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Correlation of Expression Transforming Growth Factor-β1, E-cadherin, and Ki-67 in Meningiomas

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Abstract

BACKGROUND: Meningioma is the most common primary intracranial tumors in adults, accounts for 36% of total intracranial tumors. Obtaining the clinicopathological characteristics of patients with meningioma and investigating, the association between signaling pathways with disease progression could provide a basis for therapeutic development.

AIM: This study aims to investigate the expression of transforming growth factor-β1 (TGF-β1), E-cadherin, and Ki-67 in meningiomas.

MATERIALS AND METHODS: This study examined the expression levels of E-cadherin, Ki-67, and TGF-β1 with respect to the WHO grade in patients with meningioma. A total of 62 meningioma samples were analyzed. By the WHO criteria, 54 specimens were diagnosed as the WHO Grade 1, 6 as Grade 2, and 2 as Grade 3. Grade 1 was classified as low-grade meningioma, while Grade 2 and Grade 3 were classified as high-grade meningioma (HGM).

RESULTS: In this study, the mean age diagnosis was 41.97 ± 9.79 years old, with female: male ratio of 8:1. There was no association between age, sex, and tumor location with the progression of meningioma. Immune-characterization revealed that HGM was associated with the higher number of Ki-67$^+$ cells ($p < 0.0001$) and lower expression of TGF-β1 and E-cadherin ($p < 0.001$). The number of Ki-67$^+$ cells was inversely correlated with TGF-β1 and E-cadherin ($p < 0.05$). TGF-β1 expression was positively correlated with E-cadherin expression ($p < 0.0001$).

CONCLUSION: This study concluded that HGM was highly proliferative (high Ki-67$^+$) and invasive (low E-cadherin), with dysregulated TGF-β1 signaling. In addition, younger age at diagnosis and high female: male ratio in our series suggests that Indonesian females might possess specific risk factors for having meningioma.

Introduction

Meningioma is the most common primary intracranial tumors in adults, accounts for 36% of total intracranial tumors in the USA, with an incidence about 7.61/100,000 population [1]. The high recurrence of meningiomas remains a hurdle in clinical settings. The recurrence rate is not only determined by surgical grading but also histopathological grading. About 7–32% benign meningiomas will relapse after total resection [2]. Prior study indicated that classical WHO grading failed to predict meningioma prognosis [3]. Lack of literatures regarding clinicopathological characteristics of meningioma in Indonesia adds more challenges for decision-making in the clinics.

Transforming growth factor-β (TGF-β) induces a pleiotropic pathway that is modulated by the cellular context and its integration with other signaling pathways. In cancer, TGF-β induces cytostatic and apoptotic responses in early-stage tumors, while inducing proliferation, invasion, angiogenesis, and immune evasion in advanced cancer [4]. Several conflicting evidences about TGF-β role in meningioma progression, initial study reported that TGF-β addition promotes meningioma cell proliferation [5], while later studies reported that dysregulation or loss of TGF-β signaling contributes to meningioma progression or meningioma agenesis [6],[7].

E-cadherin is a crucial molecule in intercellular adhesion in epithelial tissues. It is localized on the surfaces of epithelial cells in regions of cell-cell contact known as an adherent junction [8]. Besides its role in physiological condition, this highly conserved gene contributes to malignant transformation, especially in tumor development and progression. The loss of E-cadherin is regarded as a major molecular event for dysfunction in cell-cell adhesion, particularly during epithelial–mesenchymal transition (EMT) [9]. Most tumors have abnormal cellular architecture and loss of tissue integrity, thus lead to local invasion and metastasis [10]. Prior studies in meningiomas hinted

that E-cadherin was dysregulated in meningioma and might contribute to meningioma agenesis [11],[12].

The association between TGF-β1 and E-cadherin has been reported in several tumors. In gastric cancer, TGF-β1 overexpression contributes to decreased expression of E-cadherin; this phenomenon involves in the progression of gastric cancer [13]. A similar association was observed in colorectal cancer, TGF-β1 expression is inversely correlated with E-cadherin expression [14]. In this study, we aim to investigate TGF-β1 and E-cadherin expression in meningioma, to clarify the association between TGF-β1, E-cadherin, and Ki-67, and to gain better insight regarding those signaling in meningioma genesis. In addition, we also aim to obtain the clinicopathological characteristics of patients with meningioma in Indonesia and to provide a basis for therapeutic development.

