Clinicopathological significance of concurrent ErbB receptor expression in human meningioma

SVERRE HELGE TORP[1,2], MAGNUS BOSSUM ARNLI[3] and DAVID SCHEIE[4]

[1]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, NO-7491 Trondheim; [2]Department of Pathology, St. Olavs Hospital, Trondheim University Hospital, 7006 Trondheim; [3]Department of Radiology, Østfold Hospital Trust, NO-1714 Grålum, Norway; [4]Department of Pathology, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark

Received May 29, 2023; Accepted July 17, 2023

DOI: 10.3892/mco.2023.2675

Abstract. In general, human meningiomas grow slowly and have a favourable prognosis; however, some are prone to recur despite their benign histology. Therefore, knowledge of their tumour biology is essential to determine objective biomarkers that can identify cases with an increased risk for recurrence and to generate effective treatment options. Thus, studies on the epidermal growth factor receptor (EGFR) family, comprising ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4, are important. We have recently published papers on the expression of each of these receptor proteins in human meningiomas. The present study aimed to assess the clinicopathological significance of their concurrent expression. A total of 185 grade 1 and 2 meningiomas with robust clinical data underwent immunohistochemical analyses with antibodies against the aforementioned receptors. All meningiomas exhibited upregulation of these receptor proteins relative to normal meninges. In addition, the expression of phosphorylated/activated ErbB1/EGFR1 and phosphorylated/activated ErbB2/HER2 was significantly associated with histological malignancy grade and prognosis, respectively. The concurrent upregulation of ErbB receptors in human meningioma supports their fundamental role in the tumourigenesis of these tumours, and they could thus be exploited in diagnostics, prognosis, and ultimately, in targeted clinical interventions.

Introduction

Meningiomas are the most common primary tumours of the central nervous system (CNS) constituting more than one-third (1). Their probable origin is the arachnoid cap cells of the meningeal layers. These cells have both mesenchymal and epithelial features and are morphologically, ultrastructurally, and functionally similar to meningioma cells, giving rise to the great heterogeneity in histopathology, recurrence rates, aggressivity, symptoms, and prognoses (2-4). The incidence of meningiomas increases with age, so in an ageing population they will become more prevalent. Meningiomas are rare in children, and there is a more than a twofold higher incidence among females (5,6).

Most meningiomas are benign and slow growing, but they have an intrinsic tendency to recur despite benign histology (3,4,7). Prognostication of meningiomas has primarily been based on histopathology, and according to criteria given by the World Health Organization (WHO) these tumours are divided into three malignancy grades and distinct subtypes. The 2021 WHO classification endorses use of molecular biomarkers to support classification and grading of these tumours (8,9).

Observation may be sufficient management; however, when indicated, the main treatment mostly involves surgery (10). The surgical gold standard is complete resection, as subtotal resection is strongly associated with high risk of recurrence (10). Radiation therapy may be indicated in case of incomplete resection, difficult location for surgery (i.e., skull-base meningiomas), recurrences, and high-grade tumours (10). In any case, all these treatment options have troublesome complications and side effects (10-12). Furthermore, as the incidence of meningioma increases with age, these patients also have an increased risk of various adverse events and prolonged hospitalization (13). Systemic therapy is still at the experimental stage (10,11). All in all, these aspects underline the crucial need for more objective biomarkers with which to stratify meningioma patients according to risk of recurrence and optimal treatment and follow-up regimes.

In this regard, the EGFR (epidermal growth factor receptor) family is pertinent as these receptor proteins are known to be crucial drivers of the growth and progression of many human tumours (14-17). This receptor family comprises four transmembrane tyrosine kinases: ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4 (14,15,18). These receptor proteins have an external ligand-binding

Correspondence to: Professor Sverre Helge Torp, Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Erling Skjalgsssons gate 1, NO-7491 Trondheim, Norway
E-mail: sverre.torp@ntnu.no

Key words: brain tumours, EGFR, HER, growth factor receptors, immunohistochemistry, diagnosis, prognosis, survival

domain, a transmembrane domain, and an intracellular kinase domain. Upon ligand binding, the receptor protein undergoes conformational changes leading to homo- and heterodimerisation, and subsequently active tyrosine kinase activity. Since ErbB2/HER2 lacks ligand-binding sites, and ErbB3/HER3 lacks an internal kinase domain, heterodimerisation is therefore important for their mutual activation. Activated ErbB receptors trigger a cascade of fundamental downstream signalling pathways, such as the Ras-ERK, P13K-Akt, PLC-γ1, STAT1, and Src pathways (14,17,18), which are involved in many essential cellular processes, including survival, differentiation, proliferation, metabolism, adhesion, motility, and angiogenesis (14,15,17,18). Hence, aberrant ErbB expression is implicated in many human malignancies and has shown diagnostic, prognostic, and therapeutic significance (14,16,17,19), whereas in human meningiomas the clinical significance is more ambiguous (20-26).

