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An Institutional Experience of Tumor Progression to Pituitary Carcinoma in a 15-Year Cohort of 1055 Consecutive Pituitary Neuroendocrine Tumors

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Abstract

Pituitary carcinoma is a rare disease, defined by the presence of cerebrospinal or distant metastasis of a pituitary neuroendocrine tumor (PitNET). To review our institutional experience of pituitary carcinoma, we searched the database of the UHN Endocrine Oncology Site group and the University Health Network pathology laboratory information system from 2001 to 2016. Among 1055 PitNETs from 1169 transsphenoidal resections, we identified 4 cases of pituitary carcinoma, indicating that pituitary carcinoma represents around 0.4% of PitNETs. All four patients were women. The age at initial presentation ranged from 23 to 54 years. Two patients had Cushing disease with corticotroph tumors; one was initially a densely granulated corticotroph tumor that evolved to become sparsely granulated, while the other was a Crooke cell tumor. One patient had a functioning sparsely granulated lactotroph tumor and one had a clinically silent poorly differentiated PIT1 lineage tumor. Apart from a relatively high Ki67 labeling index (≥ 10%) in three tumors, there were no cytomorphologic features at the time of initial presentation that could predict subsequent metastatic behavior. The time from diagnosis of the pituitary neuroendocrine tumor to the diagnosis of malignancy was 3 to 14 years. Therapies included somatostatin analogs, external beam radiotherapy, chemotherapies including capecitabine/temozolomide, everolimus, sunitinib, bevacizumab, and peptide receptor radionuclide therapy (PRRT). One patient died of disease 18 years after initial diagnosis, underscoring the protracted course of this ultimately fatal neuroendocrine malignancy.

Keywords Pituitary carcinoma · Pituitary neuroendocrine tumor · Metastasis · Ki67

Introduction

Pituitary carcinoma is a rare disease, defined by the presence of cerebrospinal or distant metastasis of an adenohypophysial tumor [1, 2]. The vast majority of patients who receive this diagnosis present initially with a pituitary neuroendocrine tumor (PitNET) [3] that has no distinctive features to suggest metastatic potential. The ability to distinguish these carcinomas from other aggressive PitNETs remains a challenge [4].

Only a small number of cases of pituitary carcinoma have been reported in the literature [5–45]. The majority are corticotroph tumors with Cushing disease [42, 43], but tumors of all of the various adenohypophysial cell types have been reported to be malignant. We reviewed our institutional experience with pituitary carcinoma since the publication of a previous case [26].

Materials and Methods

To review our institutional experience of pituitary carcinoma, we searched the database of the UHN Endocrine Oncology

This study was presented in abstract form at Endocrine Society as "An Institutional Experience of Pituitary Carcinomas in a 15 year Cohort of 1055 Consecutive Pituitary Neuroendocrine Tumors (PitNETs)" (Presentation Number: MON-583; Date of Presentation: March 19, 2018).

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Site group and the UHN pathology laboratory information system from 2001 to 2016 with approval of the University Health Network Research Ethics Board. Among 1055 PitNETs from 1169 transsphenoidal resections [46], we identified 4 cases of pituitary carcinoma. Here we describe the clinical and pathologic features and response to management approaches.

Results

The incidence of pituitary carcinoma was approximately 0.4% of all PitNETs. All four patients were women. The age at initial presentation ranged from 23 to 54 years. Two patients had Cushing disease, one had galactorrhea-amenorrhea syndrome, and one had a clinically non-functional poorly differentiated PIT1 lineage tumor. The time from diagnosis of PitNET to the diagnosis of malignancy was 3 to 14 years (mean, 8 years). One patient died of disease 18 years after the initial diagnosis of a PitNET. The others are alive with disease. The details of the four cases are presented (Table 1).

Case 1 A 23-year-old woman presented with a 2.8-cm clinically non-functioning pituitary tumor. She underwent transsphenoidal resection; pathology identified a poorly differentiated PIT1 lineage tumor (formerly known as "silent subtype 3 pituitary adenoma") that was composed of spindle-shaped and polygonal cells with strong PIT1 positivity, focal ER reactivity, and a Ki67 index of 15% (Fig. 1). There was global loss of nuclear PTEN expression as well as variable loss of nuclear Rb expression, but the tumor cells were positive for p27 and SDHB. There was no p53 overexpression. She had local regrowth and underwent a second transsphenoidal resection prior to the documentation of metastatic disease in the cerebellum and mediastinum 5 years after initial diagnosis (Fig. 1). Therapy with external beam radiotherapy and a number of medical therapies including the combination of capecitabine/temozolomide was unsuccessful and she continues to have disease progression. She was subsequently enrolled in a clinical trial of peptide receptor radionuclide therapy (PRRT).

Case 2 A 40-year-old woman presented with florid pituitary Cushing disease; MRI (Fig. 2) showed a 6 × 5-mm sellar tumor. She underwent transsphenoidal resection of a densely granulated corticotroph tumor (Fig. 2) with a Ki67 index of 4.7%. Recurrence 7 years later led to a second pituitary surgery and resection showed transition to a sparsely granulated corticotroph tumor consisting of chromophobic or lightly basophilic tumor cells. Both tumors showed strong keratin and variable ACTH positivity. Persistent ACTH excess and Cushing disease failed to respond to somatostatin analog therapy and she required bilateral adrenalectomy. Two years later, she was found to have a liver lesion; a liver biopsy identified metastatic neuroendocrine tumor with cytoplasmic positivity for ACTH and nuclear positivity for TPIT (Fig. 2). This confirmed the diagnosis of pituitary corticotroph carcinoma. Of note, the patient also had a papillary thyroid carcinoma diagnosed shortly before the liver lesion was identified, and she had a well-differentiated L cell appendiceal neuroendocrine tumor (NET) invading the muscularis propria with grade 2 proliferative features (Ki67 16.5%) and no ACTH immunoreactivity 1 year prior to the thyroid carcinoma. This appendiceal NET was assessed for menin, SDHB, and microsatellite instability markers (MSH6, MSH2, MLH1, and PMS2) and all were intact. Menin staining was intact in the pituitary tumor. Stains for p27 (encoded by *CDKN1B*) were negative in the pituitary lesion, consistent with its functional status [46], but the appendiceal L cell NET was positive for this marker of MEN4. Germline genetic testing for *MEN1* yielded no pathogenic alterations.