Materials and Methods

Patients

This retrospective study included 62 patients at Raden Mattaher Hospital, Jambi, who underwent surgical resection from January 2012 to December 2017, in which the diagnosis of meningioma was established. Clinical data were collected from archival medical records. Surgically resected tumor tissues were fixated in 10% – formaldehyde and preserved in paraffin-embedded blocks. Tumors were then classified and graded according to the 2016 WHO classification of CNS tumors [15]. Clinical data of patients are summarized in Table 1.

Immunohistochemistry (IHC)

Four-micron thickness slides from the tumor tissue were deparaffinized and rehydrated. Antigen retrieval was carried out with microwave and antigen retrieval solution (citrate buffer 10 mmol/L, pH 6.0). Sections were then allowed for cooling at room temperature, followed by washing 3×, each for 5 min with phosphate-buffered saline (PBS). Endogenous peroxidase activity was blocked by dipping sections in 3% H_2O_2 (Dako, USA) for 3 min, then 0.3% H_2O_2 (Dako, USA) for 30 min, and washed in three changes of PBS. Then, slices were incubated with 0.3% Triton X-100 for membrane penetration. Non-specific protein binding was blocked with 2% normal goat serum (Millipore, USA) for 20 min at room temperature. Slices were incubated with primary antibodies overnight at 40°C. After washing in three changes of PBS, slices were incubated with biotinylated secondary antibodies for 30 min at room temperature. Slices were washed with PBS ×3, followed by incubation with horseradish peroxidase labeled avidin-biotin complex (Vectastain, PK-6100, Vector Laboratories) for 30 min. After washing, the staining was developed for 5 min in a substrate medium containing 0.05% 3,3-diaminobenzidine and 0.02% H_2O_2 in Tris-HCl buffer (pH 7.6). The specificity of staining was confirmed by the absence of staining when the primary antibodies were omitted. The slices were counterstained with hematoxylin and mounted with Entellan (Millipore, USA).

