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Immunohistochemical Expression of ErbB2 in Adamantinomatous Craniopharyngiomas: A Possible Target for Immunotherapy

Adamantinomatöz Kraniofarengiomalarda ErbB2'nin İmünohistokimyasal Ekspresyonu: İmmünoterapi İçin Olası Bir Hedef

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ABSTRACT

AIM: To determine the immunohistochemical expression of ErbB2 in adamantinomatous craniopharyngiomas (ACP) and to assess its relationship with nuclear expression of β-catenin in surgically resected human ACP tissue sections and to estimate whether these tumors could be candidates for anti-ErbB2 therapy.

MATERIAL and METHODS: The ErbB2 and β-catenin immunostaining was performed on paraffin embedded tissue sections of 20 ACP using avidin-biotin-peroxidase complex method. ErbB2 immunoreactivity was interpreted according to the American Society of Clinical Oncology/ College of American Pathologists criterions for breast carcinoma.

RESULTS: Foci of nuclear reactivity for β-catenin was observed in all ACP tissue specimens mainly concentrated in whorl like arrays of the epithelial cells. Two (10%) of the cases were score 3+ for ErbB2 as demonstrated by strong complete membrane staining. However, the localization of 3+ ErbB2 cells was different from those with nuclear β-catenin immunoreactivity.

CONCLUSION: Our preliminary data demonstrate score 3+ staining for ErbB2 in 10% of ACP and different localization of 3+ ErbB2 cells and cells with nuclear β-catenin immunoreactivity. However, because of the small number of cases, further studies with larger samples should be conducted to verify and validate our preliminary data and to determine the effect of ErbB2 protein in ACP cell growth, survival and differentiation.

KEYWORDS: Adamantinomatous craniopharyngioma, Immunohistochemistry, EGFR, ErbB2, β-catenin

ÖZ

AMAÇ: Bu çalışmada, cerrahi olarak çıkarılmış insan adamantinomatöz kraniofarengiomalarında ErbB2'nin immünohistokimyasal ekspresyonunu, ErbB2 ekspresyonunun β-katenin ekspresyonu ile ilişkisini ve adamantinomatöz kraniofarengiomaların anti-ErbB2 tedavisine yanıt olasılığını tahmin etmeyi amaçladık.

YÖNTEM ve GEREÇLER: Çalışmamızda 20 adamantinomatöz kraniofarengiomanın parafin bloklarının kesitleri avdin-biotin-peroksidaz kompleks yöntemi ile boyandı. ErbB2 immünreaktivitesi Amerikan Klinik Onkoloji Derneği/Amerikan Patoloji Koleji'nin meme karsinomu kriterlerine göre değerlendirildi.

BULGULAR: Genellikle epitel hücrelerinin oluşturduğu sarmal benzeri yapılarda yoğun olmak üzere nükleer β-katenin immünreaktivite odakları tüm adamantinomatöz kraniofarengiomalarda saptandı. İki (%10) olguda ErbB2 3+ bulundu. Ancak ErbB2 3+ hücreler ile nükleer β-katenin immünreaktif hücrelerin lokalizasyonları farklı idi.

SONUÇ: Bizim ön verilerimiz adamantinomatöz kraniofarengiomaların %10'unda ErbB2'nin 3+ olduğunu ve ErbB2 3+ hücrelerin lokalizasyonunun nükleer β-katenin immünreaktif hücrelerin lokalizasyonundan farklı olduğunu göstermektedir. Bununla birlikte çalışmamız az sayıda olgu içerdiğinden dolayı ön verilerimizin doğrulanması ve ErbB2 proteininin adamantinomatöz kraniofarengioma hücrelerinin büyümesi, sağkalımı ve farklılaşması üzerindeki etkileri daha fazla sayıda olguyu içeren ileri çalışmalarla gösterilmesi gerekmektedir.