Table 1 Clinical and pathological features of four pituitary carcinomas

Patient	1	2	3	4
Age (years) at presentation	23	40	49	54
Initial pathology	Poorly differentiated PIT1 lineage tumor	Densely granulated then sparsely granulated corticotroph tumor	Crooke cell corticotroph tumor	Sparsely granulated lactotroph tumor
Ki67 labeling index (%) primary tumor	15	4.7	10	20
Pituitary surgeries (number)	2	2	3	2
Metastases	Brain (cerebellum) Mediastinum Spine	Liver	Spine Liver	Brain (fronto-temporal lobe) Spine
Medical therapies	Chemotherapy with: CAPE/TEM × 3 cycles	SSTA	Temozolomide, everolimus, sunitinib, bevacizumab	Dopamine agonists, SSTA
Radiation therapy	External beam		External beam	External beam
Outcome	Disease progression	Stable disease	Fatal 18 years after diagnosis	Stable disease

SSTA somatostatin analogs, *CAPE/TEM* capecitabine/temozolomide combination

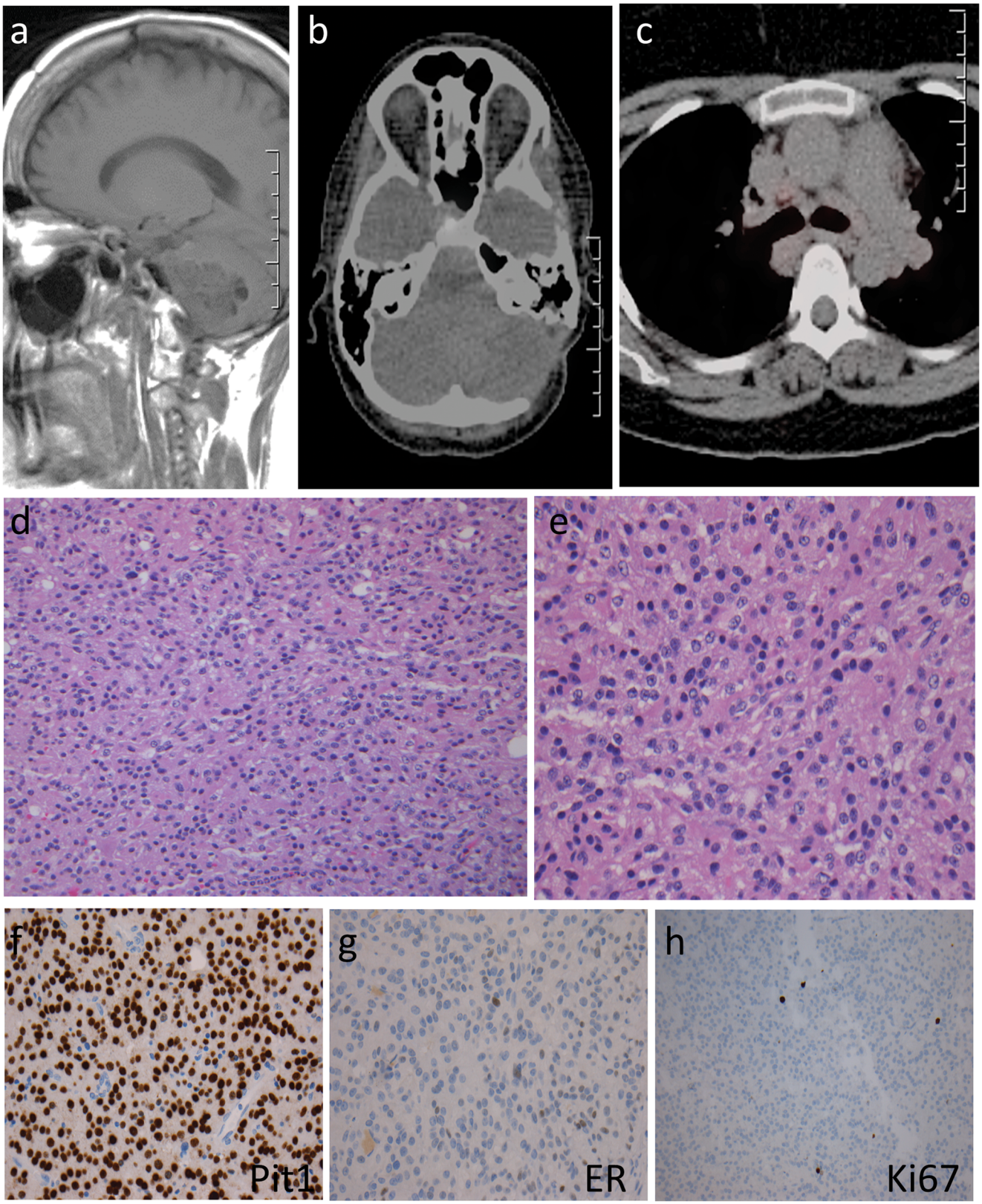


Fig. 1 This patient initially had a sellar mass (**a**) and underwent two transsphenoidal resections prior to the documentation of metastatic disease in the cerebellum (**a**, **b**) and mediastinum (**c**). The tumor was a poorly differentiated PIT1 lineage tumor that was composed of spindle-shaped and polygonal cells (**c**, **d**) with strong PIT1 positivity (**e**), focal ER reactivity (**f**), and a Ki67 index of 15% (**g**)

Case 3 A 49-year-old woman presented with Cushing disease for which she had pituitary surgery for a small intrasellar tumor. She underwent a second pituitary resection the next year due to persistent disease. She was referred to our institution with persistent disease (Fig. 3) when she was 60 years old and a third pituitary procedure was performed. This yielded a Crooke cell tumor with a Ki67 labeling index of 10% (Fig. 3). As this third pituitary resection was also unsuccessful in achieving a biochemical remission, she underwent bilateral adrenalectomy. This was followed by the rapid development of Nelson's syndrome that did not respond to external beam radiation, temozolomide, everolimus, sunitinib, or bevacizumab. In 2009, 14 years after her initial presentation, metastatic lesions in bone were shown on biopsy to represent metastatic corticotroph carcinoma (Fig. 3). She died of wide-spread disease progressive in the brain, liver, and bones at age 67.