We have recently published three papers on the expression of each member of the EGFR family in human meningiomas, and we found abundant co-expression of these receptor proteins (20-22). To our knowledge, there are no larger studies that have investigated the clinicopathological significance of this co-expression in these tumours. Here we give an overview of the status of the EGFR receptor family in human meningiomas and discuss clinical and histopathological aspects of this concurrent overexpression.

Materials and methods

Patients and samples. The patient data, histopathological examination, tissue microarray (TMA) construction, and immunohistochemical analyses have been published earlier (20-22,27,28). Briefly, all patients consecutively operated for meningiomas at St. Olavs Hospital, Trondheim, Norway, in the time frame January 1991-January 2000 were evaluated for inclusion (only primary tumours). Tumour tissue was fixed in formalin and embedded in paraffin, and after microscopy the tumours were classified and graded according to WHO 2016 guidelines (29). Exclusion criteria were patient age <18 years and spinal localization. Anaplastic WHO grade 3 meningiomas were omitted due to few cases. Finally, 185 cases were included. Follow-up time was a maximum of 18 years.

Immunohistochemistry. There was sufficient tumour tissue to construct TMAs in 163 cases. Each tumour was represented by three paraffin-embedded tissue cylinders. The remaining 22 cases not suitable for TMA construction were processed as whole-tissue sections. Standard immunohistochemistry was performed using a Dako Autostainer Plus (Dako, Glostrup, DK). For ErbB1/EGFR and ErbB2/HER2 staining, antibodies reactive against internal and external domains and phosphorylated/activated receptor were used. Antibodies targeting the internal domain were used for ErbB3/HER3 and ErbB4/HER4. A list of the primary antibodies used is shown in Table I. After incubation with the primary antibodies, the sections were incubated in a Dako EnVision system. Each immunostaining was semiquantitatively assessed and recorded as a staining index (SI) calculated as the product of the intensity and the distribution of immunoreactive tumour cells. Intensity was scored as 0 (no reaction), 1 (weak), 2 (moderate), or 3 (strong). Fraction of positive tumour cells was recorded as 0 (no positivity), 1 (<10% positive cells), 2 (10-50% positive cells), or 3 (>50% positive cells).

Statistical analyses. The survival analyses have been described earlier (20-22,27). Briefly, associations between SIs and tumour grades were assessed by Mann-Whitney U-test, and Kruskal-Wallis and Dunn tests were used to test for associations between SIs and variables with more than two groups (tumour subtypes and localization). Cox regression analyses were used in both uni- and multivariate survival analyses based on continuous SIs. Simpson resection grade (1/2 vs. 3/4), WHO performance status (0 and 1 vs. 2, 3, 4, and 5), histological malignancy grade (grade 1 vs. grade 2), and age (continuous values) were used as covariates in the multivariate analyses. Statistical significance was defined as $P<0.05$. SPSS version 24.0 (IBM Corp.) was used in the statistical analyses.

Results

A total number of 185 cases were enrolled: 129 CNS WHO grade 1 meningiomas (70%) and 56 atypical CNS WHO grade 2 meningiomas (30%), with a female:male ratio of 2.9. Most patients were radically operated and had a good performance status. Convexity meningiomas (falx and convexities) comprised 109 cases (59%), and skull base meningiomas (skull base, posterior fossa, tentoria and intraventricular) 76 cases (41%). Most tumours showed positive immunoreactivity for epithelial membrane antigen (EMA) (98.3%). Patient data are shown in Table II.

All tumours were immunoreactive for the ErbB receptors, most tumours showed high expression levels. Both cytoplasmic and membranous immunoreactivity were observed. For ErbB4/HER4, nuclear immunoreactivity was found as well. Normal meninges adjacent to the tumour tissue did not display detectable immunoreactivity. A survey of the immunohistochemical analyses is presented in Table III, and examples of typical immunostaining images of internal domains are shown in Fig. 1.

Table IV shows the clinical data. The expression pattern was generally poorly associated with tumour localization, subtypes, tumour grade, and prognosis. Among significant results, ErbB1/EGFR showed higher SIs in transitional (P=0.028) and meningothelial (P=0.044) subtypes compared with fibrous ones. The SIs of ErbB1/EGFR-ph were lower in skull-base compared with convexity meningiomas (P=0.001) and were higher in grade 2 tumours than in grade 1 (P=0.018). Further, ErbB4/HER4 SIs were higher in convexity meningiomas compared with those in the skull base (P=0.040).

Concerning prognosis, ErbB1/EGFR-ext and ErbB4/HER4-int were correlated with TTR (HR=1.099, 95% CI 0.987-1.222, P=0.084) and OS (HR=1.223, 95% CI 1.023-1.461, P=0.027) in univariate analyses, respectively. ErbB2/HER2-ph was significantly associated with TTR and OS in both univariate (TTR: HR=1.512, 95% CI 1.132-2.019, P=0.005; OS: HR=1.397, 95% CI 1.027-1.900, P=0.033) and multivariate (TTR: HR=1.512, 95% CR 1.132-2.019, P=0.005; OS: HR=1.679, 95% CI 1.213-2.323, P=0.002) analyses. Among clinical factors, high Simpson grade was associated

Table I. List of antibodies.