ANAHTAR SÖZCÜKLER: Adamantinomatöz kraniofarengioma, İmmunohistokimyasal boyama, EGFR, ErbB2, β-Katenin

INTRODUCTION

Craniopharyngiomas are nonglial epithelial tumors arising from the sellar/suprasellar region. They account for 3% of all intracranial neoplasms and for 5–10% of intracranial tumours in children (19). Histologically, craniopharyngiomas consist of two subtypes, the adamantinomatous (ACP) and the papillary (20). The ACP is the most common form and predominantly affects young children. The treatment of craniopharyngiomas remains a significant challenge. Gross total resection or subtotal resection in combination with adjuvant conventional radiotherapy are currently the treatment options for the management of craniopharyngiomas, but complete resection of these tumors is not always possible due to their large size, calcification and adherence to crucial surrounding neurovascular structures (20). Therefore, they are associated with a high rate of recurrence after incomplete therapy with significant ensuing morbidity and mortality.

Despite recent advances, the molecular mechanism that leads to ACP formation as well as markers of their development and progression are poorly understood.

ErbB2 protein, encoded by the HER2neu gene, belongs to a family of four homologous transmembrane receptors [epidermal growth factor receptor (EGFR)/ErbB1, ErbB2, ErbB3, and ErbB4] (11). Dimerization of the receptor either with a twin receptor (homodimerization) or with one of its siblings (heterodimerization) occur after binding of the ligand to the receptor and leads to phosphorylation of the intracellular tyrosine kinase residues which serve as docking sites for various effectors and transcription factors that ultimately modulate various biological responses including proliferation, survival, migration, and differentiation (11). Overexpression of the ErbB2 protein determined either by immunohistochemistry or amplification of the ErbB2 gene or both accounts for 20–25% of invasive ductal carcinomas, and is associated with aggressive clinical behavior in breast cancer patients (3). Nevertheless, ErbB2 expression was also demonstrated in various human cancers other than breast, including ovarian and endometrial cancers (22,27). Therefore, ErbB2 has been the target for immunotherapy. The overexpression of ErbB2 in prolactinomas and regulation of prolactin gene expression by ErbB2 receptor ligands have also been shown (12,28).

Activating mutations of the gene encoding β-catenin have been demonstrated in the majority of human ACP cases (10). This activating mutation makes the molecule refractive to downregulation by the APC-axin-GSK-3 β destruction complex (26). Mutation in the β-catenin gene was suggested to play a pivotal role in tumor morphogenesis and epithelial differentiation of ACP (5). Studies demonstrated a link between tumor cell migration in ACP and cells with an activated canonical Wnt signaling pathway, which is characterized by nuclear accumulation of β-catenin (17,18). Therefore, the β-catenin gene mutation and the nuclear accumulation of β-catenin demonstrated by immunohistochemistry are the characteristic features of ACP (10). Most recently, the EGFR cascade was demonstrated to play also a role in Wnt signaling activation, perhaps because of a direct interaction between EGFR and β-catenin (23).

Despite the overexpression of ErbB2 in various human cancers and pituitary adenomas (4,22), its expression in ACP, its relationship with nuclear β-catenin immunoreactivity, and its role in craniopharyngioma cell growth, survival and differentiation have not been determined so far. We therefore aimed to determine the immunohistochemical expression of ErbB2 in ACP and to assess its relationship with nuclear expression of β-catenin in surgically resected human ACP tissue sections and to estimate whether these tumors could be candidates for anti-ErbB2 therapy in this study.

MATERIAL and METHODS

For the present study, the paraffin-embedded tissue sections of 20 patients, operated at our center from 1993 to 2009 and diagnosed as adamantinomatous craniopharyngioma according to histopathological findings, were eligible for immunohistochemical analysis. Immunohistochemistry for ErbB2 was performed using avidin-biotin-peroxidase complex method. 3-5 µm cut formalin-fixed, paraffin embedded tumor tissue specimens underwent heat-induced antigen retrieval for 20 min in 0,01 M citrate buffer (PH 6.0) in the microwave. Sections were incubated for 60 minutes at room temperature with a mouse monoclonal anti-ErbB2 antibody (NCL-L-CB 11, Novocastra Laboratories, UK) at 1/40 dilution. Positive control consisted of invasive ductal carcinoma with 3+ staining for ErbB2. ErbB2 immunoexpression was evaluated on a multi-head light microscope by two observers (C.T and F.K) and was interpreted according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/ CAP) criteria for breast carcinoma (score 0, no staining or membrane staining is observed in <10% of the tumor cells; score 1+, faint/barely perceivable membrane staining is detected in >10% of the tumor cells, and only part of the membrane is stained; score 2+, weak to moderate complete membrane staining is observed in >10% of the tumor cells; score 3+, strong complete membrane staining is observed in >30% of the tumor cells)(30). Immunostaining for β-catenin was also performed using the same method and was evaluated by the same pathologists. A rabbit polyclonal antibody against β-catenin (Rb 9035-R7, Neomarkers Laboratories, USA) was used at 1/250 dilution. Data were analyzed using SPSS version 12.0.0 for Windows (SPSS Inc., Chicago, IL). Scale variables were presented as the mean ± standard deviation (mean ±SD) or percentages as appropriate. The project was approved by the local ethical board.

