Endocrine, *vol. 28, no. 1, 115–121, October 2005* 0969–711X/05/28:115–121/$30.00

Pituitary Carcinoma

Diagnosis and Treatment

M. Beatriz S. Lopes,[1] Bernd W. Scheithauer,[2] and David Schiff[3]

[1]Department of Pathology (Neuropathology), University of Virginia School of Medicine, Charlottesville, VA; [2]Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, MN; and [3]Department of Neurology (Neuro-Oncology), University of Virginia School of Medicine, Charlottesville, VA

Pituitary carcinomas are rare pituitary tumors that by definition have cerebrospinal and/or systemic metastases. Most of the tumors occur in the setting of multiple recurrences of invasive pituitary adenomas. This article reviews the clinical presentation of these tumors, their neuroimaging and pathological features, tumor pathogenesis, and possible treatment modalities.

Key Words: Pituitary neoplasm; carcinoma; pathogenesis; radiotherapy; chemotherapy.

Introduction

Pituitary carcinomas, as defined by the World Health Organization (WHO) Classification System *(1)*, are epithelial tumors of the pituitary gland that exhibit cerebrospinal and/or systemic metastasis. They are very rare tumors, constituting about 0.2% of operated pituitary tumors *(1,2)*. Approximately 150 cases have been reported in the English literature, and two comprehensive reviews of all cases have recently been published *(3,4)*. The majority of reported pituitary carcinomas are endocrine functioning tumors. Metastases are rarely present at the time of the initial pituitary tumor diagnosis. Most commonly they manifest after a variable latency period subsequent to the initial diagnosis of the primary sellar tumor. The tumors show a great tendency to both systemic and craniospinal metastasis. In general, pituitary carcinomas are associated with poor prognosis. Therapeutic options are limited.

Clinical Features

Clinical Presentation

Pituitary carcinomas develop with equal frequency in female and male patients. As in pituitary adenomas, most occur in adults and present in the 5th–6th decades of life *(2)*. The majority of carcinomas are invasive macroadenomas at the time of diagnosis. Thus, they often exhibit signs and symptoms of mass effect in addition to endocrine hyperfunction.

The great majority of reported pituitary carcinomas are hormonally active tumors with endocrine manifestations indistinguishable from those of pituitary adenomas. The most common endocrine syndromes are Cushing's disease (42%) and hyperprolactinemia (33%), followed much less commonly by acromegaly (6%) and hyperthyroidism (1%) *(3)*. Laboratory data in patients with pituitary carcinomas differ little from those of ordinary adenomas, but some studies have suggested that very high hormone levels, particularly in the face of adequate surgical treatment, are an alert for the possibility of metastases *(4)*.

Endocrinologically non-functioning tumors constitute about 15–20% of the cases including silent corticotroph, gonadotroph, and even the rare null cell carcinoma *(3,5)*. Signs and symptoms of clinically non-functioning carcinomas are similar to those associated with their benign counterparts, and mostly relate to mass effects such as visual disturbances and headaches.

The clinical course of pituitary carcinomas is quite variable. As noted above, carcinomas only rarely present with metastases concurrent with the initial sellar tumor, an event suggesting *de novo* malignancy *(6,7)*. In most instances the initial course is indistinguishable from that of an ordinary pituitary adenoma, albeit with multiple local recurrences over a long course prior to metastatic dissemination. Reported periods of latency between presentation of the sellar tumor and metastases varies enormously, ranging from 3 mo (*5* [case 3], *8*) to 19 yr (*9* [case 2]), the mean interval in one large series being 6 yr *(2)*. The latency period appears to vary somewhat according to tumor type. Pernicone et al. *(2)* reported latency periods twice as long for ACTH-secreting tumors as compared to PRL-secreting tumors (9.5 vs 4.7 yr, respectively).

Pituitary carcinomas are defined by their tendency to systemic and/or craniospinal metastasis. The rate of systemic metastasis in one large series was reported as 71% for PRL-producing tumors and 57% for ACTH-producing tumors *(2)*. In another series, 45.2% of pituitary carcinomas under-

Received June 15, 2005; Accepted July 18, 2005.

