



# Immunohistochemical Expression of EGFR and ErbB2/ HER2 in Human Meningioma. A Clinicopathological Study

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## Abstract

**Background:** meningioma is considered a common benign tumor and more frequent happen, they are slow growing primary tumors that originate from meningotheial cells of the arachnoid and spinal cord. The histological grade of the WHO and the extension of the initial surgical resection are determining prognostic factors in these tumors.

**Aim of the study:** To investigate the expression of EGFR and ErbB2 / HER2 in human meningiomas, to correlate this expression with various clinic pathological parameters (age, gender, tumor type, tumor grade), and to study the correlation between these two markers. **Methods:** this is a retrospective study including 30 cases of human meningiomas. Clinical data collected from patient's files. Immunohistochemical study of EGFR and ErbB2/HER2 performed along with scoring. **Results:** this study included 30 cases of meningioma. There was a significant statistical correlation between tumor grade and tumor histological type, as 100% of grade II were atypical meningiomas, and 77.8% of grade I were meningotheial meningiomas, with a P value 0.0001. 25/30 cases showed positive immunohistochemical expression of EGFR, 24/25 (96%) cases were grade I, 1/25 (4%), 16/25(72%) cases were meningotheial, 1/25 (4%) case angiomatous, 1/25 (4%) case atypical, 5/25 (20%) cases were fibroblastic. only 4/30 cases showed expression of HER 2/ neu, 3/4(75%) cases were female, all cases were above 30 years of age, all cases were grade I, 2/4 (50%) cases were fibroblastic and the other two cases were meningotheial type.

**Conclusions:** EGFR is frequently over expressed in meningiomas, there was a significant difference between mean of EGFR and HER 2, EGFR have more positive results than HER 2.

**Key Words:** Meningioma, EGFR, ErbB2/HER2.

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## Introduction

Meningiomas accounts for 30% of intra-cranial tumors in adults, they are common little developing primary tumor in central nervous. Despite being predominantly benign, many cases recur (Backer-Grondahl et al. 2014, Perry A et al.2007). Two third of cerebral meningiomas occur in women, and 90% of spinal cord meningiomas occurs in middle aged or elderly group (Ostrom QT et al. 2013, Thuijs NB et al. 2012), they are rare but usually aggressive in children (Ostrom QT et al. 2013). The 2016 CNS classification officially represents an

update of the 2007 4<sup>th</sup> edition rather than a formal 5<sup>th</sup> edition. Summary of the 2016 WHO cataloguing scheme for grading meningioma:

- **Grade (I):** “meningotheial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lympho-plasmocytic rich, metaplastic”.
- **Grade (II):** “Choroid, clear cell, atypical:- increased mitosis 4-19 mitosis/ 10HPF, brain invasion”.

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**At least 3 structures:**

1. High cellularity
  2. Protuberant nucleoli
  3. Minor cell with increase N/C ratio
  4. Sheeting
  5. Foci of spontaneous necrosis
- **Grade (III):** “papillary, rhabdoid, anaplastic (malignant): overtly malignant cytology (resemble carcinoma), melanoma, high-grade sarcoma”.

The WHO classification of the CNS tumors stratifies meningioma in three major groups, reflected by: grade I (benign), grade II (intermediate), grade III (malignant) (Perry A et al. 2007 and Norden AD et al. 2010). Epidermal growth factor receptor (EGFR) also called HER1/ c-erb-B1, is a member of growth factor receptor family. Composed of 170 KDa transmembrane receptor that induces tyrosin kinase activity affecting cell growth, it has been found to be overexpressed in many cancers such as gliomas and small cell carcinoma of the lung. EGFR and the ligands EGF (epidermal growth factor) and TGF alpha (transforming growth factor alpha) has been shown to be overexpressed in human meningioma, non-neoplastic meningeal tissue have no activity representative a potential tumorigenic character of EGFR, meningiomas consist of membranous and cytoplasmic reactivity (Andersson U et al 2004 and Carroll RS et. al. 1997). “Human epidermal growth factor receptor 2 (HER2/neu)”, have important action in cells production, apoptosis, cell motility and cell union, apoptosis, cell motility and cell union, it is recognized in numerous malignancies like breast, gastric, ovarian, esophageal, renal. Etc. with poor prognosis in some of these tumors. Also can be a curing goal with monoclonal antibodies that cooperate with the receptors (Mahzouni P et al. 2012 and Olsen RJ et al. 2005). Aim of this study is to investigate the expression of EGFR and ErbB2/HER2 in human meningioma and correlate this expression with various clinicopathological parameters (age, gender, type of the tumor, grade of the tumor) and the correlation between the two markers.