RESULTS

The present study included 20 patients (10 female, 10 male), ranged in age between 5-61 years old (24.9±17.38 years). Patient characteristics and immunohistochemistry results were presented in Table I. In this study, the provided tissues for immunohistochemistry were obtained at first surgery in 13 (65%) and at surgeries carried out after at least one recurrence in remaining 7 (35%) cases. Among the 20 cases

Table I: Patients Characteristics and Immunohistochemistry Results

Case	Patient age / Gender	Tumor location	ErbB2 expression score	Nuclear β-catenin expression	Recurrence/ outcome
1	15/F	sellar/suprasellar	0	+	No
2	12/M	suprasellar (3rd vent)	0	+	Yes, 2. Surgery
3	61/M	suprasellar	0	+	Yes, 2. surgery
4	12/F	sellar/suprasellar	3+	+	Died soon after the 1st surgery
5	43/F	suprasellar	0	+	Died soon after the 1st surgery
6	22/F	sellar	0	+	No
7	30/M	sellar/suprasellar	3+	+	Yes, 2 recurrences, 3 surgeries, RT
8	56/F	suprasellar	0	+	No
9	9/M	suprasellar	0	+	No
10	14/F	sellar/suprasellar	0	+	No
11	18/M	suprasellar	0	+	No
12	5/M	suprasellar	0	+	No
13	23/F	sellar/suprasellar	0	+	No
14	6/M	suprasellar	0	+	No
15	23/F	sellar/suprasellar	0	+	Yes, 2nd surgery
16	23/M	sellar/suprasellar	0	+	Yes, 2nd surgery
17	13/M	suprasellar	0	+	No
18	56/F	suprasellar	0	+	Yes, 2nd surgery, died soon after the 2nd surgery
19	15/M	sellar	0	+	No
20	42/F	sellar/suprasellar	0	+	No

evaluated, 2 (10%) were score 3+ for ErbB2 (Figure 1A-C) and the remaining 18 cases were score 0 (Figure 1D). Patchy cytoplasmic staining was observed in 10 (50%) cases. ErbB2 positive cells were distributed randomly throughout the tumor cells but with higher amounts near to the surface squamous cells and in cells bordering the foci of ''wet keratinizations''. Negative membrane staining was found in palisaded basal layer cells (Figure 1C). Different levels of ErbB2 positivity was also observed in cells of reactive gliosis bordering the tumors.

Foci of nuclear reactivity for β-catenin was observed in all ACP tissue specimens, mainly concentrated in epithelial cells within the whorl-like arrays, including those with 3+ ErbB2 immunoexpression (Figure 1E) However, cytoplasmic and membrane immunoreactivity for β-catenin was also found in some other portions of the ACP tissue specimens (Figure 1F). Membrane immunostaining for β-catenin was concentrated in areas of squamous cells and between areas of ''wet keratinizations'' and cysts. Nuclear and cytoplasmic β-catenin immunoreactivity was also observed in palisaded epithelial cells, in areas that were negative for ErbB2 (Figure 1F). However, no membrane immunoreactivity for ErbB2 was observed in whorl-like arrays of the epithelial cells, the area that mainly showed nuclear immunoreactivity for β-catenin.

Both patients with 3+ ErbB2 staining had large and invasive sellar/suprasellar tumors. One of these patients was a 12-year-old female who died soon after the first surgery and the other was a 30-year-old male patient who had undergone 3 consecutive surgeries and radiotherapy due to the recurrence of the tumor. He is being followed for panhypopituitarism, excessive weight gain and diabetes insipidus that developed after repeated surgeries and radiotherapy.