Author to whom all correspondence and reprint requests should be addressed: M. Beatriz S. Lopes, MD, Division of Neuropathology, Department of Pathology, University of Virginia School of Medicine, 1215 Lee Street, 3rd Floor, Room 3060, P.O. Box 800214, Charlottesville, VA 22908. E-mail: msl2e@virginia.edu

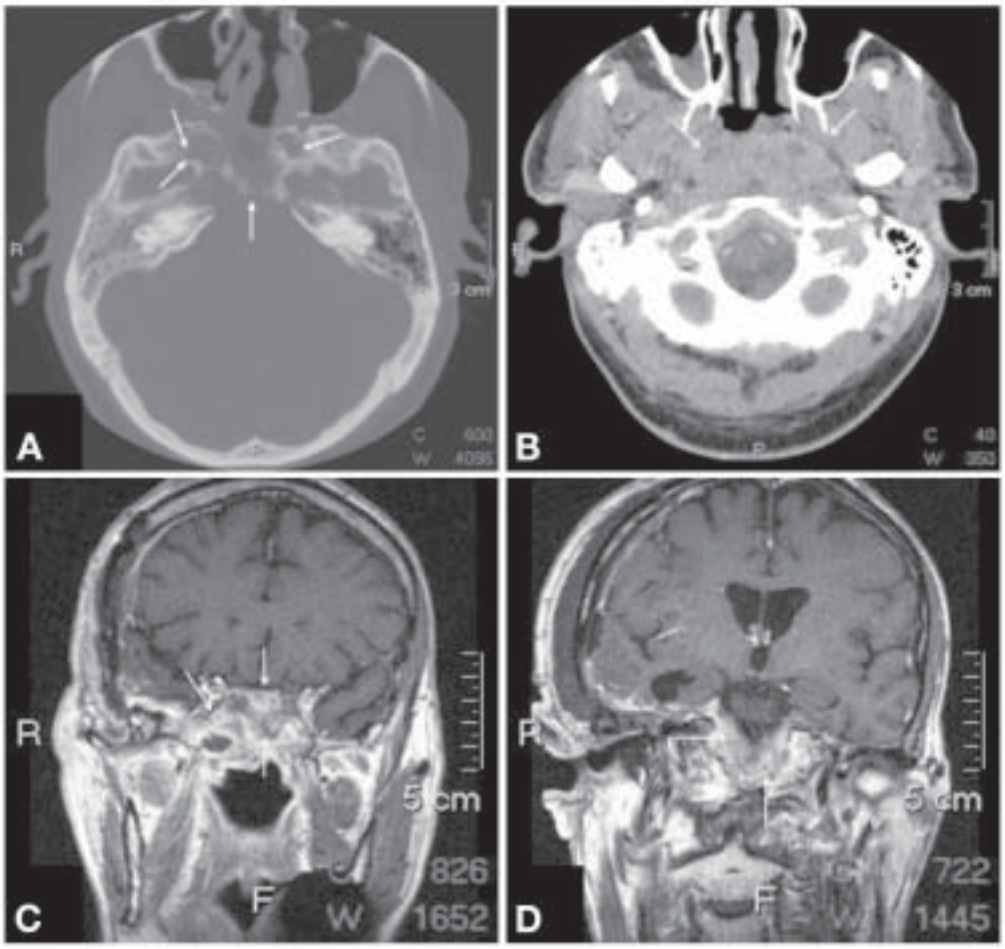

Fig. 1. Neuroimaging of a patient with null-cell pituitary carcinoma (same patient as Fig. 2). The patient underwent two surgical resections (1994, 2000) and sellar radiation therapy before these images. (**A**) Bone windows of CT scan through the skull base demonstrate marked erosion involving the sphenoid bone and petrous apices (arrows) [data of procedure (DOP) 06/2001]. (**B**) Contrast-enhanced CT through the nasopharynx shows extremely enlarged bilateral metastatic retropharyngeal lymph nodes (arrows) with central necrosis [DOP 12/2002]. (**C,D**). Coronal gadolinium-enhanced T1-weighted MRI images reveal an inhomogeneously enhancing infiltrating mass involving the sella turcica, sphenoid sinus, nasopharyngeal soft tissues, and clivus (arrows) [DOP 05/2005].

went intracranial and/or spinal dissemination alone, 38.7% systemic metastasis alone, and 16.1% both intracranial and extracranial spread *(10)*.

Symptoms relate to metastases vary according to site of involvement. In the central nervous system (CNS), metastases have reportedly involved the cerebral cortex, cerebellum, spinal cord, leptomeninges, and dura. Most cases feature leptomeningeal spread via cerebrospinal fluid (CSF) with seeding of multiple superficial metastases *(11,12)*. Dural metastases may mimic meningiomas *(13)*. Intradural, extramedullary lesions often produce signs of spinal cord compression *(12)*. It has been suggested that metastases situated well within brain parenchyma may be the result of reverse venous flow *(10)*.

Systemic metastases most commonly involve cervical lymph nodes (Fig. 1), liver, bones, and lungs *(1)*. Rare cases have been reported to metastasize to heart, kidney, pancreas, ovary, skeletal muscle, the eyes, and even the middle ear *(10)*. Systemic dissemination is believed to occur by lymphatic and/or hematogeneous routes. In cases in which the cavernous sinus has been invaded by the tumor, spread probably occurs via the superior petrosal sinus *(10)*.

