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Clinical Study

Current indications for the surgical treatment of prolactinomas

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ABSTRACT

The purpose of this study was to examine the current indications for transsphenoidal surgery in the prolactinoma patient population, and to determine the outcomes of patients who undergo such operations. Transsphenoidal surgery may be indicated in prolactinoma patients who are resistant and/or intolerant to dopamine agonist (DA) therapy. We performed a retrospective review of the medical records of prolactinoma patients over a 6 year period (April 2008 to April 2014) at a large volume academic center. The median follow-up time was 12.0 months (range: 3–69). All patients who were included in the study (n = 66) were treated with DA therapy and subsequently underwent an endonasal transsphenoidal operation. Of the 66 patients, 44 were women (mean age 34.2 years) and 22 were men (mean 41.7 years). There were 29 (43.9%) intolerant patients and 29 (43.9%) resistant patients. Postoperatively, 18 intolerant patients (66.7%) had normalized prolactin levels without the need for DA therapy, and five (17.2%) required DA to normalize their prolactin levels ($p = 0.02$). Six patients (20.6%) had persistently elevated prolactin levels but were no longer receiving DA treatment ($p < 0.001$). Postoperatively, 10 resistant patients (35.7%) had normal prolactin levels without DA therapy, and seven patients (25%) were treated with DA therapy to normalize their prolactin levels ($p = 0.22$). Eight patients (28.6%) had supraphysiologic prolactin levels but were no longer taking a DA ($p < 0.001$). Three patients (10.7%) were hyperprolactinemic, despite postoperative treatment with DA ($p < 0.001$). After an appropriate treatment interval with multiple DA, radiographic follow-up, and careful clinical evaluation, prolactinoma patients can be offered surgery as an effective therapeutic option.

1. Introduction

Prolactin-secreting adenomas are the most common subtype of all primary pituitary tumors, representing approximately 40% of all pituitary adenomas [1]. Although predominantly benign and classified as World Health Organization Grade I tumors [2], prolactinomas present with significant clinical sequelae due to mass effect and/or increased serum prolactin levels [3]. Hyperprolactinemia is a common endocrine disorder that is often related to the oversecretion of prolactin, but can also be caused by an interference of dopamine transport related to tumor mass effect on the infundibulum [4].

Prolactinomas are unique in that they are pituitary tumors that can be treated successfully with medical therapy. Dopamine agonists (DA) have been in use for many years, with bromocriptine (BRC) as the treatment of choice. BRC was then tested in 1985 as part of a prospective multicenter trial for the treatment of macroprolactinomas [5]. Prolactin was normalized in two-thirds of all tumors, and the size of the tumor was decreased by more than half in 46% of patients, by half in 18%, and by a quarter in 36% in a 6 week period [5]. Since that time, bromocriptine has been replaced by cabergoline (CAB) as the first line DA treatment because of a lower side effect profile, increased half-life, and convenience of administration [3,6–12].

When patients do not experience normalization of their prolactin levels, or when there is lack of radiographic shrinkage/stabilization of the tumor with DA therapy, they are classified as resistant to DA treatment, and surgery may become the appropriate next step [9,13–17,11]. Resistance to BRC has been defined as the failure to normalize serum prolactin levels after having received a daily dose of 15 mg of BRC for 3 months [9,15–17]. CAB resistance is defined as the failure to normalize serum prolactin levels after having received a weekly dose of 1.5–3.0 mg over a 3 month period, although some advocate titration to higher doses [9,15–17]. Furthermore, tumors that are cystic, have intratumoral

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hemorrhage, and/or present with apoplexy, do not typically shrink with DA therapy, and surgery is almost always recommended to relieve the symptoms [18]. When treated surgically, patients with prolactinomas have variable success, as measured by their prolactin normalization. A recent meta-analysis reported that 73.7% of patients with microadenomas and 32.4% of patients with macroadenomas had normal prolactin levels 1–3 months after surgery [19,20].

Some patients may not be resistant to DA therapy, but are unable to tolerate the side effects of this therapy [6,21,14,22]. Reported side effects attributed to DA therapy include headache, mood changes, cognitive problems, nausea/vomiting, insomnia, fatigue and orthostatic hypotension [4]. It is estimated that 12% of patients on BRC and 3% of patients on CAB are unable to tolerate DA and, therefore, they are candidates for surgical intervention [12]. Other indications for surgery include patient preference, cerebrospinal fluid (CSF) leak due to shrinkage of the tumor, or medical comorbidities that prohibit the patient from receiving DA therapy.

The aim of this study is to report our current experience, indications for, and results of endoscopic transsphenoidal surgery in patients with prolactinomas at a quaternary care specialty hospital.

2. Methods

Medical records from a single, high volume, academic center were reviewed, and 66 consecutive prolactinoma patients who underwent transsphenoidal resection between April 1 2008 and April 1 2014 were included in the study. Patients were included if they had positive identification of an intrasellar mass lesion on MRI, had undergone surgical resection, and had immunohistochemical confirmation of prolactin-secreting tumor cells. Patients were excluded if they underwent open cranial surgery exclusively. Notably, patients were not excluded by the presence/absence of hypersecretion along other pituitary axes (for example, tumors that stained positive for both prolactin and growth hormone secretion were included in the data).