Antibody	Supplier	Cat. no.	Clonality	Clone/epitope	Dilution
ErbB1/EGFR					
Internal domain (ErbB1/EGFR-int)	Novocastra, Leica Biosystems	NCL-L-EGFR-384	Moab	EGFR.25	1:100
External domain (ErbB1/EGFR-ext)	Novocastra, Leica Biosystems	NCL-EGFR	Moab	EGFR.113	1:10
Phosphorylated (ErbB1/EGFR-ph)	EMD Millipore	04-341	Moab	Anti-phospho-EGFR (Tyr1173)	1:45
ErbB2/HER2					
Internal domain (ErbB2/HER2-int)	Novocastra, Leica Biosystems	NCL-L-CB11	Moab	CB11	1:40
External domain (ErbB2/HER2-ext)	Thermo Fisher Scientific	MA5-16348	Moab	SP3	1:10
Phosphorylated (ErbB2/HER2-ph)	Cell Signaling Technology	2243	Moab	6B12	1:10
ErbB3/HER3					
Internal domain (ErbB3/HER3-int)	Novocastra, Leica Biosystems	NCL-c-erbB-3	Moab	RTJ-1 IgM	1:10
ErbB4/HER4					
Internal domain (ErbB4/HER4-int)	Thermo Fisher Scientific	MA1-861	Moab	HFR1 IgG2b	1:50

Moab, monoclonal antibody.

Table II. Patient data.

Parameter	Grade 1	Grade 2	Total
Number of cases	129 (69.7%)	56 (30.2%)	185
Median age at operation, years (range)	58 (27-84)	62 (25-86)	59 (25-86)
Sex, male/female	29/100	18/38	47/138
Simpson grade, I/II/III/IV	33/53/18/25	11/27/11/7	44/80/29/32
WHO Performance Status, 0/1/2/3/4	18/89/20/2/0	6/41/7/1/1	25/130/27/3/1
Localization, convexity (including falcine)/skull base (including posterior fossa, tentorial and intraventricular)	64/65	45/11	109/76

WHO, World Health Organization.

with poorer prognosis in multivariate analysis (HR=0.36, 95% CI 0.21-0.60, P<0.001).

Discussion

By means of immunohistochemistry we have shown concurrent overexpression of all members of the EGFR family in our series of meningiomas, whereas the clinical significance was limited where only ErbB2/HER2-ph was significantly associated with prognosis in multivariate analyses.

Malignant transformation of normal cells involves accumulation of several genetic changes, whereas subsequent steps in tumour progression, such as clonal growth, invasion, and angiogenesis, are in high degree mediated by growth factors and their receptors (19). Common genetic changes in human meningiomas are loss of chromosome 22q (60-70% in sporadic meningiomas) and mutations in *NF2*, *TRAF7, SMO, AKT1, KLF4, SMARCB1, BAP1, TERT* promoter, homozygous deletions of *CDKN2A/B*, and H3K27me loss (5,30,31). These genetic events are linked to and affect intracellular signalling pathways, including those mediated by the EGFR family, and play important roles in tumour growth and progression (14,17,19,30). Thus, concurrent overexpression of the ErbB receptors together with the reported molecular genetic events, constitutes a strong synchronous driving force on intracellular pathways fundamental to the tumourigenesis

Table III. Immunohistochemical results.

ErbB receptor	Benign (n=129), number immunoreactive (%)	Atypical (n=56), number immunoreactive (%)
ErbB1/EGFR-internal domain	129 (100%)	56 (100%)
ErbB1/EGFR-external domain	128 (99.2%)	56 (100%)
ErbB1/EGFR-phosphorylated	128 (99.2%)	56 (100%)
ErbB2/HER2-internal domain	129 (100%)	56 (100%)
ErbB2/HER2-external domain	67 (51.9%)	23 (41.1%)
ErbB2/HER2-phosphorylated	15 (11.6%)	5 (9.1%)
ErbB3/HER3-internal domain	126 (97.7%)	56 (100%)
ErbB4/HER4-internal domain	129 (100%)	56 (100%)

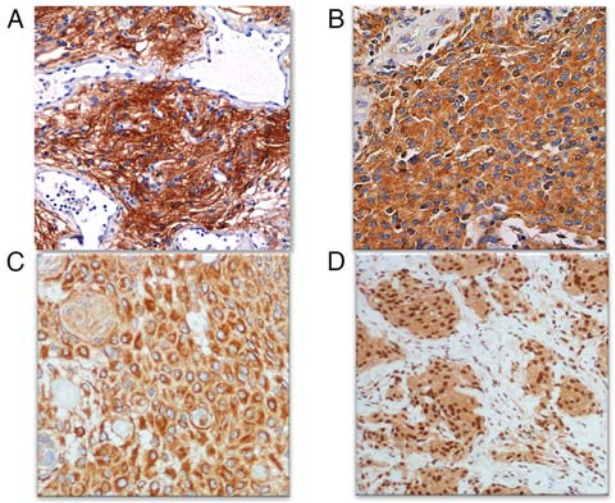

Figure 1. Immunohistochemical staining for internal domains of: (A) ErbB1/EGFR, (B) ErbB2/HER2, (C) ErbB3/HER3, and (D) ErbB4/HER4 (magnification, x200).