**Method**

This is a retrospective study including 30 cases of intra-cranial meningiomas collected at the period October 2018- November 2019. Cases collected from the histopathology laboratory department of neurosurgery hospital in Baghdad/ Iraq. All cases were biopsies from craniotomy procedure. “Paraffin blocks cut into 4.5 microns thin sections (three

slides from each case)”. Hematoxylin and eosin stained segments tested microscopically in order to confirm the diagnosis and the grade of the tumor, and clinical data of the cases collected from hospital files. Subtyping and grouping of meningioma cases according to WHO 2016 standards. Immunohistochemically study performed for EGFR and ErbB2/HER2 for each case. Section from skin used as positive control for EGFR, and sections of HER2/ neu positive invasive ductal carcinoma of the breast, EGFR clone Ep22, source rabbit monoclonal, Pathn Situ ready to use antibody (detect both phosphorylated and un-phosphorylated EGFR). ErbB2/HER2 clone EP3, source rabbit monoclonal, Pathn Situ ready to use antibody.

**Immunohistochemically analysis of EGFR:** the criteria for positive immunohistochemically reaction of EGFR is of brown membranous and/or cytoplasmic staining as indicated by the manufacturer literature.

**Scores were from 0 to 3 as follow**

Negative (0) = no positive cells in the whole section

Score (1+) = number of positive cells less than 21 10%

Score (2+) = number of positive cells 10% - 50%

Score (3+) = number of positive cells more than 50%

Regarding intensity scoring of EGFR: score (0) no staining, score (1+) faint membranous or cytoplasmic staining, score (2+) unequivocal membranous or cytoplasmic staining, score (3+) strong and complete plasma membrane staining. Score 2+ and 3+ regarded as EGFR positive (Torp SH et al. 2007). **Immunohistochemically analysis of HER2/neu:** done according scoring system for breast malignancy. Scores (0) and (1+) considered negative, scores (2+) and (3+) were considered positive (Mahzouni P et al. 2012). **Statistical analysis:** analysis of the data done by statistical package for social sciences (SPSS) edition of twenty-five. The relationship between I.H.C expression as well as specific information evaluated by Chi- square test; it was regarded as significant when P value is below 0.05.



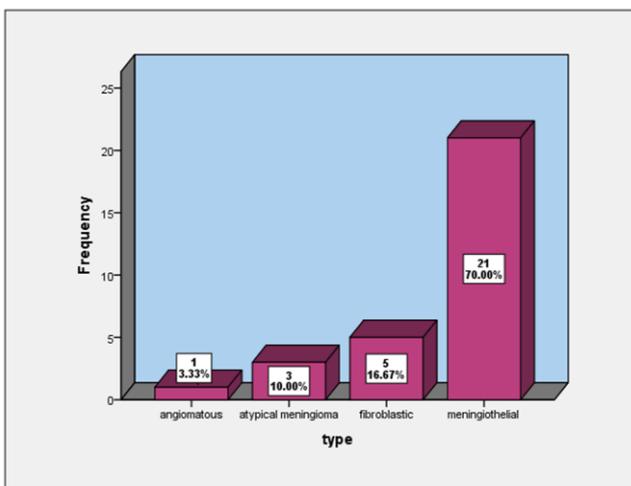
**Results**

*Distribution of Variables (Gender, Age, Grade and Type Meningioma)*

This is retrospective cross sectional study for 30 cases of meningioma, mean age of patients (46 ± 16) years old, ranges between 5- 81 years, (86.7%) of patient above 30 years old. In the current study 23 (76.7%) cases are females and 7 (23.3%) are males. Regarding histological type of meningioma: 21/30 (70%) of cases are meningiothelial, 5/30(16.7%) are fibroblastic, 3/30(10%) are atypical, and 1/30(3.3%) is angiomatous. Regarding grade of the tumor: 27/30 (90%) of cases are grade I, and 3/30 (10%) are grade II, as show in table (1) and figure (1).