The medical records were examined for the following data: age at time of surgery, sex, symptoms upon presentation, preoperative and postoperative endocrine status (including serum hormone levels), type and duration of preoperative medical management, preoperative radiologic presentation (maximum dimensions, estimated tumor volume, degree of suprasellar extension), surgical indications (symptoms of medication intolerance and/or tumor/prolactin resistance while still on DA therapy), surgical technique (transsphenoidal, microscopic *versus* endoscopic, presence and type of intraoperative CSF leak, use of abdominal fat graft, use of nasal packing, and/or lumbar drain), pathologic specimen findings (microscopic description, typical or atypical characterization, immunohistochemistry, MIB-1 proliferation index), and postoperative course (hospital course, length of inpatient stay, hormone replacement therapy, adjunctive chemotherapy or radiation therapy, gross total resection on postoperative imaging, presence of any complications or need for further reoperation). The postoperative complications that were tracked included symptomatic inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus (DI), postoperative CSF leak, meningitis, surgical site infection, new onset visual disturbances, reoperation/readmission within 30 days, postoperative epistaxis, steroid-induced psychosis, and sinus complications. All radiologic variables were confirmed with finalized reports from senior radiologists at our institution. The total tumor size was estimated as one half the total product of the maximum tumor dimensions in each plane (for example, a tumor with maximum dimensions measuring $1 \times 2 \times 2.5$ cm would have a total estimated tumor volume of $5/2 = 2.5$ cm^3) [23].

Basic patient demographics, as well as preoperative and perioperative characteristics, were summarized using counts and percentages for nominal variables, and means/medians and standard deviations/ranges for continuous variables. The patients were categorized according to sex, and further evaluated for significant sex difference in terms of tumor size (micro *versus* macroadenoma), age, and highest or lowest preoperative prolactin level. The resistant and intolerant patients were then examined for improvement of symptoms, tumor shrinkage, and normalization of prolactin levels following surgery. Pathologic characteristics (immunohistochemistry findings and MIB-1 proliferation indices) and postoperative complications were also summarized using counts and percentages or means and standard deviations, as appropriate. Dopamine resistance was defined as a lack of serum prolactin normalization (5–20 ng/ml) and/or lack of radiographic shrinkage/stabilization of the tumor, despite escalating DA therapy over a 3 month period.

The significance tests were conducted using a chi-squared test and Maental–Hanzal odds ratios (OR) for nominal variables, Student's *t*-test for continuous variables, and analysis of variance for continuous variables with greater than two categories. The data were analyzed using SPSS software (version 22; IBM Corporation, Armonk, NY, USA). An alpha level <0.05 was considered statistically significant.

3. Results

Overall, 66 patients with prolactinomas were included in the study, 44 women (mean age 34.2 years; range: 18–54) and 22 men (mean age 41.7 years; range: 16–65), and all presented with hyperprolactinemia. These adenomas were discovered incidentally in three (6.8%) women and one (4.5%) man. The majority of women presented with headaches (70.5%), dysmenorrhea (63.6%) and galactorrhea (50%), whereas most men presented with hypopituitarism (86.4%) and headaches (72.7%). The majority of women (95.5%) and men (86.3%) had been treated with at least one form of DA prior to surgery. The median follow-up time for all patients was 12.0 months (range: 3–69; Table 1).

The imaging characteristics of the prolactinoma patients are presented in Table 1. We found that 40.9% of patients (n = 27) presented for a surgical consultation with tumors classified as microadenoma (largest tumor diameter <1.0 cm), and 59.1% of patients (n = 39) presented with macroadenomas (largest diameter $\geqslant$ 1.0 cm). Radiographically, 24 patients had suprasellar extension (26.2%), 32 (48.5%) had cystic components within the tumor, and 11 prolactinomas (16.7%) were found to invade parasellar structures. The mean maximum diameter of the tumors was 3.5 cm (Table 1).

Overall, 19 of the prolactinoma patients (28.8%) did not tolerate the side effects of DA therapy. Nineteen (28.7%) had neither radiographic tumor shrinkage nor clinical decrement in serum prolactin levels and received an operative intervention. Ten patients (15.1%) were both resistant and intolerant to medical treatment. One pregnant patient opted out of receiving a DA prior to surgery, and one schizophrenic patient could not tolerate DA. Two patients presented with apoplexy and mildly elevated serum prolactin levels, and were taken to surgery urgently for decompression of the mass effect (mean serum prolactin 112 ng/mL). Eleven (16.7%) were presumed to have stalk effect only prior to the operation, and then were postoperatively discovered to have a pathologic diagnosis of prolactinoma. One patient opted to forgo medical treatment with a DA and elected to proceed straight to surgical intervention (Table 1).

Table 2 outlines the preoperative use of DA therapy in 45 patients (68.2%). The majority of patients had received CAB alone