1.2 kHz spectral band width, 1024 data points, a 1700 ms repetition time, a 135 ms echo time, and a 90 degree flip angle. The VOI was 80 × 80 mm with 15 mm slice thickness and was partitioned into 5 × 5 mm voxels.