Imaging Findings

As a general approach to pituitary tumors, high-resolution gadolinium-enhanced magnetic resonance (MR) imaging is the preferred diagnostic method for analyzing extension of disease *(14)*. Pituitary carcinomas most commonly occur in the setting of a known invasive macroadenoma. The intrasellar component typically demonstrates aggressive behavior with sellar destruction as well as suprasellar and often parasellar extension (Fig. 1). The cavernous sinus is generally involved. It is of note that neuroimaging studies do not reliably distinguish locally invasive pituitary adenomas from tumors that will progress to carcinoma. For the discovery of systemic and CNS metastases, several radio-

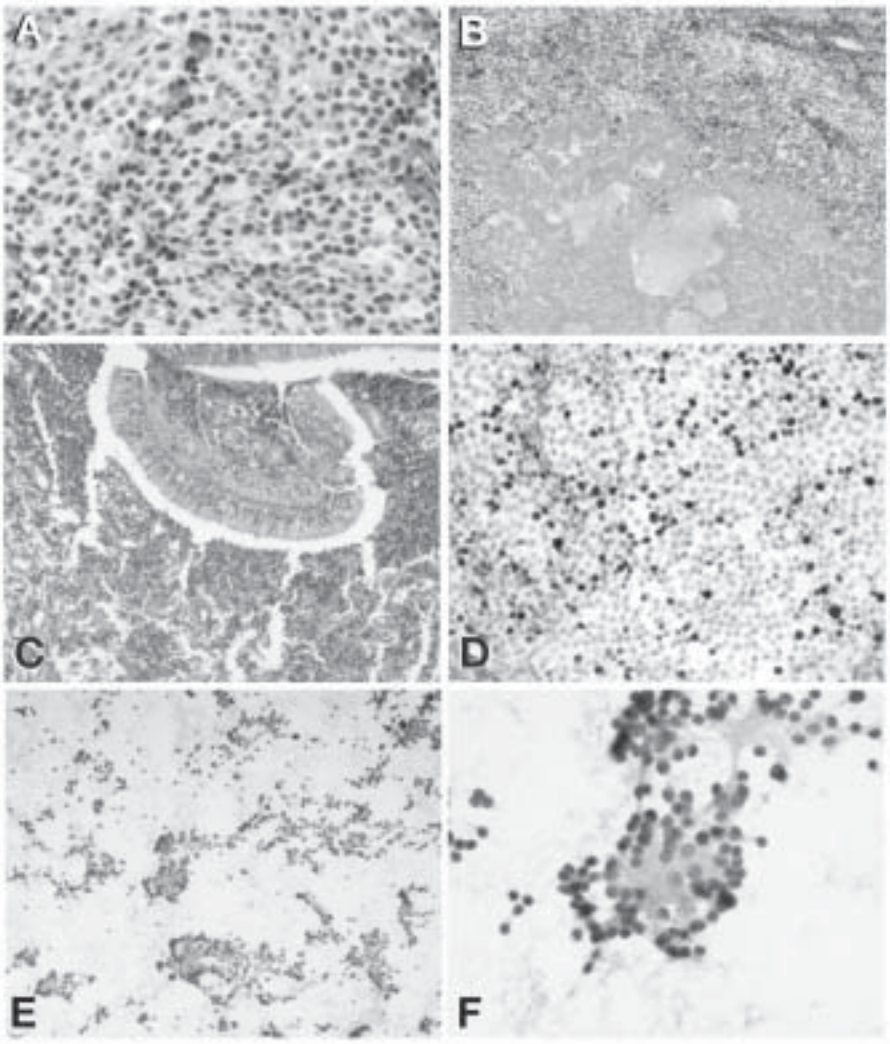

Fig. 2. Histopathology of a patient with null-cell pituitary carcinoma (same patient as Fig. 1). (**A,B**). Sellar tumor showing a chromophobic adenoma with minimal atypia but large areas of necrosis probably secondary to previous radation therapy treatment [date of procedure (DOP) 6/2001]. (**C**) Frank invasion of the sphenoid sinus mucosa and bone (not shown) was seen in a craniotomy resection performed in 12/2002. (**D**) Ki-67 immunostain in the same specimen as (**C**) showed very high labeling. (**E–F**). Fine needle aspiration performed on retropharyngeal lymph nodes (see Fig. 1B) showed papillary-like arrangements of neuroendocrine cells with cytological features similar to the sellar and sphenoid sinus specimens confirming the diagnosis of a pituitary carcinoma [DOP 12/2002].

logical methods may be used including CT and MR scans. Studies comparing the MR imaging characteristics of both the primary intrasellar tumors and metastatic lesions have noted no significant differences in basic radiologic features or signal abnormalities *(15)*.