Table 1: Summary of patients characteristics

No	Sex	Age	Location	Histological type	WHO grade
1	Female	46	Cranial vault	Meningotheliomatous	1
2	Male	66	Cranial vault	Meningotheliomatous	1
3	Female	43	Cranial vault	Meningotheliomatous	1
4	Female	31	Cranial vault	Meningotheliomatous	1
5	Female	42	Cranial vault	Psamommatous	1
6	Female	55	Cranial vault	Meningotheliomatous	1
7	Female	42	Cranial vault	Psamommatous	1
8	Female	39	Cranial vault	Meningotheliomatous	1
9	Male	50	Skull base	Meningotheliomatous	1
10	Female	43	Cranial vault	Meningotheliomatous	1
11	Female	40	Cranial vault	Meningotheliomatous	1
12	Female	28	Cranial vault	Angiomatous	1
13	Female	38	Cranial vault	Meningotheliomatous	1
14	Male	38	Cranial vault	Angiomatous	1
15	Female	28	Skull base	Meningotheliomatous	1
16	Female	43	Skull base	Fibroblastic	1
17	Female	45	Cranial vault	Psamommatous	1
18	Female	28	Skull base	Meningotheliomatous	1
19	Female	56	Cranial vault	Meningotheliomatous	1
20	Female	42	Skull base	Meningotheliomatous	1
21	Female	34	Cranial vault	Meningotheliomatous	1
22	Female	43	Skull base	Meningotheliomatous	1
23	Male	35	Cranial vault	Angiomatous	1
24	Female	32	Cranial vault	Psamommatous	1
25	Female	47	Skull base	Meningotheliomatous	1
26	Female	23	Cranial vault	Fibroblastic	1
27	Male	33	Cranial vault	Angiomatous	1
28	Female	48	Cranial vault	Meningotheliomatous	1
29	Female	45	Cranial vault	Meningotheliomatous	1
30	Female	36	Skull base	Meningotheliomatous	1
31	Female	46	Skull base	Meningotheliomatous	1
32	Female	68	Cranial vault	Psamommatous	1
33	Male	41	Cranial vault	Meningotheliomatous	1
34	Female	30	Cranial vault	Meningotheliomatous	1
35	Female	24	Cranial vault	Angiomatous	1
36	Female	43	Skull base	Meningotheliomatous	1
37	Female	46	Cranial vault	Meningotheliomatous	1
38	Female	60	Skull base	Meningotheliomatous	1
39	Female	56	Cranial vault	Angiomatous	1
40	Female	43	Cranial vault	Meningotheliomatous	1
41	Female	38	Cranial vault	Meningotheliomatous	1
42	Female	44	Cranial vault	Angiomatous	1
43	Female	52	Skull base	Meningotheliomatous	1
44	Female	35	Cranial vault	Fibroblastic	1
45	Male	44	Skull base	Angiomatous	1
46	Male	48	Cranial vault	Meningotheliomatous	1
47	Female	26	Skull base	Angiomatous	1
48	Female	39	Cranial vault	Meningotheliomatous	1
49	Female	40	Cranial vault	Psamommatous	1
50	Female	43	cranial vault	Meningotheliomatous	1
51	Female	38	Skull base	Angiomatous	1
52	Female	36	Skull base	Fibroblastic	1
53	Female	30	Cranial vault	Microcystic	1
54	Female	40	Cranial vault	Psamommatous	1
55	Female	44	Cranial vault	Atypical	2
56	Female	51	Skull base	Chordoid	2
57	Female	51	Skull base	Atypical	2
58	Female	66	Cranial vault	Chordoid	2
59	Female	33	Cranial vault	Atypical	2
60	Female	35	Skull base	Atypical	2
61	Female	48	Cranial vault	Anaplastic	3
62	Female	45	Cranial vault	Anaplastic	3

IHC analysis

Slices were observed and images were captured with Olympus BX51 (Tokyo, Japan) by a blinded experimenter. The percentage of Ki-67+ cells was counted on five non-overlapping fields at ×40 objective magnification, at least 500 cells. Semi-quantitative scoring was utilized to determine TGF-β1

and E-cadherin immunoreactivity. The average counts of the five regions were used for the final report.

Research ethics

Ethical approval was obtained from the Faculty of Medicine, Andalas University, and Dr. M. Djamil Hospital, Padang, Committee of Ethics.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.03. The data were evaluated for normality distribution before statistical comparison. Fisher Exact test was used to examine the difference between female and cranial vault proportion between low-grade meningioma (LGM, WHO Grade I) and high-grade meningioma (HGM, WHO Grade II-III). T-test was used to examine the difference of age at diagnosis between LGM and HGM. The Mann–Whitney U-test was used to examine the difference between LGM and HGM, in terms of Ki-67, E-cadherin, and TGF-β1 expression. The association between each variable was evaluated by linear regression. The statistically different consider significant when $p < 0.05$.

Results

Patients characteristics

We enrolled 62 patients diagnosed with cranial meningiomas, which tumor specimens were available. By the WHO criteria [15], 54 of the specimens were diagnosed as Grade I, six as Grade II, and two as Grade III. In the case of Grade I meningioma, meningiotheliomatous was the most common type, about 59.26% (32/54), followed by angiomatous (18.52%), psammomatous (12.96%), fibroblastic (7.41%), and microcystic (1.85%). In the case of Grade II, atypical was the most common type, about 66.67% (4/6), the other type was chordoid (33.33%). All Grade III meningiomas were anaplastic variants (2/2). To ease further analysis, we classified Grade I meningiomas as LGM and Grade II-III meningiomas as HGM.

There was no difference in the mean age at the diagnosis of meningioma between LGM and HGM (41.28 ± 9.61 vs. 46.63 ± 10.32, $p = 0.1508$). In this study, meningioma was rarely observed in the elderly population (>65 years old, 4.84% [3/62]). The female proportion was not statistically different between LGM and HGM (46/54 vs. 8/8, $p = 0.5810$). In this study, we observed a high female proportion (±8:1), which higher than literatures [2,16]. There was no difference in cranial vault meningioma proportion between LGM (70.37%, 38/54) and HGM (62.50%, 5/3, $p = 0.6917$). Patient characteristics are summarized in Table 1.

