Original research

HER2 STATUS IN GASTRIC ADENOCARCINOMA: COMPARISON BETWEEN MATCHED ENDOSCOPIC BIOPSY AND GASTRECTOMY SPECIMENS

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DOI: 10.38103/jcmhch.2021.69.10

ABSTRACT

Purpose: *To evaluate the concordance between HER2 status in matched endoscopic biopsy and gastrectomy specimens of gastric adenocarcinoma patients.*

Patients and Methods: *Fifty-five gastric adenocarcinoma patients were diagnosed by upper GI endoscopic biopsy and treated with gastrectomy. HER2 status was assessed by immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) on both endoscopic biopsy and gastrectomy specimens. HER2-positive status was defined as a score IHC 3+, or IHC 2+ with a positive result in FISH. Data were collected from June, 2014 to July, 2016 in HCMC Oncology Hospital.*

Results: *HER2-positive status was identified in 9.6%. The concordance in HER2 status between matched endoscopic biopsy and surgical specimens was 98% (Kappa=0.879).*

Conclusion: *There was a very high concordance in HER2 status between the results performed with surgical specimens and matched endoscopic specimens. HER2 status assessed on endoscopic biopsy specimens could be reliable for treatment decisions using anti-HER2 agents in patients with advanced gastric carcinoma.*

Keywords*: Concordance, HER2 status, endoscopic specimens, gastrectomy specimens, gastric adenocarcinoma.*

I. INTRODUCTION

According to Globocan 2012, gastric cancer is one of the four most common cancers in Vietnam [1]. Cancer Registry of HCMC in 2014 shows that gastric cancer is the fourth of most common cancers in male, ASR is 9.2/100,000 [2].

Gastric cancer patients are usually admitted to hospital at advanced stage and most of them are not suitable for operation. Chemotherapy and palliative care are options for treatment. At the moment, the mean of overall survival (OS) of these patients is around 11.2 months [3]. Recently, a combination of *HER2* targetedtherapy (Trastuzumab) with chemotherapy showed an improvement for OS up to 16 months [3]. This effect was studied in advanced adenocarcinoma gastric cancer patients

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- **Received:** 19/04/2021; **Revised:** 10/05/2021;
- **Accepted:** 22/05/2021
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whose *HER2* overexpression on tumor cells had been confirmed. Both endoscopic biopsy and resection specimens are accepted for *HER2* test [4]. Nevertheless, in unresectable patients, *HER2* test can only be approached on endoscopic specimens.

In Vietnam, 8 studies were made to understand the status of *HER2* expression in gastric cancer [5-12]. *HER2* tests were reported to be assessed on endoscopic biopsy or gastrectomy specimens. Although, non was performed to compare the *HER2* expression on both matched specimens of the same patients. In our study, we attempted to find out the concordance of *HER2* status of adenocarcinoma gastric between matched endoscopic biopsy (ES) and gastrectomy specimens (GS).

II. PATIENTS AND METHODS

The study was approved by the Ethics Committeeof HCMC University of Medicine and Pharmacy and HCMC Oncology Hospital. Patients were performed upper GI endoscopy, gastrectomy and *HER2* testing (immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH)) at HCMC Oncology Hospital. Data were collected from June, 2014 to July, 2016. Protocols for gastric endoscopy and gastrectomy were strictly applied.

Criteria of recruitment: same patients had pathological tumor tissue diagnosis as adenocarcinoma for ES and GS. Tissue samples were assured about quality and quantity for IHC and FISH test. Patients who had been treated with chemotherapy or radiotherapy; or who disagreed to be involved in the research were excluded from this study.

HER2 status, as a main variable, was defined as a qualitative variable which received 2 values as positive or negative. *HER2* status waspositive in case IHC (3+), or IHC (2+) and FISH(+). *HER2* status was negative in case IHC (1+, 0), or IHC (2+) and FISH (-) [13]. Testing algorithm for determination of *HER2* status is presented in Figure 1. IHC assessment was performed by experienced pathologists following guidelinesscoring *HER2* expression on endoscopic biopsy and surgical specimen **(Table 1 and 2)**. FISH result was based on recommendation from ASCO/CAP, 2013 [14].

Data were collected through research forms. All statisticalanalys is were performed using SPSS Version 20.0 for Windows. Qualitative variables were presented as percentages. Quantitative variableswere provided as the mean and standard deviation. Cohen's Kappa was used to measure the degree of agreement of *HER2* statusbetween endoscopic biopsy and gastrectomy specimens. All statistical tests were performed two-sided, and p-values <0.05 were statistical lysignifi cant.