**Table 1.** Distribution of variables (gender, Age, grade and histologic type)

variables	frequency	percentage
<b>gender</b>		
female	23	76.7
male	7	23.3
Total	30	100.0
<b>type</b>		
angiomatous	1	3.3
atypical meningioma	3	10.0
fibroblastic	5	16.7
meningiothelial	21	70.0
Total	30	100.0
<b>grade</b>		
I	27	90.0
II	3	10.0
Total	30	100.0
<b>Age</b>		
30 and below	4	13.3
above 30	26	86.7
Total	30	100.0



**Figure 1.** Distribution of histological type of meningioma

*Association between Grade and other Variables Including: Gender, Age and Histological Type of Meningioma*

**Table 2.** Association between Grade and (gender, Age and histologic type)

variables		Grade		P-value
		I	II	
<b>gender</b>	<b>Female</b>	20	3	0.43
	%	74.1%	100.0%	
	<b>Male</b>	7	0	
	%	25.9%	0.0%	
	<b>Total</b>	27	3	
	%	100.0%	100.0%	
<b>Age</b>	<b>30 and below</b>	3	1	0.36
	%	11.1%	33.3%	
	<b>above 30</b>	24	2	
	%	88.9%	66.7%	
	<b>Total</b>	27	3	
	%	100.0%	100.0%	
<b>Type</b>	<b>angiomatous</b>	1	0	0.0001
	%	3.7%	0.0%	
	<b>atypical meningioma</b>	0	3	
	%	0.0%	100.0%	
	<b>fibroblastic</b>	5	0	
	%	18.5%	0.0%	
	<b>meningiothelia I</b>	21	0	
	%	77.8%	0.0%	
	<b>Total</b>	27	3	
	%	100.0%	100.0%	

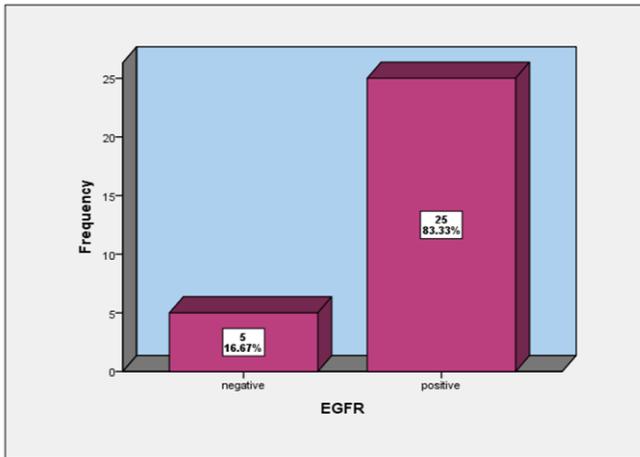
**P-value ≤ 0.05 (significant)**

There is a significant statistical correlation between tumor grade and tumor histological type, as 100% of grade II are atypical meningiomas, and 77.8% of grade I is meningiothelial meningiomas, with a P value 0.0001. There is no significant association between grade and other variables including gender and age as shown in table 2.