IHC results of meningioma patients

To gain insight about TGF-β1 and E-cadherin association in meningioma, we performed IHC to examine: Ki-67, TGF-β1, and E-cadherin. We observed that HGM tumor specimens were more proliferative than LGM (Ki-67+ cells: 11.38 ± 2.15% vs. 3.83 ± 1.05%, $p < 0.0001$, Mann–Whitney U-test, Figures 1a, d, g and 2a).

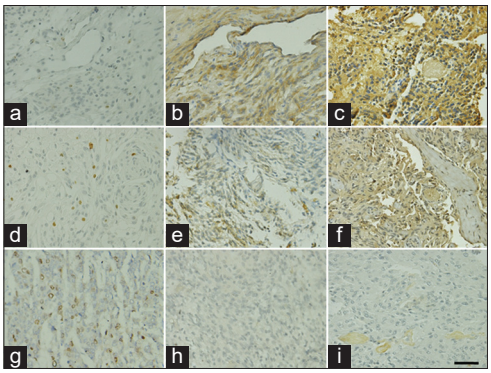

Figure 1: Representative immunostaining on meningioma tissues. Ki-67 was nuclear staining (left panel). E-cadherin (middle panel) was cytoplasmic staining. TGF-β1 was cytoplasmic and extracellular matrix staining (right panel). Low Ki-67+ meningiomas were associated with high expression of E-cadherin and TGF-β1 (upper panel). Moderate Ki-67+ meningiomas were associated with moderate expression of E-Cadherin and TGF-β1 (middle panel). High Ki-67+ meningiomas were associated with low expression of E-cadherin and TGF-β1 (lower panel). Scale Bar = 100 μm. TGF-β1: Transforming growth factor-β1

In this study, we observed that E-cadherin expression was lower in HGM than LGM (7.32 ± 2.17 vs. 4.25 ± 1.17, $p < 0.0001$, Mann–Whitney U-test, Figures 1b, e, h and 2b). TGF-β1 expression was also observed to be lower in HGM than LGM (6.39 ± 2.03 vs. 3.75 ± 1.58, $p = 0.0002$, Mann–Whitney U-test, Figures 1c, f, i and 2c). Further analysis revealed that the number of Ki-67+ cells was inversely correlated with E-cadherin and TGF-β1 expression (Figure 2d and e). We also confirmed that E-cadherin expression was associated with TGF-β1 expression (Figure 2f).

Discussion

In this series, the majority of meningiomas were LGM (87.10%, 54/62), this finding is consistent with reported literatures, LGM accounts for 70–90% of total meningiomas [17],[18] suggesting that the proportion of aggressive meningiomas (HGM) in Indonesia is similar with other countries. The majority of meningiomas