Radionuclide and functional imaging studies using specific radiotracers have also been employed in an effort to quantify extension of disease and to identify metastases. These include meta-iodo-benzylguanidine (MIBG), octreotide (^{111}In-pentreotide) *(16,17)*, dopamine D2-receptor ligands (^{123}I-epidepride) *(18)*, and tumor metabolites (^{18}F-deoxyglucose; 11C-L-methionine) *(19)* scintigraphy scans. Although often in isolated case reports, all these methods have facilitate the detection of metastatic lesions and the assessment of treatment effect. The widespread clinical application of these techniques requires still more experience and the establishment of diagnostic guidelines *(20)*.

Pathological Features

Histopathology and Immunohistochemistry

At present, the diagnosis of pituitary carcinoma is dependent on the demonstration of metastatic spread. There are as yet no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from carcinomas in their sellar phase (Fig. 2). Standard morphologic features associated with malignancy including hypercellularity, nuclear/cellular pleomorphism, mitotic activity, necrosis, and dural/osseous invasion are commonly seen in carcinomas. However, these morphologic features may also be

present in varying degrees in ordinary and atypical pituitary adenomas, either with or without invasive behavior. Thus, tumors with these features do not necessarily progress to malignancy. Mitotic activity varies considerably in primary tumors; a mean of 2.5 mitoses/10 hpf was reported in one large study *(2)*. Some carcinomas lack mitotic figures entirely *(5)*. However, metastatic lesions tend to feature greater degrees of cytologic atypia and mitotic activity, the mean value being 6 mitoses/10 hpf in the previous study *(2)*.

Just like adenomas, pituitary carcinomas are immunopositive for neuroendocrine markers including synaptophysin and chromogranin A. The immunoprofile for pituitary hormones is somewhat similar to that of adenomas, with the exception that carcinomas are most often immunoreactive for PRL and ACTH. Thus, they are associated with hyperprolactinemia and with either Cushing's disease or Nelson's syndrome, respectively. Five examples of silent corticotroph carcinomas have also been described *(5)*. Pituitary carcinomas are only rarely immunoreactive for GH, LH/FSH, or TSH *(3,4)*.

Proliferation Markers and Cell Cycle Inhibitors

Studies of proliferative activity in pituitary adenomas, particularly those using the proliferative marker Ki-67 (monoclonal antibody MIB-1), have shown the majority of noninvasive adenomas to have a low growth fraction, most indices being less than 3% *(21–23)*. In comparison, mean growth fractions were significantly higher in invasive adenomas and pituitary carcinomas *(21,24)* (Fig. 2). Pituitary tumors exhibiting an elevated mitotic index, a Ki-67 labeling index higher than 3%, and significant immunoreactivity for p53 (see below) are designated "atypical" adenomas and should raise suspicion of malignant potential *(23)*. Even though Ki-67 indices are often higher in carcinomas than adenomas, particularly in metastatic deposits, the overlap of labeling indices is considerable; indeed, some carcinomas exhibit very low Ki-67 labeling indices *(1,2,5)*.

The cyclin-dependent kinase inhibitor p27 is a cell cycle inhibitor widely expressed in normal pituitary tissue *(25)*. Mutation of the *p27* gene has not been documented in human pituitary tumors. Nonetheless, nuclear p27 protein expression is significantly decreased in adenomas as compared with normal pituitary, and is much lower in pituitary carcinomas as compared with both normal pituitary tissue and pituitary adenomas *(25,26)*. In general, Ki-67 labeling is negatively correlated with p27 nuclear staining *(25)*.

Pathogenesis and Molecular Cytogenetics

The development of pituitary tumors appears to be a multistep and multicausal process in which endocrine factors, hereditary genetic disposition, and specific somatic mutations serve as contributing factors. In recent years intense laboratory investigation in search for identifying and characterize mutation(s) of candidate oncogenes and tumor suppressor genes in pituitary tumorigenesis has been undertaken. Nonetheless, little is known about the mechanisms involved in human pituitary tumorigenesis and tumor progression. The very rarity of pituitary carcinomas further prevents definite conclusions regarding the molecular mechanism underlying their pathogenesis.