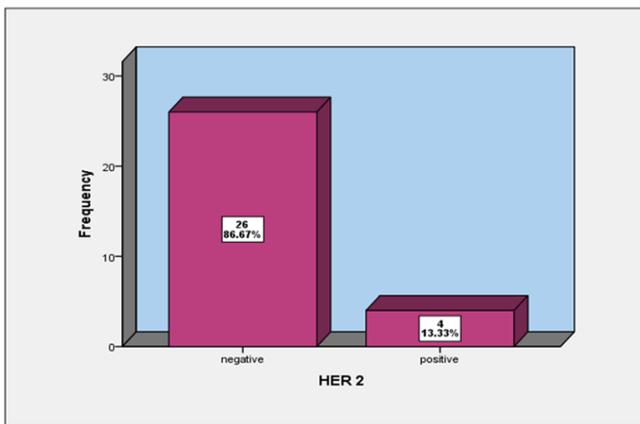
**Immunohistochemical Expression of EGFR and ErbB2/ HER2 in Meningioma:**

Twenty-five cases out of 30 (83.33%) cases were positive EGFR and 5/30 (16.67%) cases did not show expression. Only 4/30 (13.33%) cases express ErbB2/ HER2, these results are shown in figures 2, 3, 4).

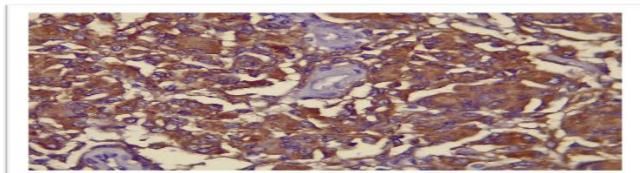




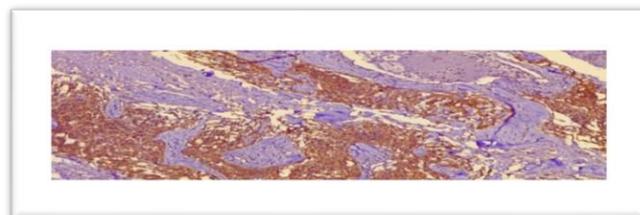
**Figure 2.** EGFR immunohistochemical expression distribution in meningioma



**Figure 3.** HER 2 immunohistochemical expression distribution in meningioma



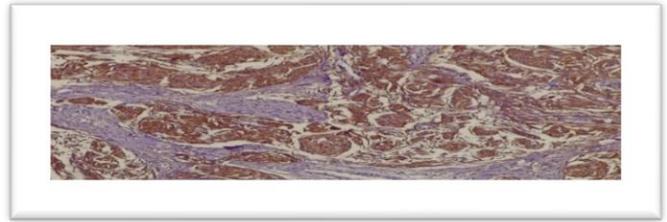
**A**



**B**



**C**



**D**

**Figure 4.** (A): meningotheial meningioma immunohistochemical expression of EGFR strong positivity: brown stain cytoplasmic and membranous. Mp (B): meningotheial meningioma immunohistochemical expression of EGFR strong positivity: brown stain cytoplasmic and membranous. LP. (C): fibroblastic meningioma immunohistochemical expression of HER2/neu strong positivity: brown stain cytoplasmic and membranous. LP. (D): meningotheial meningioma immunohistochemical expression of HER2/neu strong positivity: brown stain cytoplasmic and membranous. LP

**Association between HER 2 Expression and Variables: Gender, Age, Grade and Type of Meningioma**

only 4/30 cases showed expression of HER 2/ neu in this study, these case were as follows: 3/4(75%) cases were female, all cases were above 30 years of age, all cases were grade I, 2/4 (50%) cases were fibroblastic and the other two cases were meningotheial type. There is no significant statistical correlation between HER2 immunohistochemical expression and any of the 23 variables studied, as shown in table 3.

**Table 3.** Association between HER 2 immunohistochemical expression and (gender, Age, grade and type of meningioma)

variables	HER 2		P-value
	negative	positive	
gender	Female	3	0.68
	%	76.9%	
	Male	1	
	%	23.1%	
	Total	4	
Age	30 and below	0	0.55
	%	0.0%	
	above 30	4	
	%	84.6%	
	Total	4	
Grade	I	4	0.64
	%	88.5%	
	II	0	
	%	0.0%	
	Total	4	
Type	angiomatous	0	0.27
	%	3.8%	
	atypical meningioma	0	
	%	0.0%	
	fibroblastic	2	
	%	50.0%	
	meningotheial	2	
%	50.0%		
Total	4		
%	100.0%		

**P-value ≤ 0.05 (significant).**



**Association between EGFR Expression and Variables: Gender, Age, Grade and Type of Meningioma**

in this study 25/30 cases showed positive immunohistochemical expression of EGFR, these cases were distributed as follows: 19/25 (76%) cases were female, 22/25 (88%) cases were above age of 30 years, 24/25 (96%) cases were grade I, 1/25 (4%) case was grade II, 16/25(72%) cases were meningiothelial, 1/25 (4%) case angiomatous, 1/25 (4%) case atypical, 5/25 (20%) cases were fibroblastic. There is no significant statistical correlation between EGFR immunohistochemical expression and any of the variables studied, as shown in table 4.