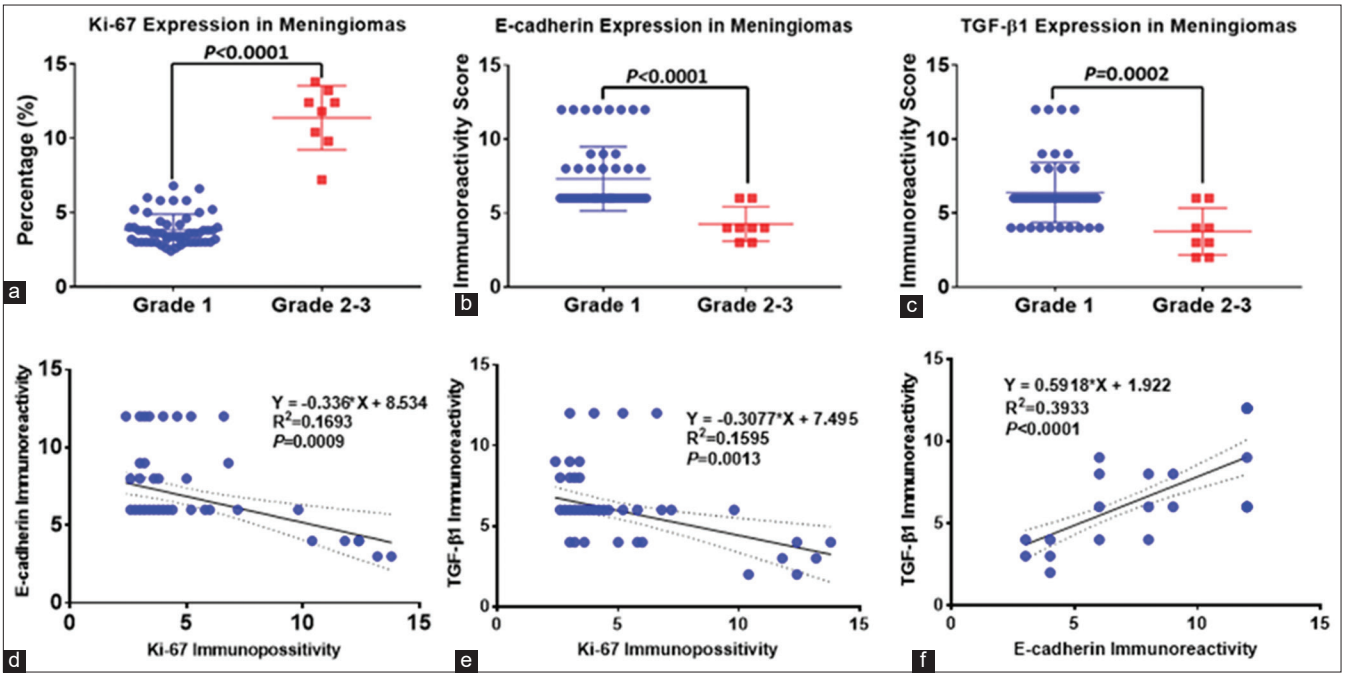

Figure 2: Semi-quantitative analysis of immunostaining. (a) Ki-67 expression was observed to be higher in HGM (WHO Grade 2–3) (3.83 ± 1.05 vs. 11.83 ± 2.15, p < 0.0001, Mann–Whitney U-test). (b) E-cadherin expression was lower in HGM than LGM (7.32 ± 2.17 vs. 4.25 ± 1.17, p < 0.0001, Mann–Whitney U-test). (c) TGF-β1 expression was lower in HGM than LGM (6.39 ± 2.03 vs. 3.75 ± 1.58, p = 0.0002, Mann–Whitney U-test). (d) E-cadherin expression was inversely correlated with Ki-67 expression. (e) TGF-β1 expression was inversely correlated with Ki-67 expression. (f) E-cadherin expression was associated with TGF-β1 expression. HGM: High-grade meningioma. LGM: Low-grade meningioma

were located in the cranial vault (convexity, falx, and parasagittal), accounts for 69.35% (43/62) of total patients; this finding resembles the reported proportion in India [19]. Additionally, during 2012–2018, in Dr Hasan Sadikin Hospital (Tertiary Neurosurgery Center, Bandung, Indonesia), cranial vault meningioma only accounts for ±25% from a total of 717 meningiomas (Hermanto and Faried, unpublished data). This discrepancy might be attributed to genetic background as well as the tendency for referring difficult cases (skull base meningioma) to the tertiary care hospital.

In this series, meningiomas were commonly observed in middle-aged (30–55 years old) population with a female predominance (8:1); meanwhile, the reported incidence of meningioma is higher in elderly, with the female:male ratio of 3.5:1 [2],[19],[20]. The previous study indicated that male and convexity meningiomas are the risk factors for having HGM [2],[21]; however, we did not those associations in our series. Together, our findings suggest that Indonesian females possess specific risk factors that might increase the likelihood of having meningioma.