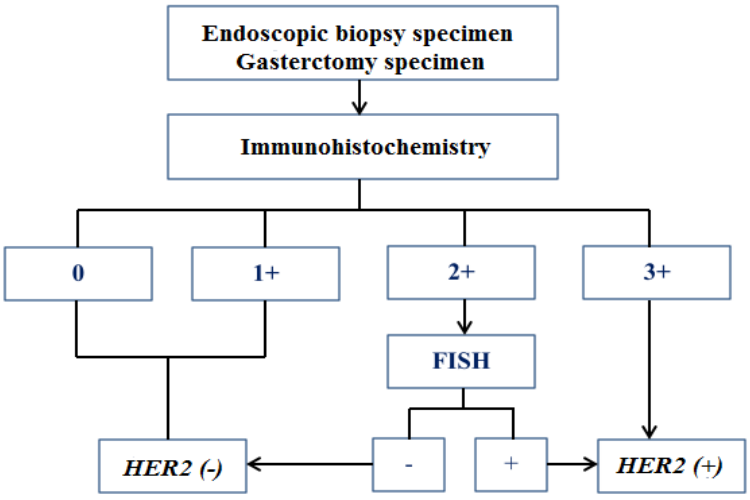

Figure 1: Testing algorithm for determination of *HER2* status in this study

Table 1: Immunohistochemistry scoring for *HER2* expression in gastric cancer on biopsy specimen [15]

Score	Biopsy specimen	*HER2* assessment
0	No reactivity in any tumor cells	Negative
1+	Tumor cell cluster (at least 5 tumor cells)* with faint or barely membranous reactivity irrespective of tumor cells stained	Negative
2+	Tumor cell cluster* with weak to moderate, complete basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Tumor cell cluster* with strong, complete basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

Table 2: Immunohistochemistry scoring for HER2 expression in gastric cancer on surgical specimen [15]

Scoring	Surgical specimen	*HER2* assessment
0	No reactivity or membranous reactivity in < 10% of tumor cells	Negative
1+	Faint or barely perceptible membranous reactivityin ≥ 10% of tumor cells, cells reactive only in part of their membrane	Negative
2+	Weak to moderate, complete basolateral or lateral membranous reactivity in ≥ 10% of tumor cells	Equivocal
3+	Strong, complete basolateral or lateral membranous reactivity in ≥ 10% of tumor cells	Positive

III. RESULTS

A total of 52 patients patients were eligible for this study. Characteristics of the patients in the study were described in **(Table 3)**.

Table 3: Characteristics of patients in this study

Age	57 ± 10 ys (35-78)
Sex	Male/Female: 3.3
Location	Cardia: 3 (6%) Body: 13 (25%) Antrum: 36 (69%)
Histological grade	Grade 1: 5 (10%) Grade 2: 23 (44%) Grade 3: 24 (46%)
Histologic type (Lauren)	Intestine: 20 (38%) Diffuse: 13 (25%) Mixed: 19 (37%)

The concordance rate in *HER2* status between endoscopic biopsy and surgical specimenwas described in **(Table 4)**.

Table 4: Concordance of *HER2* status on endoscopic biopsy and surgical specimens

HER2 status/ Endoscopic biopsy specimen	*HER2* status/ Surgical specimen		Total
	Negative	Positive	
Negative	47	1	48
Positive	0	4	4
Total	47	5 (9.6%)	52

HER2-positive statuswas 9.6% (95% CI: 1.6-17.6%). The concordance in *HER2* results between endoscopic biopsy and surgical specimens was 98%, Cohen's Kappa was 0.879 (p< 0,001).

One case was discordant (2%) with *HER2* positive on gastrectomy specimenbut negative on endoscopic biopsy specimen. Characteristics of this case were showed in **(Table 5)**.

Table 5: Characteristics of the discordant case

Location	Antrum
Macroscopic type	Ulcerative tumour with elevated distinct borders (Borrmanntype II)
Lauren histologic type	Mixed
Histological grade	Grade 2

VI. DISCUSSION

HER2-positivestatus

The percentage of *HER2* overexpression, so-called *HER2*-positive, in gastric adenocarcinoma differed from study to study. It wasfrom 6.8 to 34% if only IHC test was used, and from 7.1% to 42.6% if IHC was combined with FISH test.In 2008, Hoffmann M. published his standardized criteria to assess the results of *HER2* by IHC test on gastric cancer specimens. Acording to this article, concordance of *HER2* resultbet ween IHC and FISH tests was 93.5%, and the equivocal cases needed to be retested with FISH to determine accurately *HER2* status. The standardized criteria of Hoffman M. had been used by ToGA study and other studiessince then.