of human meningiomas. This is in accordance with the study of Hilton *et al*, who reported the activation of many growth factor receptors and their signalling pathways (32). This overexpression of the ErbB receptors was poorly associated with proliferative activity (i.e., mitotic activity), atypical histological features, and tumour grade (apart from ErbB1/EGFR-ph), suggesting that the receptor proteins are more involved in aspects of tumour biology, such as cell survival (including apoptosis), angiogenesis, cell motility and metabolism (14,19,33), than in tumour progression.

Various growth factors bind to and activate ErbB receptors (14,17,19), such as epidermal growth factor and transforming growth factor-alpha, which also have been detected in meningioma cells (22,34). Their release/shedding is proposed to be a rate-limiting step determining levels of ligands in the tissue (35,36). These ligands bind to their specific ErbB receptor with various affinities and with formation of homo- and heterodimers (14,15). The various combinations of ligands and dimers also stand out as important regulatory mechanisms (14,35). These findings support the existence of local autocrine and paracrine growth loops in the meningioma tissue, but non-neoplastic cells, such as fibroblasts, endothelial cells, and macrophages, are also involved. This cross talk is essential for tumour biology with regard to infiltration, migration, angiogenesis, local inflammatory responses, and establishment and maintenance of the tumour microenvironment (14,19,36,37). These aspects may be reflected by the infiltrative growth of meningioma in dura, bone, and brain tissue (the latter typical for aggressive meningiomas), vascularization, and inflammatory response (4,14,15,38). In this regard, ErbB receptors have been shown to induce an immunosuppressive tumour microenvironment by regulating the immune system, and in this manner enable tumour escape from anti-tumour immune responses (38). This may be important in the observed acquired resistance to multitargeted therapies as well as to immune checkpoint inhibitors (38).

Activation of ErbB receptors trigger various intracellular signalling pathways, such as the phosphatidylinositol 3-kinase/Akt (PKB) pathway, the Ras/Raf/MEK/ERK1/2 pathway, and the phospholipase C (PLCγ) pathway (14,15,17,18). This complex ErbB network is regarded as a robust cellular signalling system in tumours, as many receptors activate common pathways (14,38,39). This may also partly explain why ErbB1/EGFR alone has not worked as a valuable therapeutic target (14,33,38) and thus constitutes a rationale for application of multi-tyrosine kinase inhibitors (10,40-42).

Both membranous and cytoplasmic immunoreactivity were observed in agreement with their transmembrane localization and their fate after activation, including endocytosis, ubiquitylation, and degradation as well as recycling (14). The clinical relevance of either the membranous or the cytoplasmic immunoreactivity was not investigated, as the mesenchymal features of meningioma tumour tissue make such a distinction difficult. However, this issue is of relevance in other tumour types, such as breast and lung cancer where only membranous ErbB2/HER2 is accepted (43,44). Nuclear ErbB receptor immunoreactivity has been reported in various human malignancies as well, but to our knowledge not in human meningiomas (14,17,45,46). We found; however nuclear immunoreactivity for ErbB4/HER4 (20) that may be involved in transcriptional regulation, signal transmission, cell proliferation, and DNA repair and replication. They have also been linked to genomic instability, chemo- and radio-resistance, and various clinicopathological states (14,17,45,46).

Overexpression of ErbB1/EGFR has been commonly found in human meningiomas (22-25,47,48) and may be due to ligand overproduction, increased transcription or translation, or endocytic pathway regulation as *EGFR* gene amplification has not

Table IV. Survey of ErbB receptor expression and clinical associations.

ErbB receptor	Localization (convexity vs. skull base)	Association with subtypes	Association with histological malignancy grade	Association with to TTR	Association with OS
ErbB1/EGFR-int	NS	NS	NS	NS	NS
ErbB1/EGFR-ext	NS	S[c]	NS	S[e]	NS
ErbB1/EGFR-ph	S[a]	NS	S[d]	NS	NS
ErbB2/HER2-int	NS	NS	NS	NS	NS
ErbB2/HER2-ext	NS	NS	NS	NS	NS
ErbB2/HER2-ph	NS	NS	NS	S[f]	S[g]
ErbB3/HER3-int	NS	NS	NS	NS	NS
ErbB4/HER4-int	S[b]	NS	NS	NS	S[h]