We observed a unique association between WHO Grade, Ki-67, E-cadherin, and TGF-β1, suggesting HGM was highly proliferative (high Ki-67+) and invasive (low E-cadherin), with dysregulated TGF-β1 signaling. The role of TGF-β signaling in cancer is intriguing, exhibiting context-dependent effects. It may act as a tumor suppressing factor or tumor promoting factor. In normal cells and early-stage cancers, TGF-β inhibits cell growth and promotes apoptosis [22]. However, its activation in late-stage cancers promotes cell growth, immune evasion, angiogenesis, chemoresistance, and invasion [22]. Several reports indicated that the upregulation of TGF-β in cancers promotes downregulation of E-cadherin and contributes to the EMT [13],[14],[23]. Interestingly, we found that TGF-β1 is downregulated in HGM, although HGM is more proliferative and invasive. Previous studies demonstrated that TGF-β addition inhibits meningioma cell proliferation [6],[24]. Gene expression profile also indicated that there is a loss of TGF-β signaling in HGM [7]. Hence, it seems likely that TGF-β exerts an inhibitory effect on LGM and that loss of TGF-β signaling results in progression to malignancy.

This study is limited by a small number of HGM, the malignant tumor itself is known for its intra- and inter-tumoral heterogeneity. Of note, several reports indicated that activation of TGF-β signaling promotes proliferation and meningioma cells [5],[25], therefore further *in vitro* and *in vivo* investigations are needed to clarify the context-dependent of TGF-β signaling in meningioma. Younger age at diagnosis and high female: male ratio in our series suggests that Indonesian females might possess specific risk factors for having meningioma; it also needs for further investigation.

In this study, we found that HGM was highly proliferative (high Ki-67+) and invasive (low E-cadherin), with dysregulated TGF-β1 signaling. TGF-β1 is downregulated in HGM; hence, it seems likely that TGF-β exerts an inhibitory effect on LGM and that loss of TGF-β signaling results in progression to malignancy. In addition, younger age at diagnosis and high female: male ratio in our series suggest that Indonesian females might possess specific risk factors for having meningioma.