Table 6: *HER2*-positive status in worldwide studies

Authors	Country	N	*HER2* (+) (%)
Giuffre et al (2012) [5]	Italy	109	21.1
Watson et al (2013) [16]	France	218	14.7
Wang et al (2014) [17]	China	128	14
Ahn et al (2015) [18]	Korea	102	14.5
Huang et al (2016) [19]	Taiwan	180	7.8

The difference in *HER2* - positivestatus between studies all over the world **(Table 6)** may due to the difference in patients (gastric cancer only or with esophagogastric junction cancer) and may be in ethnicity.

In 8 Vietnamese studies about *HER2* expression in gastric cancer to date, only 4 studies **(Table 7)** had performed both IHC and FISH test for assessment *HER2* status. Our results showed no differencein comparison with these 4 studies (p> 0.05).

Table 7: *HER2*-positive status in Vietnamese studies

Author	Type of specimen	N	*HER2* (+)
ThaiA.T. et al [12]	Surgical specimen	168	11.9% (*)
Doan T.N.[5]	Surgical specimen	70	14.3% (*)
Phan D.A.Tet al [9]	Surgical specimen	208	16.3% (*)
PhamH.C. [11]	Endoscopic biopsy specimen	98	7.1% (*)
This study	Endoscopic biopsy and Surgical specimen	52	9.6% (1.6-17.6%)

(*) modified by definition of *HER2*-positive in this study.

Concordance in *HER2* status between matched endoscopic biopsy and surgical specimens

The high concordance in *HER2* status between matched endoscopic biopsy and gastrectomy specimenshas been reported in medical literature **(Table 8)**.

Table 8: Concordance in *HER2* status bet weenmatched endoscopic biopsy and surgical specimens

Authors	Year	N	Concordance rate
Pirrelli M. [20]	2012	61	92%
Grillo F. [21]	2013	103	89%
Wang T. [17]	2014	128	96%
Huang S-C [19]	2016	180	96%

This study also showed a very high concordance in *HER2* status bet weenmatched endoscopic biopsy and surgical specimens in gastric cancer (98%, Kappa = 0.879), and it was not significantly different from other studies.

The reason why the concordance rate can not achieve 100% between two types of specimen is the heterogeneity of *HER2* expression in adenocarcinoma gastric cancer [21], [18,22]. In one study in Hamburg, a survey of 109 samples of gastric cancer resection in 5-9 different areas of primary tumour, only 11 tumours showed homogeneity in *HER2* expression, 4 tumours with *HER2*-positive in 1/6 to 6/9 areas [22].

In this study, the discordant case with *HER2*-negative in endoscopic biopsy specimen but positive in gastrectomy specimen hadmixedhistologic type according to Lauren classification, which usually shows heterogeneity in *HER2* expression.

To diagnose accurately *HER2* status of unresectable gastric cancer patients whose primary tumour initially *HER2* - negative, some resolutions have been suggested:

+ Repeatingupper GI endoscopy biopsy with more number of samples, especially when primary tumour is in cardia or intestinal histologic type according to Lauren classification.

Park S.R. *et al* repeated endoscopic biopsy on 183 patients with adenocarcinoma gastric cancer with average number of samples as 10, they detected 16 more *HER*2 - positive cases (8.7%) [23].

+ Performing biopsy metastastic or recurrent tumours, if possible [24].

Peng Z. *et al*[25], in a systematic review of 18 studies with 1867 adenocarcinoma gastric cancer patients, identified the concordance rate in *HER2* status bet weenpaired primary tumour and metastatic sites as 93% (ranged from 76% to 98%).

Park S.R. *et al* performed biopsy on metastatic lesions of 175 adenocarcinoma gastric cancer patients with Her2 negative, there had been 10 more *HER2*-postive (5.7%) [23].

V. CONCLUSION

There was a very high concordance in *HER2* status between the results performed on surgical specimens and matched endoscopic specimens.

HER2 status assessed on endoscopic biopsy specimens could be reliable for treatment decisions using anti-*HER2* agents in patients with advanced gastric carcinoma.

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