DISCUSSION

In the present study, 20 cases of ACP assessed for ErbB2 and β-catenin immunoexpression. Of the 20 cases evaluated, 2 (10%) demonstrated score 3+ immunoreactivity for ErbB2 and all of the cases showed nuclear immunoreactivity for β-catenin which is the hallmark of ACP (10).

β-catenin functions as a key mediator in the Wnt-signaling pathway which is related to the cell proliferation, differentiation and migration (7). Activation of β-catenin has been suggested to activate expression of a variety of target genes including *Lef1*, *Axin1* and *CyclinD1* (6), a major regulator of the progression of cells into the proliferative stage of the cell cycle. Andoniadou et al. indicated that nucleocytoplasmic β-catenin cluster cells act as a source of mitogenic and pro-survival for themselves and surrounding membranous β-catenin ACP cells by enhancing expression of mitogenic signals including members of the hedgehog–secreted signals, fibroblast growth factor and bone morphogenetic

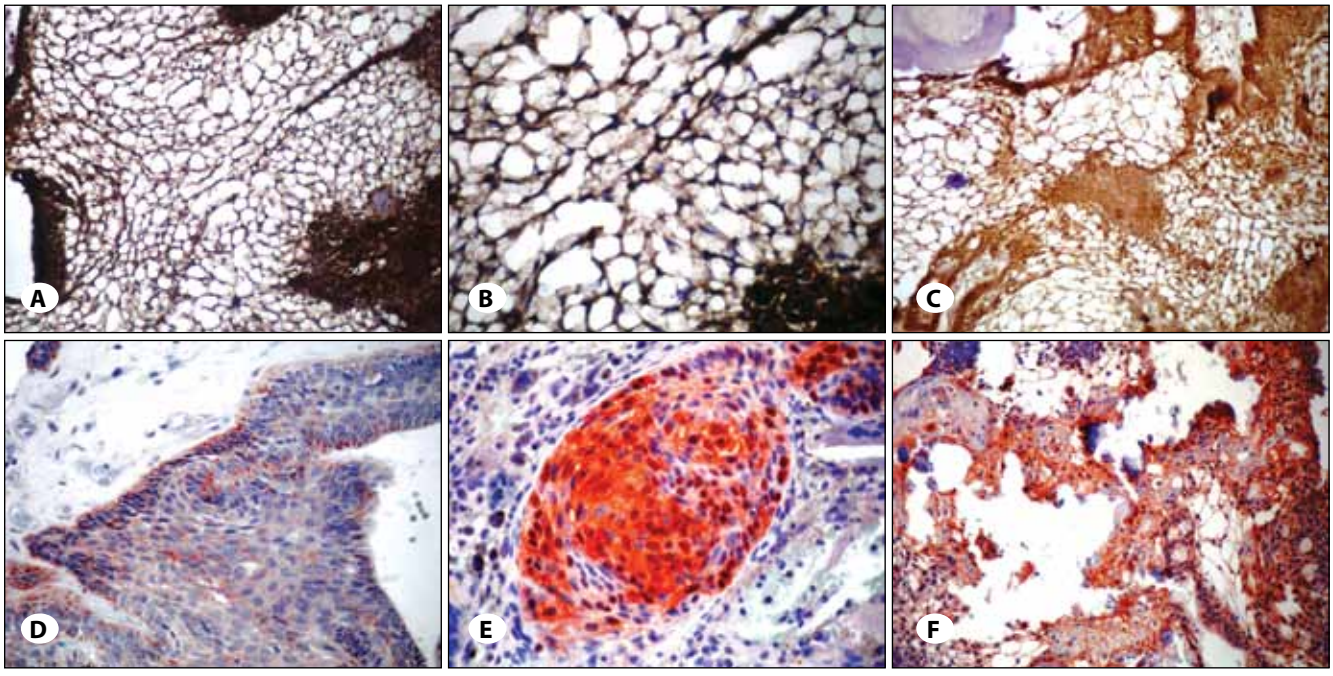

Figure 1: (A,B and C) Score 3+ ErbB2 staining in adamantinomatous craniopharyngioma **(A and B: Case 4; C: Case 7**). **(D)** Score 0 ErbB2 staining in adamantinomatous craniopharyngioma. **(E)** Nuclear and cytoplasmic β-catenin immunoreactivity mainly concentrated in whorl like arrays of the epithelial cells. **(F)** Cytoplasmic and membrane β-catenin immunoreactivity in adamantinomatous craniopharyngioma (A, C, D and E x 200, B x 400, F x 100).