X-chromosomal inactivation analyses indicate that the majority of adenomas and carcinomas are monoclonal in nature *(27)*. Examination of a single case of carcinoma in a patient with Cushing's disease, in which primary, recurrent, and metastatic tumors were analyzed, showed monoclonality in all three lesions with a similar allelic pattern *(28)*. However, loss of heterozygosity (LOH) analysis at multiple microsatellite loci on several chromosomes demonstrated that the metastatic deposits had a novel loss-to-retention pattern at two distinct loci in comparison with the primary and recurrent pituitary tumors. This suggested the possibility that distinct clonal expansions confer different biological behavior to mestastatic deposits as compared to recurrent tumors *(28)*.

Comparative genomic hydridization (CGH) studies in pituitary adenomas have shown gains and losses involving all chromosomes, particularly in recurrent tumors. Because the chromosomal regions involved differ widely between and even within studies, no general conclusions can be drawn at this point. To date, only four pituitary carcinoma metastases, two ACTH- and two PRL-secreting tumors, have been studied for chromosomal aberrations by this method *(29)*. Chromosomal imbalances were found to be high (average 8.3), gains being more commonly encountered than losses. The most common changes were gains of chromosomes 5, 7p, and 14q.

Screening for several tumor suppressor genes and oncogenes has failed to identify significant mutations that might play a role in pituitary tumorigenesis. Although mutations of the tumor suppressor gene *TP53* are the most common genetic event associated with human cancers, *TP53* gene mutations and chromosome 17p deletions have not been demonstrated in pituitary adenomas or carcinomas *(30)*. Nonetheless, immunohistochemical studies for the *TP53* gene product have showed overexpression of p53 protein in a number of highly invasive adenomas and carcinomas, thus suggesting that mechanisms other than gene mutation may be implicated in overexpression of the protein *(31)*.

Point mutations of the H-*ras* protooncogene have been identified in distant pituitary carcinoma metastases, but not in their respective primary lesions *(32)*. In yet several other carcinomas similarly examined, no H-*ras* mutations were documented *(32,33)*.

Screening of numerous adenomas failed to reveal mutations of the *RB* tumor suppressor gene *(34,35)*. However, allelic loss of *RB* has been demonstrated in a few invasive adenomas and pituitary carcinomas *(36)*.

In combination, these results suggest that although mutations in *TP53,* H-*ras*, and *RB* genes are not directly associated with pituitary tumorigenesis, these oncogenes and tumor

suppressor genes may play a role in the progression to carcinoma and metastases.

Individual descriptions of other genetic alterations have been reported in pituitary carcinomas. Epidermal growth factor receptor (EGFR/HER-1) and other members of the EGFR subfamily (HER-2/neu, HER-3, and HER-4) play an important role in the pathogenesis of many human malignancies and, through the actions of their ligands, participate in autocrine and paracrine stimulation of cancer cells with resultant clinically aggressive disease *(37)*. EGFR expression has been described in seven pituitary carcinomas and was found to be higher than in adenomas *(38)*, thus suggesting a possible role of EGFR in pituitary tumor progression. Furthermore, HER-2/neu protein expression has been demonstrated in two cases of pituitary carcinoma (*9* [case 1], *39*). *HER-2/neu* gene amplification was confirmed in one of the two cases with increased amplification taking place between the first recurrence and metastasis *(9)*. Interestingly, the progressive gene amplification positively correlated with increase in histological anaplasia, proliferative activity, and p53 labeling, thus suggesting that *HER-2/neu* amplification may result in progressive dedifferentiation of tumor cells *(9)*.

Galectin-3, a β-galactoside-binding protein, has been implicated in cell proliferation and differentiation, tumor cell adhesion, angiogenesis, apoptosis, tumor progression, and metastasis. In pituitary, galectin-3 has been shown to be restricted to PRL and ACTH cells in both the normal gland and in benign and malignant pituitary tumors, suggesting that the molecular mechanisms involved in tumorigenesis may be cell-type-specific *(40)*. It is of note that expression of this protein is largely restricted to the two most common cell types associated with pituitary carcinomas—PRL and ACTH cells *(40)*.

Treatment

The optimal management of pituitary carcinoma remains ill-defined and must be individualized. Several factors contribute to the lack of clear management guidelines. First and foremost, these are rare tumors, with about 150 well-described cases in the English literature. Moreover, these tumors can arise from multiple cell types, each of which manifests differing biological properties and in some cases potential sensitivity to hormonal manipulation. By definition pituitary carcinomas have already metastasized, rendering surgical cure impossible. Furthermore, these tumors may metastasize either systemically or within the CNS, particularly in the spinal fluid. CNS metastases create a unique treatment challenge, since the blood–brain barrier (BBB) excludes most chemotherapeutic agents. Finally, metastatic neuroendocrine tumors arising from other organs generally lack adequate treatment as well. Therapeutic modalities utilized to control pituitary carcinomas include surgery, radiation (fractionated radiotherapy or single-fraction radiosurgery), hormonal manipulation, and cytotoxic chemotherapy.