**Table 4.** Association between EGFR immunohistochemical expression and (gender, Age, grade and type of meningioma)

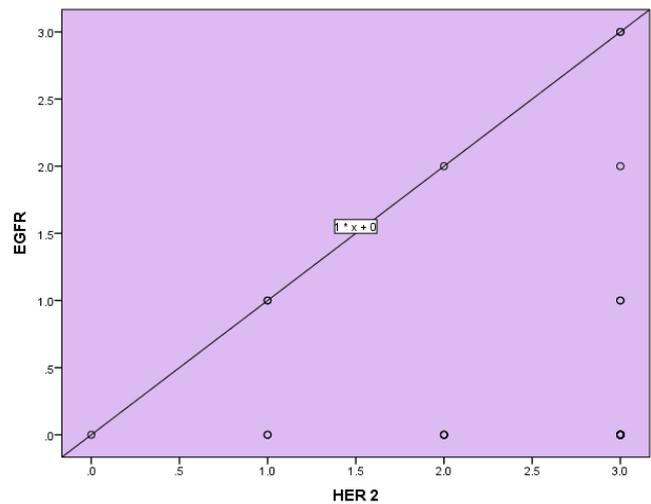
variable s		EGFR		P-value
		negative	positive	
gender	Female	4	19	0.67
	%	80.0%	76.0%	
	Male	1	6	
	%	20.0%	24.0%	
	Total	5	25	
	%	100.0%	100.0%	
Age	30 and below	1	3	0.54
	%	20.0%	12.0%	
	above 30	4	22	
	%	80.0%	88.0%	
	Total	5	25	
	%	100.0%	100.0%	
Grade	I	3	24	0.64
	%	60.0%	96.0%	
	II	2	1	
	%	40.0%	4.0%	
	Total	5	25	
	%	100.0%	100.0%	
Type	angiomatous	0	1	0.083
	%	0.0%	4.0%	
	atypical meningioma	2	1	
	%	40.0%	4.0%	
	fibroblastic	0	5	
	%	0.0%	20.0%	
	meningiothelial	3	18	
%	60.0%	72.0%		
Total	5	25		
	%	100.0%	100.0%	

**P-value ≤ 0.05 (significant).**

**Correlation between EGFR and HER 2 Expression**

There is no significant correlation between mean of EGFR and HER 2, in addition, there is significant difference between mean of EGFR and HER 2, EGFR

have more positive results than HER 2, as shown in figure 5 and table 5.



Pearson Correlation = 0.65, P-value = 0.73

**Figure 5.** Correlation between EGFR and HER 2, there is no significant correlation.

**Table 5.** Difference between EGFR and HER 2 expression

	Mean	N	t	P-value
HER 2	0.47	30	9.1	<b>0.0001</b>
EGFR	2.47	30		

**P-value ≤ 0.05 (significant)**

**Discussion**

Meningiomas are common central nervous system tumors, although slow growing they can be a major cause of morbidity and mortality. Numerous journals description powerful search new molecular indicators that may help as possible therapeutic goals (Andersson U et al. 2004 and Bianco R et al. 2007). In this study 30 cases of meningiomas were analyzed, age range between 8-81 years, 26 (86.7%) cases above 30 years, 23(76.7%) cases were female, 27(90%) cases were grade I, 3(10%) cases were grade II, and no grade III. most of the cases were meningiothelial type 21(70%), there was significant correlation between tumor grade and histological type. In the current study EGFR expression was detected in 25/30 (83.33%) cases of all meningiomas sample tested, it was found to be higher in grade I 24/25 (96%), when compared with grade II only 1/25 (4%) case. there was no statistical correlation between EGFR immunohistochemical expression and any of the parameter studied, including: age, gender, grade and histologic type. Report results vary on EGFR expression in meningioma, ranges from 33% -100% respectively, in majority of the studies the range of expression is between 50% and 60% respectively (Lusis EA et al.