factor families (1). So, the activation of β-catenin pathway and its aberrant nuclear accumulation plays a causal role in the development and growth of ACP. Cani et al. demonstrated nuclear β-catenin staining pattern in all of ACP tissue specimens analyzed by immunohistochemistry (7). Cao et al. and Buslei et al. also demonstrated nuclear and cytoplasmic expression of β-catenin in the majority of human ACP tissue samples, mainly concentrated in epithelial cells within the whorl-like arrays (5,8). In addition, Buslei et al. suggested that nuclear accumulation of β-catenin plays a pivotal role in morphogenesis and epithelial differentiation of ACP (5,8). Our study results were consistent with all of these studies and indicated nuclear accumulation of β-catenin in all of the ACP tissue specimens, predominantly accumulated in epithelial cells within the whorl-like arrays (7,8). Our results also support that aberrant nuclear β-catenin expression may be involved in morphogenesis and growth of ACP (5,8). However, the localization of cells with nuclear β-catenin immunoreactivity which was mainly accumulated in epithelial cells within the whorl-like arrays was different from cells with 3+ ErbB2 immunoreactivity. So, if the ErbB2 protein plays a role in tumor growth, survival or differentiation of some ACP, the mechanism of action may be different from β-catenin pathway. However, because of the small number of ACP, particularly those with score 3+ ErbB2 expression, the effect of ErbB2 protein in ACP cell growth, survival and differentiation should be determined in functional studies with larger sample sizes.

Although craniopharyngiomas correspond histologically to tumoral grade I according to the World Health Organization (WHO) classification, they often behave as aggressive tumors and cause significant mortality and morbidity (19,32). Malignant transformation of craniopharyngiomas either after radiotherapy or without previous radiotherapy has also been reported (15). The preferred goal of therapy for a craniopharyngioma is the total resection of the tumor. However, most of craniopharyngiomas invade the optic chiasma and other surrounding brain tissues as well as the vessels of the Circle of Willis, which preclude a total resection of the tumor (31). On the other hand, recurrence could occur in 0–62% of cases after gross total resection and in 25–100% of cases after subtotal resection (21). Recurrence may also occur in up to 20% of the cases after radiotherapy performed for residual disease (14). So, there is no satisfying treatment option other than gross total or subtotal resection followed by adjuvant radiotherapy.

Trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of ErbB2, is used for the treatment of ErbB2 positive breast cancer. When combined with chemotherapy, trastuzumab has been demonstrated to be effective in patients with ErbB2-positive metastatic breast cancer (2). However, trastuzumab has also been demonstrated to be effective when used as single agent in the treatment of metastatic ErbB2-positive breast cancer (29). Although trastuzumab does not cross the blood-brain barrier due to its large molecule size, its administration via the intrathecal route has been reported to be effective for brain metastasis of ErbB2 positive breast cancer (24). In recent years, research efforts have focused on improving the delivery of trastuzumab to the

central nervous system. Lapatinib, which is a new generation of small molecule tyrosine kinase inhibitors and monoclonal antibodies targeting two or more ErbB receptors, has been shown to have clinical benefit in trastuzumab-refractory ErbB2 positive breast cancer (25). Evidence has suggested its efficacy in ErbB2 positive breast cancer with brain metastasis (25).