Surgery

The role of surgery is most clear-cut for CNS metastases, where relatively small tumors can produce substantial neurologic problems. CNS metastases tend to spread through the spinal fluid, and such patients often have one or several visible subarachnoid nodules. These nodules may compress the spinal cord, nerve roots at the skull base, or brain parenchyma. Symptoms and signs depend on the location. When there is a single symptomatic tumor, surgery is usually effective at alleviating neural compression. For example, Pernicone et al. *(2)* reported a patient who survived eight years with pituitary carcinoma, undergoing four craniotomies over that period for removal of cerebellar metastases. Similarly, O'Brien et al. *(41)* reported a patient with four years of intracranial tumor control following a neurosurgical procedure.

The role of surgery for systemic metastases is less well-defined, and general principles of surgical oncology pertain. Occasional patients may benefit from resection of vertebral metastasis producing spinal cord compression, or from removal of liver or lung lesions in paucimetastatic disease.

Radiation

Fractionated radiotherapy is generally believed to be useful in the management of pituitary adenomas. Radiation controls tumor growth for 80–90% of patients with nonfunctioning adenomas and 67–89% of hormonally active tumors, with progression-free rates of 92%, 89%, and 79% at 5, 10, and 15 yr *(42)*. Control rates of excessive hormonal secretion are lower— 44–79% for prolactinomas, 70–90% for growth hormone-secreting adenomas, and 50–83% of adults with adenomas secreting ACTH *(42)*. Unfortunately, there is no requirement that metastases be as responsive to radiotherapy as the primary tumor. Approximately two-thirds of patients who develop pituitary carcinoma have had prior radiotherapy to their pituitary adenoma. Although radiotherapy is sometimes employed in the management of metastases from pituitary carcinoma, there is no large reported series bearing upon its efficacy. Long-term local control with fractionated radiation is at least occasionally achieved. Landman et al. *(43)* reported a patient with multiple subarachnoid intracranial metastases from an ACTH-secreting carcinoma. Following subtotal tumor resection, the patient received 2400 cGy whole brain radiotherapy and remained in remission 21 yr later. Other case reports indicate the response is sometimes much less favorable *(8,44)*.

Radiosurgery

Radiosurgery, whether administered with Gamma Knife, a proton beam, or a linear accelerator–based unit, is assuming an increasingly important role in the management of

pituitary adenomas. Reported rates of tumor control rival those of fractionated radiotherapy *(45)*, although the duration of follow-up is not so robust. The risks of radiation-induced neoplasm and vasculopathy are likely lower with radiosurgery. Radiosurgery represents a rational tool to control intracranial metastases of pituitary carcinoma, with the caveats that it will not alleviate neurologic deficits from a symptomatic lesion as conventional surgery and may not be feasible if subarachnoid dissemination is too diffuse or if metastases are too large (typically > 3.5 cm in diameter).

Hormonal Therapy

Hormonal manipulation is often beneficial in prolactinomas (dopamine agonists) and in acromegaly (somatostatin analogs). Unfortunately, in many cases of pituitary carcinomas arising from prolactin and growth hormone–secreting tumors, patients have already received these drugs and their tumors have escaped hormonal suppression. Nonetheless, these agents are often tried. There are a few reports of prolactin-secreting carcinomas responding to high doses of dopamine analogs *(19,46)* and one case of a growth hormone–secreting carcinoma responding to bromocriptine *(47)*.

Chemotherapy

As pituitary carcinoma is by definition metastatic disease, it is not surprising that cytotoxic chemotherapy has been employed in its management. Unfortunately, most reports are single case reports. The largest reported experience is that of Kaltas and colleagues *(48)*, who utilized chemotherapy in four patients with pituitary carcinoma and three with highly aggressive but non-metastatic pituitary adenomas. They utilized CCNU (an oral alkylating agent that penetrates the BBB well) with 5-fluorouracil (which achieves fair penetration of the BBB); this combination was chosen because it had some activity against systemic neuroendocrine tumors. Two patients had symptomatic improvement and two with more than 50% hormonal reduction. Only one patient (with an aggressive adenoma) had a radiographic tumor response. One patient with isolated CNS metastases survived 10 yr; the three patients with systemic metastases had a median survival of 5 mo. Another patient had previously responded to cisplatin and etoposide for 3 yr before progressing. They concluded that chemotherapy may be of some value, particularly in delaying progression or in achieving temporary remission *(48)*. Other reports also suggest some efficacy. Kaiser et al. *(49)* treated a patient with an ACTH-secreting carcinoma metastatic to liver, lung, and bones with four cycles of cyclophosphamide, adriamycin, and 5-fluorouracil. Imaging demonstrated stable tumor size for 3 yr, and ACTH levels dropped modestly. McCutcheon et al. *(50)* treated a rapidly enlarging non-functioning pituitary carcinoma with two cycles of cyclophosphamide, adriamycin, and dacarbazine with cessation of tumor growth prior to surgery. In general, chemotherapy should be considered for carcinomas that have been treated with both surgery and radiotherapy for which there are no immediately attractive surgical or radiotherapeutic options.