Case 4 A 54-year-old woman had a 2.5-cm sellar tumor with hyperprolactinemia (729 μg/L; normal range 1.2–29.9) that failed to respond to dopamine agonist therapies. She underwent transsphenoidal surgery. At surgery, the tumor was highly fibrotic and could not be completely resected. The tumor had strong nuclear positivity for PIT1 and ER (Fig. 4); interpretation of the PRL staining was suboptimal due to extensive fibrosis and non-specific background, but there was Golgi pattern accentuation of reactivity, consistent with a sparsely granulated lactotroph tumor. Stains for SF1 and other pituitary hormones were all negative. The Ki67 labeling index was 20% despite medical therapy that would have been expected to reduce proliferation by a lactotroph tumor. A second surgical procedure did not successfully normalize prolactin levels. She then developed tumor in the right fronto-temporal lobe that was biopsied and proved to be metastatic lactotroph carcinoma. She underwent external beam radiation therapy and somatostatin analog therapy. At the age of 60 she developed biopsy-proven metastatic pituitary carcinoma in the L2 vertebral spine. Genetic testing revealed an *MEN1:c.1117C>T* representing a sequence variant of unknown significance.

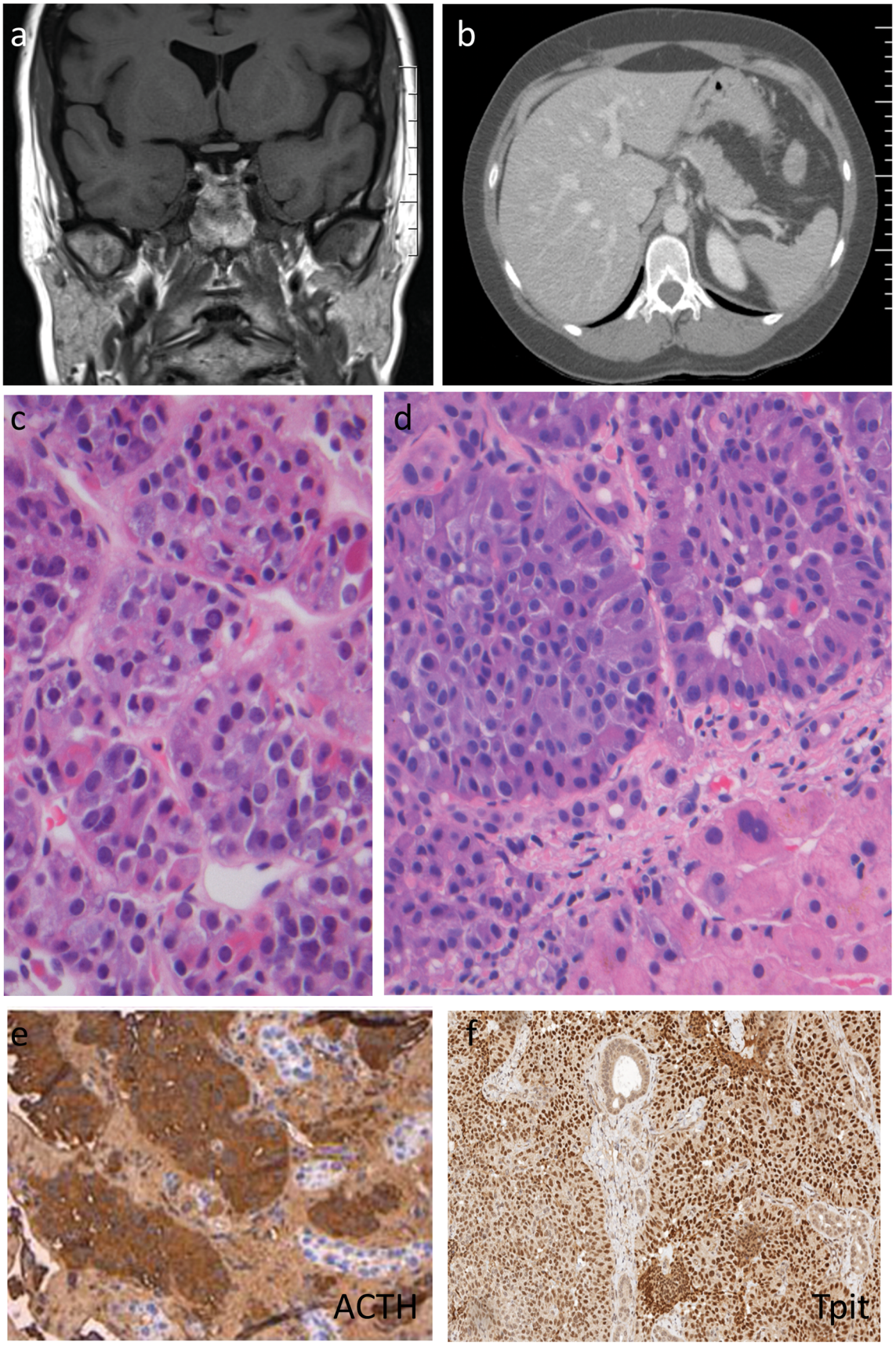
Discussion

Our case series indicates that pituitary carcinoma represents approximately 0.4% of all PitNETs. In our series, all patients with pituitary carcinoma were female and the ages at initial presentation ranged from 23 to 54 years; the time to development of metastasis ranged from 3 to 14 years from the initial diagnosis of a PitNET. Apart from a relatively high Ki67 labeling index (≥ 10%) in three tumors, there were no cytomorphologic features at the time of initial presentation that could predict subsequent metastatic behavior.