The expression of ErbB2 was also demonstrated in both functioning and non-functioning pituitary adenomas, particularly in those showing aggressive behavior (9). The regulation of hormonal secretion, cell morphology and proliferation by ErbB2 tyrosin kinase inhibitors was also shown in experimental studies (9). In a study conducted by Fukuoka et al. lapatinib was shown to suppress both prolactin mRNA expression and secretion in cultured human prolactinoma tissues (12). In the same study, Lapatinib treatment was also demonstrated to cause tumor shrinkage and serum prolactin suppression both in HER2CA transfectant-inoculated Wistar-Furth rats and in estrogen-induced Fischer rat prolactinomas (12). Most recently, Fukuoka et al. demonstrated also supressed expression of proopiomelanocortin by gefitinib, a EGFR tyrosin kinase inhibitor, in surgically resected human and canine corticotroph cultured tumors (13). Hölsken et al analyzed the effect of EGFR activation on cell motility in 11 primary ACP cell cultures. They found increased migration and invasion capacity with activation of the EGFR. They also found reduced motility of activated EGFR when exposed to gefitinib (16). A significant enhanced expression of Fascin, the target gene of β-catenin, was also found after EGFR activation that was inhibited in the majority of cases by gefitinib treatment (16). All of these studies highlight the importance of targeted therapeutics for the treatment of pituitary adenomas and ACP. However, to date, the expression of ErbB2 had not been determined in craniopharyngioma of any subtype.

In this study 2 cases were score 3+ for ErbB2 and both cases were large and sellar/suprasellar tumors and one of them was a tumor with more than one recurrence. However, as demonstrated in table 1, most of the tumors, including 5 other recurrent cases were negative for ErbB2. Therefore, due to the small cohort of tumors, the association between ErbB2 protein and recurrence of ACP should be determined in further studies.

In summary, our preliminary data demonstrate score 3+ staining for ErbB2 in 10% of ACP and different localization of 3+ ErbB2 cells and cells with nuclear β-catenin immunoreactivity. However, because of the small number of cases, further studies with larger samples should be conducted to verify and validate our preliminary data and to determine the effect of ErbB2 protein in ACP cell growth, survival and differentiation.

REFERENCES

1. Andoniadou CL, Gaston-Massuet C, Reddy R, Schneider RP, Blasco MA, Le Tissier P, Jacques TS, Pevny LH, Dattani MT, Martinez-Barbera JP: Identification of novel pathways involved in the pathogenesis of human adamantinomatous craniopharyngioma. Acta Neuropathol doi: 10.1007/s00401-012-0957-9
2. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L: Treatment of HER2-positive breast cancer: Current status and future perspectives. Nat Rev Clin Oncol 9(1):16-32, 2011
3. Blackwell KL, Burstein HJ, Storniolo AM, Rugo, H, Sledge G, Koehler M, Ellis C, Casey M, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J: Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer J Clin Oncol 28: 1124-1130, 2010
4. Botelho CH, Magalhaes AV, Mello PA, Schmitt FC, Casulari LA: Expression of p53, Ki-67 and cerbB2 in growth hormone-and/or prolactin-secreting pituitary adenomas. Arq Neuropsiquiatr 64: 60–66, 2006
5. Buslei R, Hölsken A, Hofmann B, Kreutzer J, Siebzehnrubl F, Hans V, Oppel F, Buchfelder M, Fahlbusch R, Blümcke I: Nuclear beta-catenin accumulation associates with epithelial morphogenesis in craniopharyngiomas. Acta Neuropathol 113(5):585-590, 2007
6. Camper SA: Beta-catenin stimulates pituitary stem cells to form aggressive tumors. Proc Natl Acad Sci U S A. 108(28):11303-11304, 2011
7. Cani CM, Matushita H, Carvalho LR, Soares IC, Brito LP, Almeida MQ, Mendonça BB: PROP1 and CTNNB1 expression in adamantinomatous craniopharyngiomas with or without β-catenin mutations. Clinics (Sao Paulo) 66(11):1849-1854, 2011
8. Cao J, Lin JP, Yang LX, Chen K, Huang ZS: Expression of aberrant beta-catenin and impaired p63 in craniopharyngiomas. Br J Neurosurg 24(3):249-256, 2010
9. Cooper O, Vlotides G, Fukuoka H, Greene MI, Melmed S: Expression and function of ErbB receptors and ligands in the pituitary. Endocr Relat Cancer 18: R197-R211, 2011
10. Edgar MA, Rosenblum MK: The differential diagnosis of central nervous system tumors: A critical examination of some recent immunohistochemical applications. Arch Pathol Lab Med 132(3):500-509, 2008
11. Elsahwi KS, Santin AD: erbB2 Overexpression in Uterine Serous Cancer: A molecular target for trastuzumab therapy. Obstet Gynecol Int 2011:128295, 2011
12. Fukuoka H, Cooper O, Mizutani J, Tong Y, Ren SG, Bannykh S, Melmed S: HER2/ErbB2 receptor signaling in rat and human prolactinoma cells: Strategy for targeted prolactinoma therapy. Mol Endocrinol 25: 92-103, 2011
13. Fukuoka H, Cooper O, Ben-Shlomo A, Mamelak A, Ren SG, Bruyette D, Melmed S: EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas. J Clin Invest 121(12):4712-4721, 2011

