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Original article

Atypical meningioma. A study on recurrence and disease-specific survival

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ABSTRACT

Background. – To analyse the outcome of patients with WHO grade II meningioma and identify factors that may influence recurrence and survival.
Material and methods. – Between January 2000 and October 2016, a retrospective search identified 215 WHO grade II meningiomas operated on at our institution. A survival analysis was conducted on clinical and histological criteria.
Results. – Eighteen patients (8.4%) had a previous history of grade I meningioma. The cohort underwent a total of 302 surgical resections and 29.7% received radiotherapy. Forty-one patients (19.1%) had been re-operated on for a WHO grade II meningioma relapse. Median follow-up was 4.5 years. At the end of the study, 105 patients (53.6%) had no residual tumour on the last scan. Surgical recurrence-free survival at 5 years was 82%, 95% CI [75.9–88.5]. Secondary grade II meningioma (HR = 4.27, $P = 0.001$), Simpson resection grade 1 and 2 vs. 3, 4 and 5 (HR = 0.25, $P = 0.001$) and, Ki-67 index (HR = 0.22, $P < 0.001$) were independently associated with the surgical recurrence-free survival. Forty-four patients died from their tumours (20.5%). Cause-specific survival probability at 5 years was 83.2%, 95% CI [77.6–89.1]. Age at diagnosis (HR = 0.31, $P < 0.001$), Simpson resection grade 1 and 2 vs. 3, 4 and 5 (HR = 0.32, $P < 0.001$) and, redo surgery for recurrence (HR = 2.39, $P = 0.010$) were independently associated with the cause-specific survival. Patients who received radiotherapy did not demonstrate either a reduced risk of recurrence or a longer survival ($P = 0.280$).
Conclusion. – In this large series, atypical meningioma recurrence correlated with progression from grade I to II, incomplete resection and high Ki-67 index; shorter survival with an older age, incomplete resection, and redo surgery for recurrence. We did not observe a significant improvement in any of the clinical outcomes after radiotherapy.

1. Abbreviations

CI	confidence interval
MGTR	macroscopic gross total resection
HPF	high power field
HR	hazard ratio
IQR	inter quartile range
WHO	World Health Organization
RT	radiotherapy
STR	sub total resection
TR	total resection

2. Introduction

Meningiomas, which are thought to arise from arachnoid cap cells, account for 13–26% of intracranial tumours and are benign in about 90% of cases [1]. The 2000, 2007 and 2016 World Health Organisation (WHO) classification of tumours affecting the central nervous system recognizes three grades of meningioma. The chordoid, the clear cell and, the most common, atypical meningioma correspond to the WHO Grade II.

In the new 2016 version, the grading of meningiomas did not undergo revisions, save for the introduction of brain invasion as a criterion for the diagnosis of atypical meningioma. While it has long been recognized that the presence of brain invasion in a WHO grade I meningioma confers recurrence and mortality rates similar to those of a WHO grade II meningioma in general, prior WHO classifications had considered invasion a staging feature rather than a grading feature and opted to discuss brain invasion as a separate

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heading. In the 2016 classification, brain invasion joins a mitotic count of 4 or more as a histological criterion that can alone suffice for diagnosing an atypical meningioma [2].

Atypical meningiomas are tumours with increased mitotic activity with 4 mitoses or more per 10 high power fields (HPFs) and/or have at least three of the following characteristics: sheet-like growth, spontaneous necrosis, increased cellularity, prominent nucleoli, and small cells with high nuclear to cytoplasmic ratio. Complete surgical excision is the treatment of choice in all types of meningioma. Further optimal management is difficult to establish, the role of postoperative radiotherapy as a standard adjuvant treatment remains controversial [3].

The aim of this study was to investigate clinical and pathological prognostic factors associated with surgical recurrence and the survival of patients with WHO grade II meningioma, with an emphasis on the effect of postoperative radiotherapy in the prevention of recurrence and death.

3. Methods

3.1. Clinical material

A retrospective neuropathology database search was carried out at the Queen Elizabeth University Hospital, Glasgow, Scotland. Inclusion criteria were meningioma diagnosed between January 2000 and October 2016; pathology diagnosis of grade II meningioma according to WHO 2000, 2007 or 2016 in use at time of surgery. If necessary, cases diagnosed before 2007 and corresponding to the WHO 2000 criteria grading system were reclassified according to the current WHO grading system. No patient was excluded. All patients with a diagnosis of WHO Grade II/atypical/clear cell/chordoid meningioma were included in this study including patients with a recurrent meningioma whose grade had progressed from I to II. Histology slides were reviewed in cases of recurrence. However, all pathology reports were carefully examined. Meningioma sub-type, mitosis count per 10 HPFs (mitotic index), Ki-67 index (MIB-1), presence of necrosis and brain invasion were separately extracted. In cases of recurrence, histology reports were compared with those from previous resections.