The pathogenesis of malignant transformation in pituitary carcinoma is unknown. There have been reports of *RAS* mutations [47, 48]; other studies have suggested alterations in *ATRX*, *PTEN*, and *Tp53* [45, 49]. Biomarkers that have been applied in diagnosis include galectin-3 [50] and p53 [51] expression as well as loss of Rb [24]. One patient was reported to have Lynch syndrome [38] and another patient was reported to have an SDHB-immunodeficient gonadotroph carcinoma in the context of germline *SDHB* mutation [39]. High Ki67 labeling indices are a feature of these tumors [52]; however, not all PitNETs with high Ki67 labeling indices progress to pituitary carcinoma. A meta-analysis published in 2016 highlighted the potential role of microRNAs, and cyclin-dependent kinase inhibitors along with vascular endothelial growth factor (VEGF), matrix metalloproteinase 9 (MMP9), and metallothionein isoform 3 (MT3) along with anti-apoptotic BCL2 in pituitary tumorigenesis including tumor invasiveness, recurrence, and metastasis [53]. While a comprehensive genomic landscape of pituitary carcinoma is yet to be defined, most alterations identified in pituitary carcinomas can also be identified in PitNETs. For this reason, at this time there are no diagnostic biomarkers or cytomorphological features that can accurately predict PitNET progression to metastatic behavior.

Effective medical therapies for pituitary carcinomas remain enigmatic. When standard dopamine and/or somatostatin analogs fail, targeted agents are frequently considered. Of these, the mTOR inhibitor everolimus [54] has been widely used in the management of pancreatic and other neuroendocrine neoplasms [55, 56]; in one case report of a metastatic pituitary carcinoma with an actionable *STK11* mutation, the addition of everolimus with radiation therapy resulted in transient disease stabilization [57]. Bevacizumab has been used with some success in one published case [40]. Sunitinib represents another major targeted agent commonly used in neuroendocrine neoplasms [58–60]; however, we are unaware of any reports demonstrating successful use of this agent in managing refractory pituitary carcinomas.

Next in line following targeted agents are chemotherapeutic agents. Classical agents have been largely ineffective. More recently, case reports have advocated the use of the alkylating agent temozolomide as a potentially useful agent in managing pituitary carcinomas [28, 29, 36, 37, 40, 43, 61]. This was initially driven by the proven effectiveness of this agent in glioblastoma multiforme [28]. One study has suggested that the status of the mismatch repair protein MSH6 may impact response to treatment with temozolomide [62]. Subsequently, the addition of capecitabine, an oral pro-drug for 5-fluro-FU, to temozolomide has been noted to synergistically enhance apoptosis [63]. This is hypothesized to be the result of depletion of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) by capecitabine, thereby potentiating temozolomide action. These findings quickly led to the currently widely adopted use of the so-called CAPE/TEM combination in the management of neuroendocrine tumors [64]. To date, however, few reports [65, 66] have extended this combination protocol to pituitary tumors. It is, therefore, noteworthy that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◀ **Fig. 2** This patient with Cushing disease had a small intrasellar tumor (**a**) and subsequently developed liver metastasis (**b**). The pituitary tumor was initially a basophilic densely granulated corticotroph tumor (**c**), but at reoperation 7 years later, the recurrent tumor had transitioned to a chromophobic sparsely granulated corticotroph tumor (not shown); both tumors showed strong keratin and variable ACTH positivity (not shown). Persistent ACTH excess and Cushing disease required bilateral adrenalectomy. A liver biopsy identified metastatic neuroendocrine tumor (**d**) with cytoplasmic positivity for ACTH (**e**) and nuclear positivity for TPIT (**f**), confirming the diagnosis of pituitary corticotroph carcinoma. This stain for TPIT was required since the patient also had a well-differentiated L cell appendiceal NET with no ACTH reactivity