Prognosis

Of 150 cases reported in the English medical literature up to 2005, 66% of patients survived less than 1 yr. The median survival with craniospinal metastases is 2.6 yr, and that of patients with systemic metastases 1 yr. All cell types producing pituitary carcinoma are more likely to produce systemic metastases than leptomeningeal metastases. Only 20% of reported cases survived more than 8 yr *(3)*, arguing against therapeutic nihilism in this rare disorder.

Conclusion

Pituitary carcinomas usually arise in the setting of invasive pituitary adenomas and are generally associated with multiple recurrences prior to the occurrence of CNS and/or systemic metastases. Current therapeutic modalities are mainly palliative, and once metastases develop the prognosis of affected patients is relatively poor. Few experience long-term survival. Current and future knowledge of the precise molecular mechanisms of pathogenesis and disease progression will facilitate the development of specific pharmacogenetic targets with a resultant advance in prognosis.

Acknowledgment

The authors thank Dr. Maurice H. Lipper (Division of Neuroradiology, University of Virginia) for contributing with Fig. 1.

References

1. Scheithauer, B. W., Kovacs, K., Horvath, K., et al. (2004). In: *WHO classification of tumours. Pathology and genetics of tumours of endocrine organs.* DeLellis, R. A., Lloyd, R. V., Heitz, P. U., and Eng, C. (eds.). IARC Press: Lyon, France.
2. Pernicone, P. J., Scheithauer, B. W., Sebo, T. J., et al. (1997). *Cancer* **79,** 804–812.
3. Ragel, B. T. and Couldwell, W. T. (2004). *Neurosurg. Focus* **16,** E7.
4. Kaltsas, G. A., Nomikos, P., Kontogoergos, G., et al. (2005). *J. Clin. Endocrinol. Metab.* **90,** 3089–3099.
5. Roncaroli, F., Scheithauer, B. W., Young, W. F., et al. (2003). *Am. J. Surg. Pathol.* **27,** 477–486.
6. Nudleman, K. L., Choi, B., and Kusske, J. A. (1985). *Neurosurgery* **16,** 90–95.
7. Luzi, P., Miracco, C., Lio, R., et al. (1987). *Hum. Pathol.* **18,** 90–92.
8. Kuroki, M., Tanaka, R., Yokoyama, M., et al. (1987). *Surg. Neurol.* **28,** 71–76.
9. Roncaroli, F., Nosé, V., Scheithauer, B. W., et al. (2003). *J. Neurosurg.* **99,** 402–408.
10. Kaltsas, G. A. and Grossman, A. B. (1998). *Pituitary* **1,** 69–81.
11. Holthouse, D. J., Robbins, P. D., Kahler, R., et al. (2001). *Endocr. Pathol.* **12,** 329–341.
12. Tysome, J., Gnanalingham, K., Chopra, I., and Mendoza, N. (2004). *Acta Neurochir.* **146,** 1251–1254.