Table 1
Patients' characteristics.

Characteristics	*n*, %
Gender male	97 (45.1%)
Median age at surgery	56.9 years, IQR [45.4–68.9]
Symptoms and clinical signs	
Motor and walking impairment	29 (18.7%)
Seizure	43 (27.7%)
Cognitive disorders	26 (16.8%)
Visual disorders	12 (7.7%)
Others	55 (25.6%)
Location	
Convexity	62 (31.2%)
Parasagittal/falx	65 (32.7%)
Skull base	53 (24.7%)
Others	26 (12.1%)
Tumour volume	42 cm^3, IQR [21.1–80.1]
Preoperative embolisation	14 (6.7%)
Resection status	
MGTR (Simpson 1, 2 and 3)	165 (77.1%)
STR (Simpson 4 and 5)	49 (22.8%)
Venous sinus invasion	77 (39.1%)
Histological sub-types	
Atypical meningioma	194 (90.7%)
Clear cell meningioma	2 (0.9%)
Chordoid meningioma	18 (8.4%)
Median mitoses count per 10 HPFs	5 per 10 HPFs, IQR [2–6]
Presence of a brain invasion	70 (33.2%)
Radiotherapy	56 (26%)
Stereotactic radiotherapy	9 (4.2%)

Patient demographic and medical data were collected retrospectively. We used radiographic and surgical reports, and all available in- and outpatient records. Patients' CT and MRI images were studied pre and postoperatively. Tumour location was initially divided into 10 categories. However, some locations e.g. spinal or petroclival had only a few cases making them unsuitable for statistical analysis. These cases were placed in a new category named "other locations".

Age at diagnosis was defined according to the date of first surgery for a grade II meningioma. Surgical resection was evaluated according to the Simpson grading scale using the operative records [4]. We defined macroscopic gross total resection (MGTR) as Simpson grade 1, 2 and 3 and, incomplete resection or subtotal resection (STR) as Simpson grade 4 and 5. If radiotherapy was given, data on the technique, overall dose and time of completion were collected.

We defined two types of recurrence. The first type was defined as a "surgical relapse", characterizing the patients who underwent a second surgical procedure for a WHO grade II meningioma recurrence (progression-free survival). The second type as a "radiological relapse" corresponded to radiological evidence of tumour regrowth in cases of total resection, or to residual tumour progression in cases of incomplete resection. For each case, we compared the surgical impression with the early postoperative gadolinium contrasted scan.

For deaths, the cause was searched and quoted differently if related or not to the surgery or the progressing meningioma disease.

Patient outcome and clinical status were assessed through medical records, the patient database and information obtained from the general practitioners. A patient who we were unable to contact two years after the surgery was considered lost to follow-up and right-censored in the survival analysis.

This retrospective study was conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the Helsinki Declaration (2008) and the French Data Protection Authority (CNIL), authorisation number: 20007178v0.

3.2. Statistical methods

Survival statistics were based on two different events: redo surgery for meningioma recurrence and death. Both time to event were calculated from the date of diagnosis i.e. the date of the first surgery for a WHO grade II meningioma. Survival function was assessed by the Kaplan-Meier method and, the Mantel Cox log-rank test was used to compare different survival functions according to clinical and therapeutic factors (cause-specific or corrected survival; individuals who died of other causes were censored) [5,6]. Because death was the most unexpected event, mortality was the primary outcome of interest and surgical recurrence the secondary. Independent prognostic factors with a P-value < 0.20 were selected in an adjusted regression by a backward elimination. A P-value < 0.05 was considered as statistically significant. Analysis was performed with the R programming language and software environment for statistical computing and graphics (R version 3.3.2 [2016-10-31]), the survival, the rms packages among others [7,8]. The statistical program and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research [9].

4. Results

4.1. Population description

Median follow-up was 4.5 years (IQR [2.1–7.8], range [0–22.97]). 2 patients (0.9%) were lost to follow-up. Of the 215 cases collected,

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