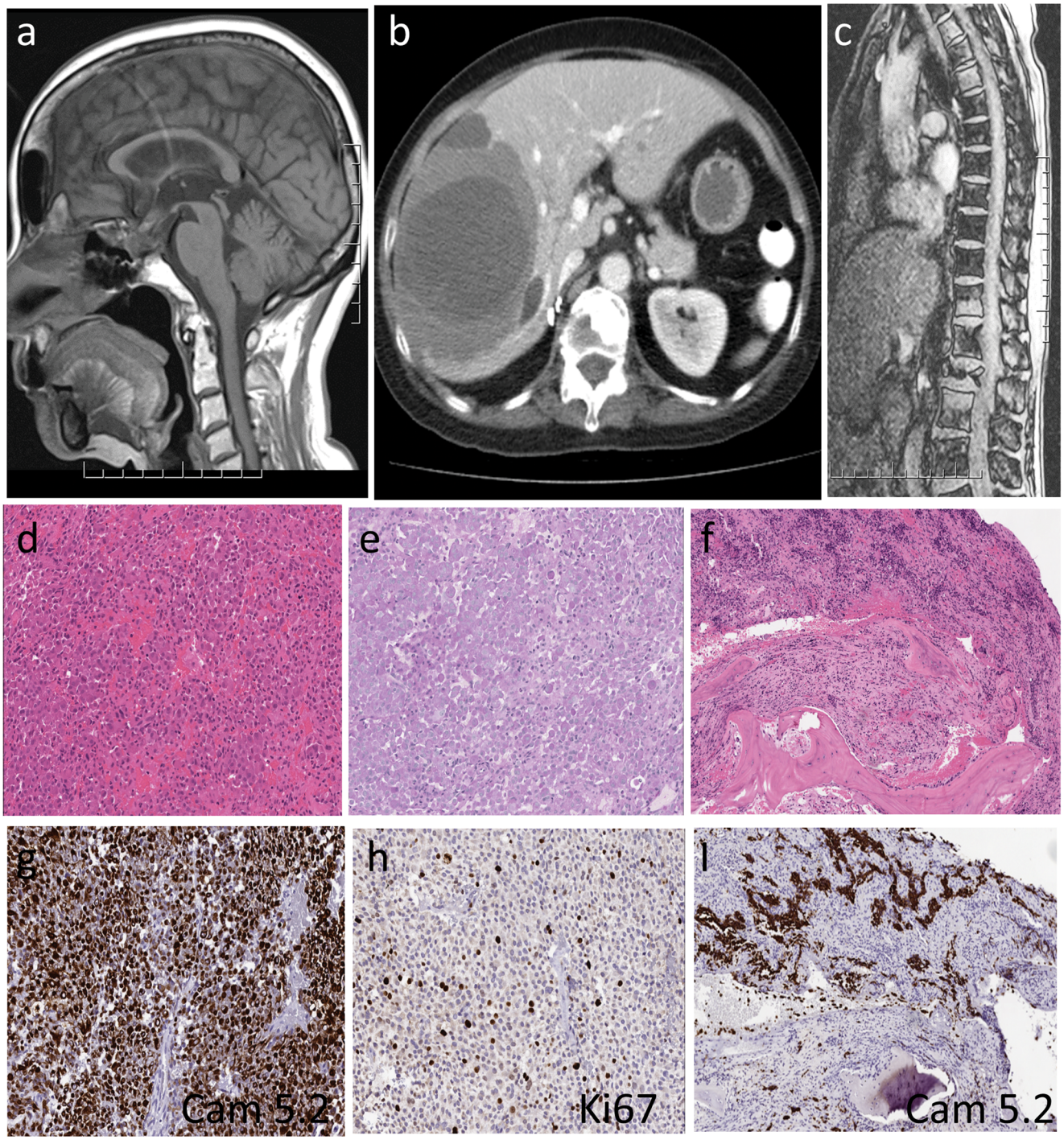

Fig. 3 This patient had Cushing disease due to a pituitary tumor (**a**) that was treated with multiple surgeries and bilateral adrenalectomy resulting in Nelson's syndrome; she ultimately developed metastatic lesions in the liver (**b**) and bone (**c**). The tumor was a Crooke cell tumor (**d**) highlighted with the PAS stain (**e**) and also identified in a bone biopsy (**f**); the pituitary tumor was strongly positive for keratins using the CAM 5.2 stain (**g**) and had a Ki67 labeling index of 10% (**h**); the bone lesion shows the same pattern of keratins (**i**) as well as ACTH (not shown), consistent with metastatic Crooke cell tumor

