بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى

مسئولية عن محتوى هذه الرسالة.

ملاحظات:

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Proportion of human epidermal growth factor receptor 2 immunohistochemical expression in endometrial carcinoma and its association with variable clinical outcomes.

Thesis

Submitted for partial fulfillment of master degree in Obstetrics and Gynecology

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Acknowledgement

Table of contents

List of Figures

16	A case of endometrioid carcinoma presented with moderate circumferential membranous staining in more than 10% of tumor cells (score 2) (HER2/NEUx400)	73
17	A case of endometrioid carcinoma presented with strong circumferential membranous staining in more than 10% of tumor cells (score 3) (HER2/NEUx400)	73
18	The correlation between HER2 expression and LVI.	78
19	The correlation between HER2 expression and PN.	79
20	The correlation between HER2 expression and tumor staging.	80
21	The correlation between HER 2 expression and tumor metastasis.	81
22	Mean survival time of different cases (recurrent, free of disease)	84
23	The relationship between HER 2 expression, DFS and mean survival time.	87
24	The relationship between DFS and estimated mean survival time.	89
25	The relationship between HER2 and estimated mean survival time.	91

List of Tables

	estimated survival time using Log Rank test	
21	Cox regression analysis for factors affecting DFS (Univariate analysis)	**92**
22	Cox regression analysis for factors affecting OS (Univariate analysis)	**93**

List of Abbreviations

EC	Endometrial carcinoma
EGR	Epidermal growth factor
HER	Human epidermal growth factor receptor
TGF-	Tansforming growth factor -
AR	Amphiregulin
HB-EGF	Heparin binding epidermal growth factor
BCL	Betacellulin
EPI	Epiregulin
IHC	Immunohistochemistry
FISH	Fluorescent in situ hybridization
TUC	Tumors of uterine corpus
LVSI	Lymphovascular space invasion
MMMT	Mixed mullerian malignant tumors
ESS	Endometrial stromal sarcoma
FIGO	International Federation of Gynecology & Obstetrics
MR	Magnetic resonance
BRCA	Breast cancer gene
WHO	World health organization
AH/EIN	Atypical hyperplasia / endometrial intraepithelial neoplasia
APA	Atypical polypoid adenomyoma
ESC	Endometrial serous carcinoma
SEIC	Serous endometrial intraepithelial carcinoma
EmGD	Endometrial glandular dysplasia
AMGP	Atypical mucinous glandular proliferation
KRAS	Kirsten rat sarcoma viral oncogene
POLE	Polymerase epsilon
PAS	Periodic acid – Schiff stain
SCC	Squamous cell carcinoma
SEER	Survillance, Epidemiology & End Result Program
US	United States
PTEN	Phosophatase and tensin gogolog
US FDA	United States food and drug administration
VEGF	Vascular endothelial growth factor
IgG	Immunoglobin G
TKs	Tyrosin Kinases

mRNA	Messenger ribonucleic acid
GI	GastroIntestinal
ATP	Adenosine triphosphate
EGF	Epidermal growth factor
EPG	Epigen
PI3K/Akt	Phosphatidylinositol 3 kinase / protein kinase B (PKB)
ERK / MAPK	Extracellular signal regulated kinase / mitogen – activated protein kinase
IGF - 1R	Insulin like growth factor
HER	Human epidermal growth factor
NSCLC	Non small cell carcinoma
ECOG	Eastern cooperative oncology group scoring
ASUH	Ain Shams University Hospital
ECDU	Early Cancer Detection Unit
SD	Standard deviation
PFS	Progression free survival
OS	Overall survival
TNM	Tumor, node & metastasis staging system
NS	Non-significant
S	Significant
HS	Highly significant
DFS	Disease free survival

PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS & GYNAECOLOGY

Title of the Protocol:

Proportion of human epidermal growth factor receptor 2 immunohistochemical expression in endometrial carcinoma and its association with variable clinical outcomes

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What is already known on this subject? AND
What does this study add?

Many studies had proved that HER2 overexpression in endometrial cancer tumors was correlated with higher grade, higher stage, lymph node metastasis as well as lower patients' survival. However; in other studies HER2 overexpression wasn't correlated with overall survival in type II tumors.

1.INTRODUCTION/ REVIEW

Endometrial carcinoma represents the sixth most common cancer among women worldwide. In Egypt it accounts for 2.6–3.5% of all cancer incidences. *El-Helw et al.,2016*

Endometrial cancer is classified histologically into type I and II tumors. Type I, endometrioid type tumors are usually well differentiated with good prognosis while type II are more aggressive and more presented by advanced stages. (*Bokhman 1983)*. For this known aggressive biologic behavior, studies have been focusing recently on the value of molecular targeted therapy to improve treatment outcomes. *Diver et al.,2016*

HER2/neu (ErbB2) is a member of the human epidermal growth factor receptor (EGFR) family of trans membrane tyrosine kinases including EGFR (HER1, ErbB1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). *Diver et al.,2015*

HER2 amplification and overexpression has been identified in many malignancies including breast, ovaries, stomach and others where it has been a validated target for treatment in some of them. *Khasraw, Bell 2015 - Hechtman, Polydorides 2012*

High-grade Endometrial carcinoma has a 17%–30% rate of HER2 gene amplification, with up to 80% of tumors exhibiting HER2 protein overexpression. *Groeneweg et al. 2014*

Both HER2 overexpression and amplification have been linked to poor prognosis in endometrial carcinoma. Several studies have demonstrated association between HER2 overexpression and poor overall survival. *Slomovitz et al. 2004 - Morrison et al. 2006 - Togami et al. 2012*

2.AIM / OBJECTIVES

Evaluation of the proportion of HER2 overexpression in endometrial carcinoma and its correlation with other known relevant variable clinical outcomes.