SI, staining index; TTR, time to recurrence; OS, overall survival; NS, not statistically significant (P>0.05); S, statistically significant (P<0.05); int, internal; ext, external; ph, phosphorylated. [a]ErbB1/EGFR-ph SIs were significantly higher in convexity than in skull-base meningiomas (P=0.001) (Kruskal-Wallis test). [b]ErbB4/HER4-int SIs were significantly higher in convexity than in skull-base meningiomas (P=0.040) (Kruskal-Wallis test). [c]ErbB1/EGFR-ext SIs were significantly lower in fibrous meningiomas than in transitional (P=0.028) and meningothelial subtypes (P=0.036) (Kruskal-Wallis test). [d]ErbB1/EGFR-ph SIs were significantly higher in WHO grade 2 meningiomas than in WHO grade 1 (P=0.018) (Mann-Whitney U-test). [e]ErbB1/EGFR-ext SIs were significantly higher in meningiomas with shorter TTR in univariate Cox regression analysis (P=0.009). [f]ErbB2/HER2-ph SIs were significantly higher in meningiomas with shorter TTR in univariate and multivariate Cox regression analyses (P=0.005 and P=0.033, respectively). [g]ErbB2/HER2-ph SIs were significantly higher in meningiomas with shorter OS in univariate and multivariate Cox regression analyses (P=0.005 and P<0.001, respectively). [h]ErbB4/HER4 SIs were significantly higher in meningiomas with shorter OS in univariate Cox regression analyses (P=0.027).

been found in these tumours (33). Actually, *EGFR* mutations have recently been detected, but the clinical significance of this is uncertain (49). Activation of the ErbB receptors leads to conformational changes and autophosphorylation. Both represent important regulatory steps (14,15). We therefore wanted to study the expression level of ErbB1/EGFR-ph. Most of our meningiomas were immunoreactive indicating a constitutively active receptor. The positive correlation with malignancy grade may be related to tumour progression; however, no prognostic value was found. The higher immunoreactivity in convexity compared with skull-base meningiomas but not any relation to subtypes, may be due to the embryonic origin of the meninges (50). ErbB1/EGFR-ext displayed weak immunostaining. We have no obvious explanation for this, but we have observed this in glioblastomas as well (51). One may speculate whether this is related to proteolytic shedding or conformational changes during ligand binding and resultant epitope availability (15,52). ErbB1/EGFR-ext was also significantly associated with decreased TTR, but only in univariate analyses. Accordingly, our findings are in agreement with the literature that ErbB1/EGFR has limited prognostic value in human meningiomas.

ErbB2/HER2 was also widely expressed in accordance with most others (21,53-57). This overexpression may be due to factors previously mentioned, but gene amplification has been found in a few tumours (55). We have; however, not found this genetic event in our studies (21,58). The expression levels between females and males have not been checked, but it has been reported not to differ (56). ErbB2/HER2 lacks extracellular ligand binding sites, so this receptor protein becomes activated because it is a favoured dimerization partner for the other ErbB receptor proteins (14,59). In contrast to the abundant expression of ErbB1/HER-ph, few cases were ErbB2/HER2-ph immunoreactive, and the labelling was weak as well. Nevertheless, it achieved statistical significance regarding prognosis in multivariate analyses. This is also in line with findings in breast and lung cancer (60,61). Thus, ErbB2/HER2-ph may be considered as a prognostic biomarker in human meningiomas, a drawback is the weak labelling, so both the immunostaining and prognostic power must be further validated.

ErbB3/HER3 and ErbB4/HER4 were highly expressed in all of our meningiomas (20), but the clinicopathologic value is scarcely described (20,23,25,62). Since ErbB3/HER3 lacks intrinsic kinase activity, its activation depends on ligand binding and/or heterodimerisation with other ErbB members, and especially ErbB2/HER2 is a prioritized partner (14,59,63). Overexpressed and activated ErbB3/HER3 has been linked to tumour progression and poor prognosis in many human cancers (17,63), whereas we do not find any such association (20). ErbB4/HER4 has been shown to have various clinical roles in human cancers (17,64). We find it to have prognostic value but only in univariate analyses, so this needs to be further investigated. ErbB4/HER4 was the only EGFR family member with nuclear expression. Studies have shown clinical relevance of this immunoreactivity (17,64). As most of our tumours displayed nuclear expression, no clinicopathological significance could be established. As for ErbB1/EGFR-ph, ErbB4/HER4 displayed higher labelling in convexity meningiomas compared with basal ones, which may be related to the meninges' embryology and *NF2* gene status (8,30,50).

Primary treatment for most meningiomas is surgery, alternatively radiotherapy (10). In case of inoperable, subtotally resected or recurrent aggressive meningiomas, chemotherapy or targeted therapy may be ventilated, but their roles in the clinical management of meningiomas are still not well established (10,41,42). Nevertheless, future therapeutic approaches may be based on identification of potential unique molecular

targets. As most growth factor receptors and tyrosine kinases are expressed in human meningiomas with subsequent activation of several intracellular signalling pathways (26,31), molecular targeted therapies including tyrosine kinase inhibitors have emerged (26,31,38,42). In this regard, pilot studies with ErbB tyrosine kinase inhibitors have largely been ineffective, mostly due to acquired resistance (38). This may be related to upregulation of downstream signalling pathways, activation of by-pass pathways, upregulated autophagy, and secondary mutations, as well as the induction of an immunosuppressive tumour microenvironment (33,38). That said, multitargeted tyrosine kinase inhibitors, anti-angiogenetic therapy (VEGF inhibitors), and mTOR inhibitors have revealed promising results (41,42). In addition, other antineoplastic drugs are under investigations as potential candidates for systemic therapy and immunotherapy of especially more aggressive meningiomas (42,65,66).