References

1. McNeill KA. Epidemiology of brain tumors. Neurol Clin. 2016;34(4):981-98. https://doi.org/10.1016/j.ncl.2016.06.014
   PMid:27720005
2. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: Novel therapeutic opportunities. Nat Rev Neurol. 2018;14(2):106-15. https://doi.org/10.1038/nrneurol.2017.168
   PMid:29302064
3. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol. 2004;57(10):1033-7. https://doi.org/10.1136/jcp.2004.018333
   PMid:15452155
4. Seoane J, Gomis RR. TGF-β family signaling in tumor suppression and cancer progression. Cold Spring Harb Perspect Biol. 2017;9(12):a022277. https://doi.org/10.1101/cshperspect.a022277
   PMid:28246180
5. Nitta T, Sato K, Okumura K. Transforming growth factor (TGF)-beta like activity of intracranial meningioma and its effect on cell growth. J Neurol Sci. 1991;101(1):19-23. https://doi.org/10.1016/0022-510x(91)90014-x
   PMid:2027025
6. Ohnson MD. Transforming growth factor beta family in the pathogenesis of meningiomas. World Neurosurg. 2017;104:113-9. https://doi.org/10.1016/j.wneu.2017.03.058
   PMid:28344175
7. Carvalho LH, Smirnov I, Baia GS, Modrusan Z, Smith JS, Jun P, *et al*. Molecular signatures define two main classes of meningiomas. Mol Cancer. 2007;6:64. https://doi.org/10.1186/1476-4598-6-64
   PMid:17937814
8. Pećina-Slaus N. Tumor suppressor gene E-cadherin and its role in normal and malignant cells. Cancer Cell Int. 2003;3(1):17. https://doi.org/10.1186/1475-2867-3-17
   PMid:14613514
9. Gheldof A, Berx G. Cadherins and epithelial-to-mesenchymal transition. Prog Mol Biol Transl Sci. 2013;116:317-36. https://doi.org/10.1016/B978-0-12-394311-8.00014-5
   PMid:23481201
10. Vleminckx K, Vakaet L Jr., Mareel M, Fiers W, van Roy F. Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell. 1991;66(1):107-19. https://doi.org/10.1016/0092-8674(91)90143-m
    PMid:2070412
11. Brunner EC, Romeike BF, Jung M, Comtesse N, Meese E. Altered expression of beta-catenin/E-cadherin in meningiomas. Histopathology. 2006;49(2):178-87. https://doi.org/10.1111/j.1365-2559.2006.02440.x
    PMid:16879395
12. Pecina-Slaus N, Cicvara-Pecina T, Kafka A. Epithelial-to-mesenchymal transition: Possible role in meningiomas. Front Biosci (Elite Ed). 2012;4:889-96. https://doi.org/10.2741/e427
    PMid:22201922
13. Zhu Y, Wu J, Ma W, Zhang H, Wang D. Expression of TGF-ß1, snail, E-cadherin and N-cadherin in gastric cancer and its significance. Chin J Clin Oncol. 2007;4(6):384-9. https://doi.org/10.1007/s11805-007-0384-1
14. Lampropoulos P, Zizi-Sermpetzoglou A, Rizos S, Kostakis A, Nikiteas N, Papavassiliou AG. Prognostic significance of transforming growth factor beta (TGF-β) signaling axis molecules and E-cadherin in colorectal cancer. Tumour Biol. 2012;33(4):1005-14. https://doi.org/10.1007/s13277-012-0333-3
    PMid:22278155
15. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol. 2016;131(6):803-20. https://doi.org/10.1007/s00401-016-1545-1
    PMid:27157931
16. Klaeboe L, Lonn S, Scheie D, Auvinen A, Christensen HC, Feychting M, *et al*. Incidence of intracranial meningiomas in Denmark, Finland, Norway and Sweden, 1968-1997. Int J Cancer. 2005;117(6):996-1001. https://doi.org/10.1002/ijc.21255
    PMid:15986431
17. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, *et al*. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol. 2002;61(3):215-25. https://doi.org/10.1093/jnen/61.3.215
    PMid:11895036
18. Kshettry VR, Ostrom QT, Kruchko C, Al-Mefty O, Barnett GH, Barnholtz-Sloan JS. Descriptive epidemiology of World Health Organization grades II and III intracranial meningiomas in the United States. Neuro Oncol. 2015;17(8):1166-73. https://doi.org/10.1093/neuonc/nov069
    PMid:26008603
19. Mubeen B, Makhdoomi R, Nayil K, Rafiq D, Kirmani A, Salim O, *et al*. Clinicopathological characteristics of meningiomas: Experience from a tertiary care hospital in the Kashmir Valley. Asian J Neurosurg. 2019;14(1):41-6. https://doi.org/10.4103/ajns.ajns_228_16
    PMid:30937006
20. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, *et al*. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol. 2015;17 Suppl 4:iv1-iv62. https://doi.org/10.1093/neuonc/nov189
    PMid:26511214
21. Magill ST, Young JS, Chae R, Aghi MK, Theodosopoulos PV, McDermott MW. Relationship between tumor location, size, and WHO grade in meningioma. Neurosurg Focus. 2018;44(4):E4. https://doi.org/10.3171/2018.1.focus17752
    PMid:29606048
22. Colak S, Ten Dijke P. Targeting TGF-β signaling in cancer. Trends Cancer. 2017;3(1):56-71. https://doi.org/10.1016/j.trecan.2016.11.008
    PMid:28718426
23. Xu J, Lamouille S, Derynck R. TGF-beta-induced epithelial to mesenchymal transition. Cell Res. 2009;19(2):156-72. https://doi.org/10.1038/cr.2009.5
    PMid:19153598
24. Johnson MD, Okediji E, Woodard A. Transforming growth factor-beta effects on meningioma cell proliferation and signal transduction pathways. J Neurooncol. 2004;66(1-2):9-16. https://doi.org/10.1023/b: neon.0000013461.35120.8a
    PMid:15015765
25. Gogineni VR, Gupta R, Nalla AK, Velpula KK, Rao JS. uPAR and cathepsin B shRNA impedes TGF-ß-driven proliferation and invasion of meningioma cells in a XIAP-dependent pathway. Cell Death Dis. 2012;3(12):e439. https://doi.org/10.1038/cddis.2012.170