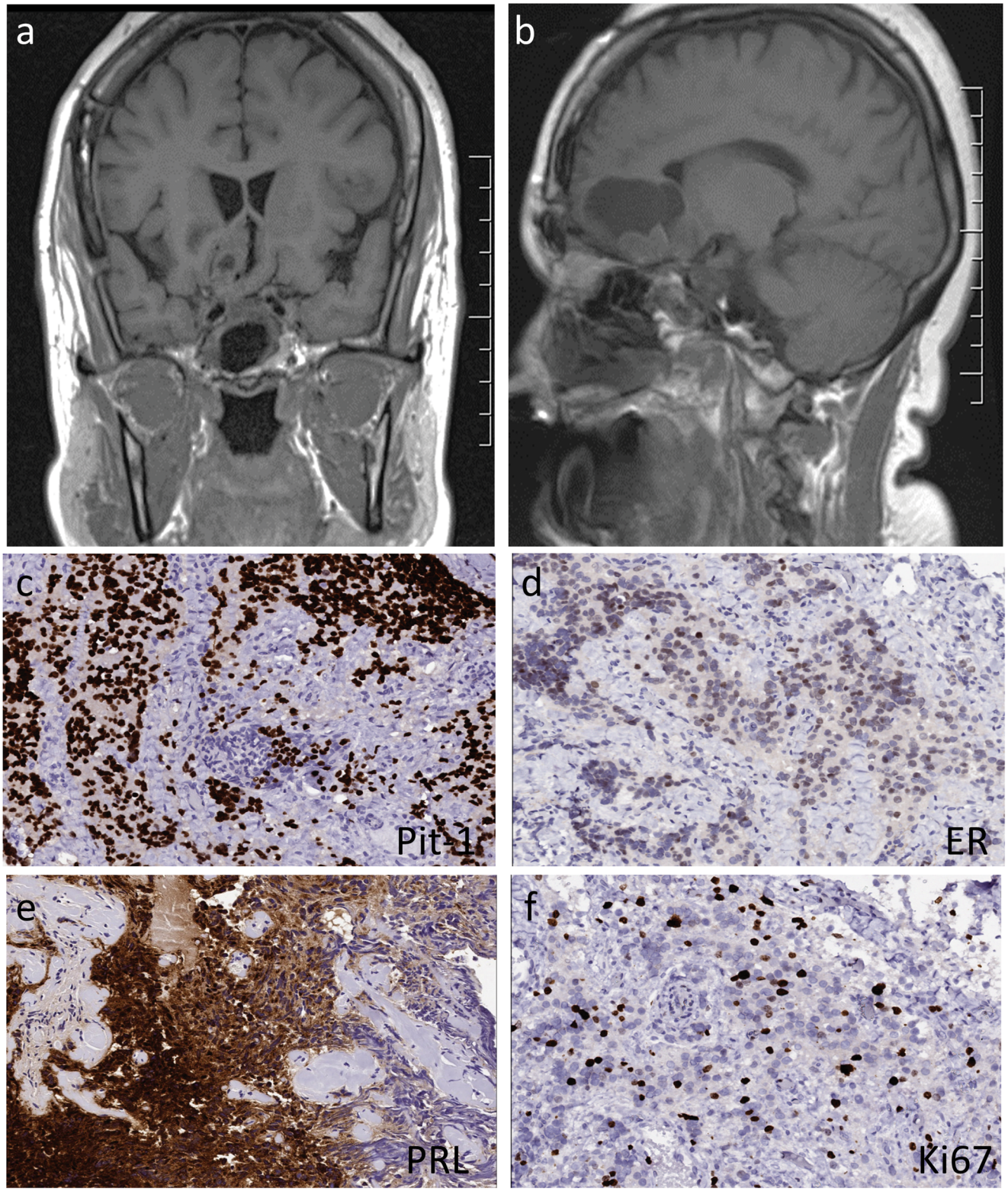

Fig. 4 This patient had a 2.5-cm sellar tumor and hyperprolactinemia that failed to respond to dopamine agonist therapies; she subsequently developed metastatic lesions in the frontal lobe (**a**, **b**) and in the L2 vertebra that had similar morphology to her primary pituitary lesion, a highly fibrotic tumor with strong nuclear positivity for PIT1 (**a**) and reactivity for ER (**b**); staining for PRL was suboptimal due to extensive fibrosis and non-specific background (**c**) but there was Golgi pattern accentuation of reactivity, consistent with a sparsely granulated lactotroph tumor. Stains for SF1 and other pituitary hormones were negative (not shown). The Ki67 was 20% (**d**)

one of our patients in this series failed to show an objective response to this oral combination chemotherapeutic regimen.

Immunotherapy is a recent addition to the armamentarium of personalized oncology therapies. A single case of pituitary carcinoma has been reported to show significant reduction of metastatic tumor mass as well as reduced ACTH levels after nivolumab and ipilimumab therapies [41].

The use of PRRT has now emerged as another major therapeutic, non-surgical approach to the management of neuroendocrine neoplasms. Using somatostatin receptor agonists [67] or more recently receptor antagonists [68] as chaperones, these peptides deliver beta- and gamma-emitting radiation upon internalization. This dual property allows for effective delivery of cytotoxic internal radiation while permitting post-treatment imaging for internal dosimetry purposes. Experience thus far in the application of PRRT to PitNET management remains quite limited [69]. We predict, however, that this and other related radiopharmaceuticals will undoubtedly become the subject of intense investigations in refractory pituitary tumors including those meeting the diagnostic threshold of carcinomas.

Compliance with Ethical Standards

Conflict of Interest Dr. Asa is a member of the Medical Advisory Boards of Leica Pathology Imaging and Ibex Medical Analytics. Dr. Ezzat has served on Medical Advisory Boards of Novartis Canada, Pfizer, Ipsen, and Esai. Drs. Alshaikh and Mete have no conflicts of interest or funding to disclose.