The strength of our studies is the rather large number of patients operated at a single neurosurgical centre with population-based referral and long follow-up. Limitations are the retrospective aspects, the inherent challenges of immunohistochemistry, and the subjective assessment of the immunostaining.

In conclusion, we have shown abundant co-expression of all ErbB receptors in human meningiomas, supporting their fundamental role in their tumourigenesis, and this overexpression may be of value in any targeted clinical strategies for these tumours.

Acknowledgements

Not applicable.

Funding

This project was funded by the Norwegian University of Science and Technology, Trondheim, Norway (project no. 81850106) and the Department of Pathology, St. Olavs Hospital, Trondheim, Norway.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SHT, DS, and MBA were involved in conceptualization of the study. SHT and MBA confirm the authenticity of all the raw data. MBA performed analyses. MBA, DS and SHT wrote the manuscript. SHT performed project administration and supervision. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of The Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics Central Norway, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway with approved waiver of consent (project number 4.2006.947).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ostrom QT, Price M, Ryan K, Edelson J, Neff C, Cioffi G, Waite KA, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol 24(Suppl 3): iii1-iii38, 2022.
2. Perry A, Gutmann DH and Reifenberger G: Molecular pathogenesis of meningiomas. J Neurooncol 70: 183-202, 2004.
3. Harter PN, Braun Y and Plate KH: Classification of meningiomas-advances and controversies. Chin Clin Oncol 6(Suppl 1): S2, 2017.
4. Mawrin C and Perry A: Pathological classification and molecular genetics of meningiomas. J Neurooncol 99: 379-391, 2010.
5. Suppiah S, Nassiri F, Bi WL, Dunn IF, Hanemann CO, Horbinski CM, Hashizume R, James CD, Mawrin C, Noushmehr H, *et al*: Molecular and translational advances in meningiomas. Neuro Oncol 21(Suppl 1): i4-i17, 2019.
6. Wiemels J, Wrensch M and Claus EB: Epidemiology and etiology of meningioma. J Neurooncol 99: 307-314, 2010.
7. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD and Lukas RV: An overview of meningiomas. Future Oncol 14: 2161-2177, 2018.
8. Gritsch S, Batchelor TT and Gonzalez Castro LN: Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. Cancer 128: 47-58, 2022.
9. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, *et al*: The 2021 WHO Classification of tumors of the central nervous system: A summary. Neuro Oncol 23: 1231-1251, 2021.
10. Goldbrunner R, Stavrinou P, Jenkinson MD, Sahm F, Mawrin C, Weber DC, Preusser M, Minniti G, Lund-Johansen M, Lefranc F, *et al*: EANO guideline on the diagnosis and management of meningiomas. Neuro Oncol 23: 1821-1834, 2021.
11. Brastianos PK, Galanis E, Butowski N, Chan JW, Dunn IF, Goldbrunner R, Herold-Mende C, Ippen FM, Mawrin C, McDermott MW, *et al*: Advances in multidisciplinary therapy for meningiomas. Neuro Oncol 21(Suppl 1): i18-i31, 2019.
12. Lacy J, Saadati H and Yu JB: Complications of brain tumors and their treatment. Hematol Oncol Clin North Am 26: 779-796, 2012.
13. Nia AM, Branch DW, Maynard K, Frank T, Yowtak-Guillet J, Patterson JT and Lall RR: How the elderly fare after brain tumor surgery compared to younger patients within a 30-day follow-up: A National surgical Quality Improvement Program analysis of 30,183 cases. J Clin Neurosci 78: 114-120, 2020.
14. Roskoski R Jr: The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacol Res 79: 34-74, 2014.
15. Lemmon MA, Schlessinger J and Ferguson KM: The EGFR family: Not so prototypical receptor tyrosine kinases. Cold Spring Harb Perspect Biol 6: a020768, 2014.
16. Uberall I, Kolar Z, Trojanec R, Berkovcova J and Hajduch M: The status and role of ErbB receptors in human cancer. Exp Mol Pathol 84: 79-89, 2008.
17. Wang Z: ErbB receptors and cancer. Methods Mol Biol 1652: 3-35, 2017.
18. Yarden Y: The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities. Eur J Cancer 37 (Suppl 4): S3-S8, 2001.

