Recent Advances in Diagnosis and Treatment of Aggressive Pituitary Tumors and Pituitary Carcinomas

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What Does Surgery Offer for Invasive/Aggressive Pituitary Adenomas?

Over the past few decades, attempts have been made to develop markers that correlate with the behavior of pituitary adenomas to identify lesions with an increased potential for malignancy (metastasis, invasion, or recurrence following treatment) [Zada G et al. *J Neurosurg 2011*].

Edward Raymond Laws, MD, Brigham & Women's Hospital, Boston, Massachusetts, USA, discussed the role of surgery in the treatment of aggressive/invasive pituitary adenomas.

Pituitary adenomas are common intracranial tumors [Sughrue ME. *Pituitary* 2011]. The overwhelming majority of tumors that arise from the pituitary parenchyma is histologically benign, and as such, death from disseminated central nervous system disease or distant metastasis is exceedingly rare [Chang EF et al. *Pituitary* 2010; Sughrue ME. *Pituitary* 2009].

Still, pituitary tumors have the ability to dramatically alter a wide range of endocrinological and physiological systems either by secreting supraphysiological levels of pituitary hormones or by interfering with the normal function of the pituitary gland [Sughrue ME. *Pituitary* 2009]. Conceivably, these tumors could alter a patient's lifespan due to their endocrinological and secondary metabolic effects [Sughre ME. *Pituitary* 2011].

Many pituitary adenomas have the capability to invade adjacent parasellar structures; data have demonstrated histological invasion of the dura in up to 80% of macroadenomas and 15% of microadenomas. Invasion of the cavernous sinus dura on either side of the lesion is most common.

With the exception of prolactinomas, which are predominantly managed pharmacologically [Marek J. *Vnitr Lek* 2010], transphenoidal microsurgery is the firstline option for treatment for most patients with nonfunctioning pituitary microadenomas or functioning macroadenomas that cause acromegaly or Cushing disease [Castro DG. *Radiation Oncology* 2010]. However, most aggressive pituitary tumors often require repeated surgery [Colao A. *Expert Opin Pharmacother* 2011].

Suprasellar extension of a pituitary tumor may lead to invasion of the diaphragm of the sella. Some tumors, particularly in acromegaly, invade inferiorly into the sphenoid sinus. These invasive tumors may present with hormonal hypersecretion and/or mass effect. The latter includes loss of vision from chiasmal or optic nerve compression and diplopia from paresis of cranial nerves that are responsible for ocular movements. Many dural structures that are involved cannot be removed safely; thus, some invasive tumors are often left behind following surgery and may be responsible for tumor recurrence.

Most pituitary carcinomas are functioning, with ACTH- and PRL-secreting carcinomas being the most common [Colao A et al. *Front Horm Res* 2010]. In a recent study of 121 consecutive patients who underwent transphenoidal surgery for pituitary adenomas during an 18-month period, 15% of the tumors met the World Health Organization (WHO) criteria for atypical lesions and tended to be aggressive, invasive macroadenomas; 94% were macroadenomas. On imaging, 83% demonstrated evidence of surrounding invasion compared with 45% of typical adenomas (p=0.004) [Zada G et al. *J Neurosurg* 2011].

Peer-Reviewed Highlights from the

Despite the poor prognosis for aggressive pituitary tumors, surgery can accomplish many goals, including:

- Relief of mass effect—restoration of vision, reversal of diplopia
- Normalization of hormonal hypersecretion
- Characterization of the tumor, including:
  - Definitive pathology—tumor subtype, immunocytochemistry
  - Measures of proliferation index (Ki-67, MIB-1), mitotic index, classification as typical or atypical
  - Other tumor markers—p53, Pit-1, Galanin
- Alerts for aggressive behavior
  - Silent ACTH adenoma
  - ACTH adenoma in Nelson syndrome
  - Mammosomatotroph tumors
  - Acidophil stem cell tumors
  - Plurihormonal tumors
- Tissue for molecular studies pertinent to adjunctive medical management; eg, dopamine D2 receptor density
- Information helpful in targeting radiotherapy/radiosurgery

Diagnosis and Nonsurgical Treatment

Gerald Raverot, MD, Hospices Civils de Lyon, Lyon, France, discussed recent advances in the diagnosis and treatment of aggressive pituitary tumors and pituitary carcinomas, classically defined as pituitary tumors with a massive invasion of the surrounding anatomical structures and rapid growth.

When aggressive pituitary neuroendocrine tumors develop, conventional treatment options are of limited success. The tumors are notoriously difficult to manage and generally unresponsive to therapy [Colao A. *Expert Opin Pharmacother* 2011] and thus associated with substantial morbidity and mortality.

Approximately 15% of pituitary tumors are aggressive with a high proliferation rate and a short postoperative time before recurrence. Only metastatic tumors, which account for 0.2% of pituitary tumors, are considered malignant.

Even if, at diagnosis, the presence of metastasis is required to define pituitary carcinomas, lesions are almost invariably first diagnosed as benign pituitary tumors. After a variable period of latency, ranging from a few months to many years, they change their natural course to an aggressive pituitary tumor that is poorly responsive to therapy [Colao A et al. *Front Horm Res* 2010].

Predicting pituitary tumor behavior remains a challenge. In 2004, the WHO developed a new classification for atypical adenomas, based on tumor markers that are thought to correlate with more aggressive pituitary tumor biology. The "atypical" variant is defined as: MIB-1 proliferative index greater than 3%, excessive p53 immunoreactivity, and increased mitotic activity [Zada G et al. *J Neurosurg* 2011]. The new designation serves as an intermediary between typical pituitary adenomas and pituitary carcinomas.

Prof. Raverot and colleagues used a combination of histological and transcriptomic approaches in human prolactin tumors to identify prognostic markers [Wierinckx A et al. *Endocr Relat Cancer* 2007; Raverot G et al. *J Clin Endocrinol Metab* 2010] and genomic alterations that are associated with prolactin tumor aggressiveness [Wierinckx A et al. *Brain Pathol* 2011].

Treatment options are often limited, and although results from chemotherapy have historically been disappointing, it has been reserved as salvage therapy [Kaltsas GA. *J Clin Endocrinol Metab* 2005]. Due to a paucity of reported cases, knowledge of the response to treatment and overall prognosis of patients with aggressive pituitary tumors or carcinomas is sparse [McCormack AI et al. *Eur J Clin Invest* 2011]. However, recent studies reported the successful use of temozolomide, an alkylating agent that is used in the management of glioblastoma and some neuroendocrine tumors, in the management of pituitary carcinomas, with a 60% response rate amongst the published cases [Raverot G et al *J Clin Endocrinol Metab* 2010].

Moreover, evidence suggests that in pituitary adenomas, both the Raf/MEK/ERK and P13K/Akt/mTOR pathways are upregulated in their initial cascade, implicating a pro-proliferative signal disturbance.

As such, mTOR inhibitors, which have recently been found to have antineoplastic activity in several human cancers, including neuroendocrine tumors, could be a good alternative for temozolomide-resistant pituitary tumors. Similarly, since HER2 overexpression has been demonstrated in prolactin tumors, the HER2/ErbB2 signaling pathway inhibitor lapatinib could prove useful.

These recent results, combined with the identification of signaling pathways that are associated with pituitary tumor aggressiveness, open new opportunities for treatment when no other therapeutic options are available.