13. Negron-Soto, J. M., Kilpatrick, M., Irani, N., and Castillo, M. (2004). *Semin. Roentgenol.* **39,** 519–521.
14. Thapar, K. and Laws, E. R. Jr. (2001). In: *Brain tumors: an encyclopedic approach.* 2nd ed. Kaye, A. H. and Laws, E. R. Jr. (eds.). Churchill Livingstone: London.
15. Matsuki, M., Kaji, Y., Matsuo, M., and Kobashi, Y. (2000). *Br. J. Radiol.* **73,** 783–785.
16. Greenman, Y., Woolf, P., Coniglio, J., et al. (1996). *J. Clin. Endocrinol. Metab.* **81,** 1628–1633.
17. Dayan, C., Guilding, T., Hearing, S., et al. (1996). *Clin. Endocrinol.* **44,** 597–602.
18. Petrossians, P., De Herder, W., Kwekkeboom, D., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 398–401.
19. Mühr, C., Bergstrom, M., Lundberg, P. O., et al. (1988). *Neurosurgery* **22,** 374–379.
20. Bombardieri, E., Seregni, E., Villano, C., et al. (2004). *Q. J. Nucl. Med. Mol. Imaging* **48,** 150–163.
21. Thapar, K., Kovacs, K., Scheithauer, B. W., et al. (1996). *Neurosurgery* **38,** 99–107.
22. Jaffrain-Rea, M. L., Di Stefano, D., Minniti, G., et al. (2002). *Endocr. Relat. Cancer* **9,** 103–113.
23. Lloyd, R. V., Kovacs, K., Young, W. F. Jr., et al. (2004). In: *WHO classification of tumours. Pathology and genetics of tumours of endocrine organs*. DeLellis, R. A., Lloyd, R. V., Heitz, P. U., and Eng, C. (eds.). IARC Press: Lyon, France.
24. Schreiber, S., Saeger, W., and Ludecke, D. K. (1999). *Pituitary* **1,** 213–220.
25. Korbonits, M., Chahal, H. S., Kaltsas, G., et al. (2002). *J. Clin. Endocrinol. Metab.* **87,** 2635–2643.
26. Musat, M., Vax, V. V., Borboli, N., et al. (2004). *Front. Horm. Res.* **32,** 34–62.
27. Clayton, R. N. and Farrell, W. E. (2001). *Brain Pathol.* **11,** 313–327.
28. Zahedi, A., Booth, G. L., Smyth, H. S., et al. (2001). *Clin. Endo-crinol.* **55,** 549–556.
29. Rickert, C. H., Scheithauer, B. W., and Paulus, W. (2001). *Acta Neuropathol.* **103,** 117–120.
30. Levy, A., Hall, L., Yeudall, W. A., and Lightman, S. L. (1994). *Clin. Endocrinol.* **41,** 809–814.
31. Thapar, K., Scheithauer, B. W., Kovacs, K., et al. (1996). *Neurosurgery* **38,** 765–771.
32. Pei, L., Melmed, S., Scheithuaer, B., et al. (1994). *J. Clin. Endocrinol. Metab.* **78,** 842–846.
33. Cai, W. Y., Alexander, J. M., Hedley-White, E. T., et al. (1994). *J. Clin. Endocrinol. Metab.* **78,** 89–93.
34. Cryns, V. L., Alexander, J. M., Klibanski, A., and Arnold, A. (1993). *J. Clin. Endocrinol. Metab.* **77,** 644–646.
35. Zhu, J., Leon, S. P., Beggs, A. H., et al (1994). *J. Clin. Endocrinol. Metab.* **78,** 922–927.
36. Pei, L., Melmed, S., Scheithauer, B., et al. (1995). *Cancer Res.* **55,** 1613–1616.
37. LeRiche, V. K., Asa, S. L., and Ezzat, S. (1996). *J. Clin. Endocrinol. Metab.* **81,** 656–662.
38. Onguru, O., Scheithaeur, B. W., Kovacs, K., et al. (2004). *Mod. Pathol.* **17,** 772–780.
39. Nosé-Alberti, V., Mesquita, M. I. S., Martin, L. C., and Kayath, M. J. (1998). *Endocr. Pathol.* **9,** 53–62.
40. Riss, D., Jin, L., Qian, X., et al. (2003). *Cancer Res.* **63,** 2251–2255.
41. O'Brien, D. P., Phillips, J. P., Rawluk, D. R., and Farrell, M. A. (1995). *Br. J. Neurosurg.* **9,** 211–218.
42. Becker, G., Kocher, M., Kortmann, R. D., et al. (2002). *Strahlenther Onkol.* **178,** 173–186.
43. Landman, R. E., Horwith, M., Peterson, R. E., et al. (2002). *J. Clin. Endocrinol. Metab.* **87,** 3084–3089.
44. Pichard, C., Gerber, S., Laloi, M., et al. (2002). *J. Endocrinol. Invest.* **25,** 65–72.
45. Laws, E. R., Sheehan, J. P., Sheehan, J. M., et al. (2004). *J. Neurooncol.* **69,** 257–272.
46. Berezin, M., Gutman, I., Tadmor, R., et al. (1992). *Acta Endocrinol.* **127,** 476–480.
47. Mountcastle, R. B., Roof, B. S., Mayfield, R. K., et al. (1989). *Am. J. Med. Sci.* **298,** 109–118.
48. Kaltsas, G. A., Mukherjee, J. J., Plowman, P. N., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 4233–4238.
49. Kaiser, F. E., Orth, D. N., Mukai, K., and Oppenheimer, J. H. (1983). *J. Clin. Endocrinol. Metab.* **57,** 649–653.
50. McCutcheon, I. E., Pieper, D. R., Fuller, G. N., et al., (2000). *Neurosurgery* **46,** 1233–1239.