14. Garnett MR, Puget S, Grill J, Sainte-Rose C: Craniopharyngioma. Orphanet J Rare Dis 2:18, 2007
15. Gao S, Shi X, Wang Y, Qian H, Liu C: Malignant transformation of craniopharyngioma: Case report and review of the literature. J Neurooncol 103: 719-725, 2011
16. Hölsken A, Gebhardt M, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R: EGFR Signaling regulates tumor cell migration in craniopharyngiomas. Clin Cancer Res 2 17:4367-4377, 2011
17. Hölsken A, Buchfelder M, Fahlbusch R, Blumcke I, Buslei R: Tumour cell migration in adamantinomatous craniopharyngiomas is promoted by activated Wnt-signalling. Acta Neuropathol 119:631–639, 2010
18. Hölsken A, Kreutzer J, Hofmann BM, Hans V, Oppel F, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R: Target gene activation of the Wnt signaling pathway in nuclear beta-catenin accumulating cells of adamantinomatous craniopharyngiomas. Brain Pathol 19:357–364, 2009
19. Janzer RC, Burger PC, Giangaspero F, Paulus W: Craniopharyngioma. In: Kleihues P, Cavenee WK (eds) World Health Organization classification of tumours of the central nervous system. IARC, Lyon, 2000:244–246
20. Karavitaki N, Cudlip S, Adams C, Wass JAH: Craniopharyngiomas. Endocr Rev 27: 371–397, 2006
21. Karavitaki N, Wass JAH: Craniopharyngiomas. Endocrinol Metab Clin N Am 37: 173–193, 2008
22. Kontogeorgos G, Stefaneanu L, Kovacs K, Cheng Z: Localization of Epidermal Growth Factor (EGF) and Epidermal Growth Factor Receptor (EGFr) in Human Pituitary Adenomas and Nontumorous Pituitaries: An Immunocytochemical Study. Endocr Pathol 7: 63–70, 1996
23. Lee CH, Hung HW, Hung PH, Shieh YS: Epidermal growth factor receptor regulates beta-catenin location, stability, and transcriptional activity in oral cancer. Mol Cancer 9:64, 2010
24. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J: Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. Breast Cancer Res Treat 127: 841-844, 2011
25. Onishi H, Morisaki T, Nakafusa Y, Nakashima Y, Yokohata K, Katano M: Objective response with lapatinib in patients with meningitis carcinomatosa derived from HER2/HER1-negative breast cancer. Int J Clin Oncol 16(6):718-721, 2011
26. Polakis P: Wnt signaling and cancer. Genes Dev 14: 1837–1851, 2000
27. Santin AD, Bellone S, Van Stedum S, Bushen W, Palmieri M, Siegel ER, De Las Casas LE, Roman JJ, Burnett A, Pecorelli S: Amplification of c-erbB2 oncogene: A major prognostic indicator in uterine serous papillary carcinoma. Cancer 104: 1391-1397, 2005
28. Vlotides G, Siegel E, Donangelo I, Gutman S, Ren SG, Melmed S: Rat prolactinoma cell growth regulation by epidermal growth factor receptor ligands. Cancer Res 68: 6377-6386, 2008
29. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ, Murphy M, Novotny WF, Burchmore M, Shak S, Stewart SJ, Press M: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20: 719-726, 2002
30. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF: American Society of Clinical Oncology; College of American Pathologists, American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 25: 118–145, 2007
31. Zada G, Laws ER: Surgical management of craniopharyngiomas in the pediatric population. Horm Res Paediatr 74: 62-66, 2010
32. Zuhur SS, Musluman AM, Tanık C, Karaman O, Ozturk FY, Ozderya A, Ozkayalar H, Aydın Y, Altuntas Y: MGMT immunoexpression in adamantinomatous craniopharyngiomas. Pituitary 14: 323-327, 2011