References

1. Asa SL. Tumors of the pituitary Gland. AFIP Atlas of Tumor Pathology, Series 4, Fascicle 15, Silverberg SG, editor. ARP Press, Silver Spring, MD, 2011.
2. Asa SL, Mete O. The Pituitary Gland. In: Mete O, Asa SL, editors. Endocrine Pathology. Cambridge: Cambridge University Press, 2016: 315–397.
3. Asa SL, Casar-Borota O, Chanson P, et al. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer 2017; 24(4):C5-C8.
4. Asa SL, Ezzat S. Aggressive Pituitary Tumors or Localized Pituitary Carcinomas: Defining Pituitary Tumors. Expert Reviews Endocrinology and Metabolism 2016; 11(2):149–162.
5. Scheithauer BW, Randall RV, Laws ER, Jr., Kovacs KT, Horvath E, Whitaker MD. Prolactin cell carcinoma of the pituitary. Clinicopathological, immunohistochemical, and ultrastructural study of a case with cranial and extracranial metastases. Cancer 1985; 55:598–604.
6. Gabrilove JL, Anderson PJ, Halmi NS. Pituitary pro-opiomelanocortin-cell carcinoma occurring in conjunction with a glioblastoma in a patient with Cushing's disease and subsequent Nelson's syndrome. Clin Endocrinol (Oxf) 1986; 25:117–126.
7. Kuroki M, Tanaka r, Yokoyama M, Shimbo Y, Ikuta F. Subarachnoid dissemination of a pituitary adenoma. Surg Neurol 1987; 28:71–76.
8. Luzi P, Miracco C, Lio R, et al. Endocrine inactive pituitary carcinoma metastasizing to cervical lymph nodes: a case report. Hum Pathol 1987; 18:90–92.
9. Mountcastle RB, Roof BS, Mayfield RK, et al. Case Report: Pituitary adenocarcinoma in an acromegalic patient: response to bromocriptine and pituitary testing: a review of the literature on 36 cases of pituitary carcinoma. Am J Med Sci 1989; 298:109–118.
10. Nawata H, Higuchi K, Ikuyama S et al. Corticotropin-releasing hormone- and adrenocorticotropin-producing pituitary carcinoma with metastases to the liver and lung in a patient with metastases to the liver and lung in a patient with Cushing's disease. J Clin Endocrinol Metab 1990; 71:1068–1073.
11. Atienza DM, Vigersky RJ, Lack EE, et al. Prolactin-producing pituitary carcinoma with pulmonary metastases. Cancer 1991; 68: 1605–1610.
12. Stewart PM, Carey MP, Graham CT, Wright AD, London DR. Growth hormone secreting pituitary carcinoma: a case report and literature review. Clin Endocrinol (Oxf) 1992; 37:189–195.
13. Petterson T, MacFarlane IA, MacKenzie JM, Shaw MDM. Prolactin secreting pituitary carcinoma. J Neurol Neurosurg Psychiatry 1992; 55:1205–1206.
14. Mixson AJ, Friedman TC, Katz DA, et al. Thyrotropin-secreting pituitary carcinoma. J Clin Endocrinol Metab 1993; 76:529–533.
15. Cartwright DM, Miller TR, Nasr AJ. Fine-needle aspiration biopsy of pituitary carcinoma with cervical lymph node metastases: a report of two cases and review of the literature. Diagn Cytopathol 1994; 11:68–73.
16. Lüdecke D, Saeger W. Carcinomas of the pituitary: definition and review of the literature. Gen Diagn Pathol 1995; 141:81–92.
17. Frost AR, Tenner S, Tenner M, Rollhauser C, Tabbara SO. ACTH-producing pituitary carcinoma presenting as the cauda equina syndrome. Arch Pathol Lab Med 1995; 119:93–96.
18. Beauchesne P, Trouillas J, Barral F, Brunon J. Gonadotropic pituitary carcinoma: case report. Neurosurg 1995; 37:810-815.
19. Saeger W, Lüdecke DK. Pituitary carcinomas. Endocr Pathol 1996; 7:21–35.
20. Garrão AF, Sobrinho LGOP, Bugalho MJ et al. ACTH-producing carcinoma of the pituitary with haematogenic metastases. European Journal of Endocrinology 1997; 137:176–180.
21. Pernicone PJ, Scheithauer B, Sebo TJ, et al. Pituitary carcinoma: A clinicopathologic study of 15 cases. Cancer 1997; 79:804–812.
22. Lormeau B, Miossec P, Sibony M, Valensi P, Attali JR. Adrenocorticotropin-producing pituitary carcinoma with liver metastasis. J Endocrinol Invest 1997; 20:230–236.
23. Nose-Alberti V, Mesquita MI, Martin LC, Kayath MJ. Adrenocorticotropin-producing pituitary carcinoma with expression of c-erbB-2 and high PCNA index: A comparative study with pituitary adenomas and normal pituitary tissues. Endocr Pathol 1998; 9(1):53–62.
24. Hinton DR, Hahn JA, Weiss MH, Couldwell WT. Loss of Rb expression in an ACTH-secreting pituitary carcinoma. Cancer Lett 1998; 126(2):209–214.
25. Kemink SA, Wesseling P, Pieters GF, Verhofstad AA, Hermus AR, Smals AG. Progression of a Nelson's adenoma to pituitary carcinoma; a case report and review of the literature. J Endocrinol Invest 1999; 22:70–75.
26. Zahedi A, Booth GL, Smyth HS, et al. Distinct clonal composition of primary and metastatic adrencorticotrophic hormone-producing pituitary carcinoma. Clin Endocrinol (Oxf) 2001; 55(4):549–556.
27. Gaffey TA, Scheithauer BW, Lloyd RV, et al. Corticotroph carcinoma of the pituitary: a clinicopathological study. Report of four cases. J Neurosurg 2002; 96(2):352–360.