2005 and Smith JS et al. 2004). There have been several studies that have studied the internal and external domains of EGFR (Guillaudeau A et al. 2012). Hilton et al 2016 demonstrated a significant higher expression of phosphorylated EGFR in neoplastic tissue compared to meningiothelial tissue and high expression of down-stream signalling molecules. There is a wide variation in literature concerning EGFR and malignancy, some references found higher expression in possibility related to tumor grade (Caltabiano R et al 2013), were as others found the opposite or no significant association (Narla S et al. 2014). Wrnicke et al 2010 demonstrated that meningiomas express EGFR in 86% of cases, there is a significant association between the intensity of staining and tumor grade, therefore they concluded that EGFR expression is inversely correlated with tumor grade in meningiomas. Arnli et al 2017, the expression level of the stimulated receptor can be beneficial in this neoplasm classifying; previous studies have not investigated the activated receptors. Membranous and cytoplasmic EGFR expression observed in meningiomas, membranous reactivity dominated in most cases. Baxter et al 2014 show that relation between great appearance of interior and outside areas and nonappearance of psammoma bodies with reduced survival. Guillaudeau et al 2012 stated that improved survival with more extracellular and correspondingly poorer survival with low expression. The differences in results because different antibodies, tumor size and remark time. The prognostic of EGFR in human meningioma seems indeterminate and requirements to be additional studied (Arnli et al 2017). In the current study our results showed immunohistochemical expression of HER 2 in 4/30 (13.33%) cases only,  $\frac{3}{4}$  (75%) cases were female, all cases were grade I, two cases were fibroblastic and two cases were meningiothelial type. There is no significant statistical correlation between EGFR immunohistochemical expression and any of the variables studied including age, gender, tumor grade and type. HER2 expression in meningioma 2% to 100% without pure association between expression and grade of tumor (Waage IS et al. 2013). Telugu et al 2016 studied 100 cases of meningiomas, 80 cases were grade I, 18 cases were grade II, and 2 cases were grade III. The woman to man ratio was 1.9:1 and the mean age was 47.8 years, HER2/ neu expression seen in 75% of grade I and 72.2% of grade II, and none of grade III with no significant difference between female and males of grade I and

grade II/III in HER2 expression and various histological subtypes of meningiomas. Loussouarn et al 2006 stated that HER2 expression in 26.5% meningiomas occur in grade I, II and III, FISH was done and exposed 40% meningiomas with high number of gene duplicate. Trop et al 1993 stated that HER2 immunostaining on frozen section and show 61.3% positive cases. Wang et al 2010 stated that HER2 expression more in recurring benign, unusual and anaplastic comparing non-recurrent benign swelling with significant association. Arnli et al 2018 they measure the appearance of HER 2 in a sequence of meningiomas with antibodies responsive against intracellular and extracellular domains as well as stimulated receptors. Immuno-reactivity was strongest for the antibodies targeting the ICD, while the ECD or the activated receptors were either negative or weak, none of the tested antibodies showed any relationship to malignant grade in arrangement with other consequences (Mahzouni P et al. 2012 and Ongaratti BR et al. 2016). Still, a current study on meningioma cell outlines establish that HER2 over-expressing malignant meningiomas were additional proliferative and aggressive (Wang W et al. 2015).

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## Conclusion

EGFR is frequently over expressed in meningiomas, there was no significant statistical correlation between its expression and parameters like tumor histologic type, grade, age and gender. HER2/ neu was expressed in minority of cases and there was no significant statistical correlation between its expression and parameters like tumor histologic, there was no significant correlation between mean of EGFR and HER 2 expression, in addition, there was a significant difference between mean of EGFR and HER 2, EGFR have more positive results than HER 2.

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