19. Witsch E, Sela M and Yarden Y: Roles for growth factors in cancer progression. Physiology (Bethesda) 25: 85-101, 2010.
20. Arnli MB, Meta R, Lydersen S and Torp SH: HER3 and HER4 are highly expressed in human meningiomas. Pathol Res Pract 215: 152551, 2019.
21. Arnli MB, Winther TL, Lydersen S and Torp SH: Prognostic value of ErbB2/HER2 in human meningiomas. PLoS One 13: e0205846, 2018.
22. Arnli MB, Backer-Grondahl T, Ytterhus B, Granli US, Lydersen S, Gulati S and Torp SH: Expression and clinical value of EGFR in human meningiomas. PeerJ 5: e3140, 2017.
23. Andersson U, Guo D, Malmer B, Bergenheim AT, Brännström T, Hedman H and Henriksson R: Epidermal growth factor receptor family (EGFR, ErbB2-4) in gliomas and meningiomas. Acta Neuropathol 108: 135-142, 2004.
24. Wickremesekera A, Hovens CM and Kaye AH: Expression of ErbB-1 and ErbB-2 in meningioma. J Clin Neurosci 17: 1155-1158, 2010.
25. Laurendeau I, Ferrer M, Garrido D, D'Haene N, Ciavarelli P, Basso A, Vidaud M, Bieche I, Salmon I and Szijan I: Gene expression profiling of ErbB receptors and ligands in human meningiomas. Cancer Invest 27: 691-698, 2009.
26. Roesler R, Souza BK and Isolan GR: Receptor tyrosine kinases as candidate prognostic biomarkers and therapeutic targets in meningioma. Int J Mol Sci 22: 11352, 2021.
27. Backer-Grondahl T, Moen BH, Sundstrom SH and Torp SH: Histopathology and prognosis in human meningiomas. APMIS 122: 856-866, 2014.
28. Backer-Grondahl T, Moen BH and Torp SH: The histopathological spectrum of human meningiomas. Int J Clin Exp Pathol 5: 231-242, 2012.
29. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P and Ellison DW: The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 131: 803-820, 2016.
30. Birzu C, Peyre M and Sahm F: Molecular alterations in meningioma: Prognostic and therapeutic perspectives. Curr Opin Oncol 32: 613-622, 2020.
31. Preusser M, Brastianos PK and Mawrin C: Advances in meningioma genetics: Novel therapeutic opportunities. Nat Rev Neurol 14: 106-115, 2018.
32. Hilton DA, Shivane A, Kirk L, Bassiri K, Enki DG and Hanemann CO: Activation of multiple growth factor signalling pathways is frequent in meningiomas. Neuropathology 36: 250-261, 2016.
33. Sigismund S, Avanzato D and Lanzetti L: Emerging functions of the EGFR in cancer. Mol Oncol 12: 3-20, 2018.
34. Carroll RS, Black PM, Zhang J, Kirsch M, Percec I, Lau N and Guha A: Expression and activation of epidermal growth factor receptors in meningiomas. J Neurosurg 87: 315-323, 1997.
35. Singh B, Carpenter G and Coffey RJ: EGF receptor ligands: Recent advances. F1000Res 5: F1000 Faculty Rev-2270, 2016.
36. Sanderson MP, Dempsey PJ and Dunbar AJ: Control of ErbB signaling through metalloprotease mediated ectodomain shedding of EGF-like factors. Growth Factors 24: 121-136, 2006.
37. Wilson KJ, Mill C, Lambert S, Buchman J, Wilson TR, Hernandez-Gordillo V, Gallo RM, Ades LM, Settleman J and Riese DJ II: EGFR ligands exhibit functional differences in models of paracrine and autocrine signaling. Growth Factors 30: 107-116, 2012.
38. Kumagai S, Koyama S and Nishikawa H: Antitumour immunity regulated by aberrant ERBB family signalling. Nat Rev Cancer 21: 181-197, 2021.
39. Citri A and Yarden Y: EGF-ERBB signalling: Towards the systems level. Nat Rev Mol Cell Biol 7: 505-516, 2006.
40. Zhao L, Zhao W, Hou Y, Wen C, Wang J, Wu P and Guo Z: An overview of managements in meningiomas. Front Oncol 10: 1523, 2020.
41. Patel B, Desai R, Pugazenthi S, Butt OH, Huang J and Kim AH: Identification and management of aggressive meningiomas. Front Oncol 12: 851758, 2022.
42. Kim L: A narrative review of targeted therapies in meningioma. Chin Clin Oncol 9: 76, 2020.
43. Moelans CB, de Weger RA, Van der Wall E and van Diest PJ: Current technologies for HER2 testing in breast cancer. Crit Rev Oncol Hematol 80: 380-392, 2011.
44. Petersen I, Dietel M, Geilenkeuser WJ, Mireskandari M, Weichert W, Steiger K, Scheel AH, Büttner R, Schirmacher P, Warth A, *et al*: EGFR immunohistochemistry as biomarker for antibody-based therapy of squamous NSCLC-Experience from the first ring trial of the German Quality Assurance Initiative for Pathology (QuIP®). Pathol Res Pract 213: 1530-1535, 2017.
45. Carpenter G and Liao HJ: Trafficking of receptor tyrosine kinases to the nucleus. Exp Cell Res 315: 1556-1566, 2009.