28. Lim S, Shahinian H, Maya MM, Yong W, Heaney AP. Temozolomide: a novel treatment for pituitary carcinoma. Lancet Oncol 2006; 7(6):518–520.
29. Fadul CE, Kominsky AL, Meyer LP et al. Long-term response of pituitary carcinoma to temozolomide. Report of two cases. J Neurosurg 2006; 105(4):621–626.
30. Brown RL, Muzzafar T, Wollman R, Weiss RE. A pituitary carcinoma secreting TSH and prolactin: a non-secreting adenoma gone awry. Eur J Endocrinol 2006; 154(5):639–643.
31. Guastamacchia E, Triggiani V, Tafaro E et al. Evolution of a prolactin-secreting pituitary microadenoma into a fatal carcinoma: a case report. Minerva Endocrinol 2007; 32(3):231–236.
32. Guzel A, Tatli M, Senturk S, Guzel E, Cayli SR, Sav A. Pituitary carcinoma presenting with multiple metastases: case report. J Child Neurol 2008; 23(12):1467–1471.
33. Pinchot SN, Sippel R, Chen H. ACTH-producing carcinoma of the pituitary with refractory Cushing's Disease and hepatic metastases: a case report and review of the literature. World J Surg Oncol 2009; 7:39.
34. Roncaroli F, Scheithauer BW, Horvath E et al. Silent Subtype 3 Carcinoma of the Pituitary: A Case Report. Neuropathol Appl Neurobiol 2009.
35. Hagen C, Schroeder HD, Hansen S, Hagen C, Andersen M. Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy. Eur J Endocrinol 2009; 161(4):631–637.
36. Raverot G, Sturm N, de Fraipont F, et al. Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. J Clin Endocrinol Metab 2010; 95(10): 4592–4599.
37. Vieira NL, Chimelli L, Pereira PJ et al. The role of temozolomide in the treatment of a patient with a pure silent pituitary somatotroph carcinoma. Endocr Pract 2013; 19(6):e145-e149.
38. Bengtsson D, Joost P, Aravidis C, et al. Corticotroph Pituitary Carcinoma in a Patient With Lynch Syndrome (LS) and Pituitary Tumors in a Nationwide LS Cohort. J Clin Endocrinol Metab 2017; 102(11):3928–3932.
39. Tufton N, Roncaroli F, Hadjidemetriou I, et al. Pituitary Carcinoma in a Patient with an SDHB Mutation. Endocr Pathol 2017; 28(4): 320–325.
40. Rotman LE, Vaughan TB, Hackney JR, Riley KO. Long-term survival following transformation of an adrenocorticotropic hormone secreting pituitary macroadenoma to a silent corticotroph pituitary carcinoma: Case report. World Neurosurg 2018.
41. Lin AL, Jonsson P, Tabar V, et al. Marked Response of a Hypermutated ACTH-Secreting Pituitary Carcinoma to Ipilimumab and Nivolumab. J Clin Endocrinol Metab 2018; 103(10):3925–3930.
42. Yoo F, Kuan EC, Heaney AP, Bergsneider M, Wang MB. Corticotrophic pituitary carcinoma with cervical metastases: case series and literature review. Pituitary 2018; 21(3):290–301.
43. McCormack A, Dekkers OM, Petersenn S, et al. Treatment of aggressive pituitary tumours and carcinomas: results of a European Society of Endocrinology (ESE) survey 2016. Eur J Endocrinol 2018; 178(3):265–276.
44. Lenders N, McCormack A. Malignant transformation in nonfunctioning pituitary adenomas (pituitary carcinoma). Pituitary 2018; 21(2):217–229.
45. Guo F, Wang G, Wang F, Xu D, Liu X. Identification of Novel Genes Involved in the Pathogenesis of an ACTH-Secreting Pituitary Carcinoma: A Case Report and Literature Review. Front Oncol 2018; 8:510.
46. Mete O, Cintosun A, Pressman I, Asa SL. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol 2018; 31(6):900–909.
47. Pei L, Melmed S, Scheithauer B, Kovacs K, Prager D. H-*ras* mutations in human pituitary carcinoma metastases. J Clin Endocrinol Metab 1994; 78:842–846.
48. Cai WY, Alexander JM, Hedley-Whyte ET, et al. *Ras* mutations in human prolactinomas and pituitary carcinomas. J Clin Endocrinol Metab 1994; 78:89–93.
49. Tanizaki Y, Jin L, Scheithauer BW, Kovacs K, Roncaroli F, Lloyd RV. P53 gene mutations in pituitary carcinomas. Endocr Pathol 2007; 18(4):217–222.
50. Riss D, Jin L, Qian X, et al. Differential expression of galectin-3 in pituitary tumors. Cancer Res 2003; 63(9):2251–2255.
51. Thapar K, Scheithauer BW, Kovacs K, Pernicone PJ, Laws ER, Jr. p53 expression in pituitary adenomas and carcinomas: Correlation with invasiveness and tumor growth fractions. Neurosurgery 1996; 38:765–771.
52. Thapar K, Kovacs K, Scheithauer BW, et al. Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. Neurosurgery 1996; 38:99–107.
53. Yang Z, Zhang T, Gao H. Genetic aspects of pituitary carcinoma: A systematic review. Medicine (Baltimore) 2016; 95(47):e5268.
54. Monsalves E, Juraschka K, Tateno T, et al. The PI3K/AKT/mTOR pathway in the pathophysiology and treatment of pituitary adenomas. Endocr Relat Cancer 2014; 21(4):R331-R344.
55. Francois RA, Maeng K, Nawab A, Kaye FJ, Hochwald SN, Zajac-Kaye M. Targeting Focal Adhesion Kinase and Resistance to mTOR Inhibition in Pancreatic Neuroendocrine Tumors. J Natl Cancer Inst 2015; 107(8), djv123.
56. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):514–523.
57. Donovan LE, Arnal AV, Wang SH, Odia Y. Widely metastatic atypical pituitary adenoma with mTOR pathway STK11(F298L) mutation treated with everolimus therapy. CNS Oncol 2016; 5(4):203–209.
58. Leibowitz-Amit R, Mete O, Asa SL, Ezzat S, Joshua AM. Malignant pheochromocytoma secreting vasoactive intestinal peptide and response to sunitinib: a case report and literature review. Endocr Pract 2014; 20(8):e145-e150.
59. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):501–513.
60. Joshua AM, Ezzat S, Asa SL, et al. Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. J Clin Endocrinol Metab 2009; 94(1):5–9.
61. Raverot G, Castinetti F, Jouanneau E, et al. Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. Clin Endocrinol (Oxf) 2012; 76(6):769–775.
62. Hirohata T, Asano K, Ogawa Y, et al. DNA mismatch repair protein (MSH6) correlated with the responses of atypical pituitary adenomas and pituitary carcinomas to temozolomide: the national cooperative study by the Japan Society for Hypothalamic and Pituitary Tumors. J Clin Endocrinol Metab 2013; 98(3):1130–1136.
63. Royce ME, Hoff PM, Pazdur R. Novel oral chemotherapy agents. Curr Oncol Rep 2000; 2(1):31–37.
64. Owen DH, Alexander AJ, Konda B, et al. Combination therapy with capecitabine and temozolomide in patients with low and high grade neuroendocrine tumors, with an exploratory analysis of O(6)-methylguanine DNA methyltransferase as a biomarker for response. Oncotarget 2017; 8(61):104046–104056.
65. Thearle MS, Freda PU, Bruce JN, Isaacson SR, Lee Y, Fine RL. Temozolomide (Temodar(R)) and capecitabine (Xeloda(R)) treatment of an aggressive corticotroph pituitary tumor. Pituitary 2011; 14(4):418–424.
66. Zacharia BE, Gulati AP, Bruce JN, et al. High response rates and prolonged survival in patients with corticotroph pituitary tumors and refractory Cushing disease from capecitabine and

temozolomide (CAPTEM): a case series. Neurosurgery 2014; 74(4):E447-E455.
67. Opalinska M, Hubalewska-Dydejczyk A, Sowa-Staszczak A. Radiolabeled peptides: current and new perspectives. Q J Nucl Med Mol Imaging 2017; 61(2):153–167.
68. Fani M, Nicolas GP, Wild D. Somatostatin Receptor Antagonists for Imaging and Therapy. J Nucl Med 2017; 58(Suppl 2):61S–66S.
69. Komor J, Reubi JC, Christ ER. Peptide receptor radionuclide therapy in a patient with disabling non-functioning pituitary adenoma. Pituitary 2014; 17(3):227–231.