3.METHODOLOGY:
Patients and Methods

★ **Type of Study:**

Retrospective case series study.

★ **Study Period:**

From August 2019 till February 2020.

★ **Study Population:**

All patients diagnosed as endometrial carcinoma in the period from January 2014 till December 2018 with full medical records in Ain Shams University Oncology Hospital and in Early Cancer Detection Unit (ECDU) at Ain Shams University Hospital (ASUH).

★ **Inclusion Criteria:**

❖ Pathologically proven high grade endometrial cancer (grade III endometrioid carcinoma, papillary serous carcinoma, clear cell carcinoma and carcinosarcoma)

❖ Patients who have follow up records in Ain Shams University Oncology Hospital and oncology unit at Ain Shams University Maternity Hospital.

❖ Patients with sufficient paraffin blocks for IHC.

❖ Eastern Cooperative Oncology Group scoring ECOG performance status: score 0-4 (Oken et al. 1982)

❖ Treated with surgery/ chemotherapy / radiotherapy or not treated at all.

★ **Exclusion criteria:**

❖ Inadequate paraffin blocks will be excluded.

❖ None histologically proven endometrial neoplasm.

❖ Other endometrial neoplasm rather than high grade carcinoma

❖ Unavailable follow up data

★ **Sampling Method:**

Ethical committee waived the patient informed consent due to the retrospective nature of the study. The personal data will be **collected and analyzed anonymously**. **Patient privacy will not be broken**.

★ **Sample Size:**

All cases of endometrial carcinoma fulfilled with inclusion and exclusion criteria will be the material of this study.

★ **Sample Justification:**

Sample size was calculated using STATA program, setting the type-1 error ( ) at 0.05 and the power (1-) at 0.9. Result from previous study **(Waqar et al, 2018)** showed that statistically significant positive association was found between HER-2/neu expression and tumor grades as 100% of positive HER2 cases were high grade compared to 15.3% only of negative HER2 cases, 7.1% of EC cases are her2 positive. Based on this, a sample of 35 EC cases will achieve 100% power to detect a difference between the group proportions of 84.7%.

★ **Study design:**

❖ We will collect patients' data from clinical oncology unit at ASUH through a five years period (2014-2018). Retrospective data (as mentioned below), will be extracted from patients files and all available prognostic data will be documented.

Age in years:		

Tumor type:	High		Low	

Depth of invasion:	Endometrium only		Myometrium		Serosa	

FIGO staging:	……………………….

Lymph node metastasis:	No		Yes		if yes mention: …………..………….

Distant metastasis:	No		Yes		if yes mention: …………..…………..

Past history of endometrial cancer or any cancer:	No		Yes		if yes mention: ……………… ……………………………….

Family history of endometrial cancer or any cancer:	No		Yes		if yes mention: ……………… ……………………………….

Overall survival in years:		

Tumor recurrence:	Yes		No	

Perineural invasion:	Yes		No	

❖ We will retrieve the patients' paraffin blocks and test for HER2 overexpression using immunohistochemistry test (IHC) for detection of HER2 proteins
❖ If results are border-line we will use chromogenic in situ hybridization test (CISH) for detection of HER2 gene.
❖ We will correlate expression with known prognostic factors as well as the patients' outcomes.
❖ Stages are defined by FIGO.

★ **Outcomes:**
❖ Find the prevalence of Her2 overexpression in the study population
❖ Evaluate the relation between Her2 overexpression and the other

various clinic- pathological factors that are known to affect the clinical outcome.

❖   Evaluate the impact of Her2 overexpression on progression free survival of the study population

❖   Evaluate the impact of Her2 overexpression on overall survival of the study population

★ **Ethical Considerations:**
Owing to retrospective nature of the study, consent will not be required but we will ensure that **all data will be collected and analyzed anonymously**. **No patients' identifier data will be collected.**

★ **Statistical Analysis:**
❖   The Data will be collected tabulated and statistically analyzed.

❖   Data will be presented, and suitable analysis will be done according to the type of data obtained for each parameter.

❖   Continuous variables will be expressed as mean ± SD or counts and percentage.

❖   Categorical variables will be expressed as median and interquartile range.

❖   Progression free survival (PFS) time and overall survival (OS) time will be analyzed using the Kaplan-Meier estimation method and log-rank test.

❖   PFS will be calculated from the date of initiation of treatment to the date of disease progression or death from any cause. If disease progression had not occurred by the time of this analysis, PFS will be considered to have been censored at the time of the last follow-up visit.

❖   OS will be measured from the date of the initiation of treatment to the date of death. OS will be considered to have been censored at the last follow-up time if death had not occurred.

❖   Descriptive statistics will be calculated to assess safety data. Statistical significance will be defined as P 0.05.

4. Other specialties to be consulted in our study

o **Oncology department:**
Dr Ghada Refaat Meckawy
Lecturer of clinical oncology.