46. Wang YN and Hung MC: Nuclear functions and subcellular trafficking mechanisms of the epidermal growth factor receptor family. Cell Biosci 2: 13, 2012.
47. Caltabiano R, Barbagallo GM, Castaing M, Cassenti A, Senetta R, Cassoni P, Albanese V and Lanzafame S: Prognostic value of EGFR expression in de novo and progressed atypical and anaplastic meningiomas: An immunohistochemical and fluorescence in situ hybridization pilot study. J Neurosurg Sci 57: 139-151, 2013.
48. Torp SH, Helseth E, Dalen A and Unsgaard G: Expression of epidermal growth factor receptor in human meningiomas and meningeal tissue. APMIS 100: 797-802, 1992.
49. Pepe F, Pisapia P, Del Basso de Caro ML, Conticelli F, Malapelle U, Troncone G and Martinez JC: Next generation sequencing identifies novel potential actionable mutations for grade I meningioma treatment. Histol Histopathol 35: 741-749, 2020.
50. Catala M: Embryonic and fetal development of structures associated with the cerebro-spinal fluid in man and other species. Part I: The ventricular system, meninges and choroid plexuses. Arch Anat Cytol Pathol 46: 153-169, 1998.
51. Torp SH, Gulati S, Johannessen E and Dalen A: Coexpression of c-erbB 1-4 receptor proteins in human glioblastomas. An immunohistochemical study. J Exp Clin Cancer Res 26: 353-359, 2007.
52. Perez-Torres M, Valle BL, Maihle NJ, Negron-Vega L, Nieves-Alicea R and Cora EM: Shedding of epidermal growth factor receptor is a regulated process that occurs with overexpression in malignant cells. Exp Cell Res 314: 2907-2918, 2008.
53. Torp SH, Helseth E, Unsgaard G and Dalen A: C-erbB-2/HER-2 protein in human intracranial tumours. Eur J Cancer 29A: 1604-1606, 1993.
54. Potti A, Forseen SE, Koka VK, Pervez H, Koch M, Fraiman G, Mehdi SA and Levitt R: Determination of HER-2/neu overexpression and clinical predictors of survival in a cohort of 347 patients with primary malignant brain tumors. Cancer Invest 22: 537-544, 2004.
55. Loussouarn D, Brunon J, Avet-Loiseau H, Campone M and Mosnier JF: Prognostic value of HER2 expression in meningiomas: An immunohistochemical and fluorescence in situ hybridization study. Hum Pathol 37: 415-421, 2006.
56. Telugu RB, Chowhan AK, Rukmangadha N, Patnayak R, Phaneendra BV, Prasad BC and Reddy MK: Human epidermal growth factor receptor 2/neu protein expression in meningiomas: An immunohistochemical study. J Neurosci Rural Pract 7: 526-531, 2016.
57. Schlegel J, Ullrich B, Stumm G, Gass P, Harwerth IM, Hynes NE and Kiessling M: Expression of the c-erbB-2-encoded oncoprotein and progesterone receptor in human meningiomas. Acta Neuropathol 86: 473-479, 1993.
58. Helseth E, Unsgaard G, Dalen A, Fure H, Skandsen T, Odegaard A and Vik R: Amplification of the epidermal growth factor receptor gene in biopsy specimens from human intracranial tumours. Br J Neurosurg 2: 217-225, 1988.
59. Yarden Y and Pines G: The ERBB network: At last, cancer therapy meets systems biology. Nat Rev Cancer 12: 553-563, 2012.
60. Kurebayashi J, Kanomata N, Yamashita T, Shimo T, Mizutoh A, Moriya T and Sonoo H: Prognostic value of phosphorylated HER2 in HER2-positive breast cancer patients treated with adjuvant trastuzumab. Breast Cancer 22: 292-299, 2015.
61. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T and Tsuta K: HER2 gene mutations in non-small cell lung carcinomas: Concurrence with Her2 gene amplification and Her2 protein expression and phosphorylation. Lung Cancer 87: 14-22, 2015.
62. Cimino PJ, Yoda RA, Wirsching HG, Warrick JI, Dorschner MO and Ferreira M: Genomic profiling of anaplastic meningioma identifies recurrent genetic alterations with relevance to lower-grade meningioma. Neuropathol Appl Neurobiol 45: 179-182, 2019.

63. Haikala HM and Jänne PA: Thirty years of HER3: From basic biology to therapeutic interventions. Clin Cancer Res 27: 3528-3539, 2021.
64. El-Gamal MI, Mewafi NH, Abdelmotteleb NE, Emara MA, Tarazi H, Sbenati RM, Madkour MM, Zaraei SO, Shahin AI and Anbar HS: A Review of HER4 (ErbB4) kinase, its impact on cancer, and its inhibitors. Molecules 26: 7376, 2021.
65. Jungwirth G, Yu T, Liu F, Cao J, Alaa Eddine M, Moustafa M, Abdollahi A, Warta R, Unterberg A and Herold-Mende C: Pharmacological landscape of FDA-Approved anticancer drugs reveals sensitivities to ixabepilone, romidepsin, omacetaxine, and carfilzomib in aggressive meningiomas. Clin Cancer Res 29: 233-243, 2023.
66. Falzone L, Bordonaro R and Libra M: SnapShot: Cancer chemotherapy. Cell 186: 1816-1816.el, 2023.