COEXPRESSION OF HER2 AND P53 IN GASTRIC AND ESOPHAGEAL ADENOCARCINOMA

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ABSTRACT

Background and objectives: Gastric and esophageal adenocarcinoma remains deadly diseases with an on rise incidence. The recently discovered cancer-related molecular markers, such as HER2 and p53, help facilitate response to preoperative therapy and improve overall survival. This study was aimed to detect the immunoexpression of HER2 and p53 in gastric and esophageal adenocarcinoma and to determine the association of these two markers with clinicopathological parameters.

Method: The study was conducted in the Central Laboratory and Directorate of Health, Duhok-Iraq during a period from May 2009 to September 2014 on 101 gastric and esophageal adenocarcinoma cases. Using monoclonal antibodies against HER2 receptors and p53 nuclear protein, slides were stained with the fully automated immunostaining instrument, Ventana Benchmark.

Results: Total positive HER2 immunoexpression was demonstrated in 33.7% of cases with a significantly higher dense HER2 (3+) expression in esophageal adenocarcinoma compared with its gastric counterpart. p53 nuclear staining was observed in 62.4% of cases; it was significantly higher in gastric cancer than esophageal adenocarcinoma. HER2 was limited to the intestinal type whereas p53 was found to be expressed in both intestinal and diffuse types. No significant coexpression was demonstrated between HER2 and p53 in any of gastric or esophageal adenocarcinoma.

Conclusions: HER2 expression was limited to the intestinal type gastric adenocarcinoma. No significant coexpression of HER2 and p53 was demonstrated in both of gastric and esophageal adenocarcinoma.

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Keywords: HER2, p53, gastroesophageal adenocarcinoma.

Gastric and esophageal (gastroesophageal) adenocarcinomas form a substantial number of cancer cases with a dramatic rising incidence over the past 20 years, particularly among young adults[1-7]. The overall 5-year survival rates are up to 27% with no significant change over the past 40 years despite advances in surgical treatment and chemotherapy[2,4,5,6,8]. Discovery of new molecular markers and novel pharmacogenetic traits helped improve patients care, fostered hope and applied new directions of cure[9-12]. Markers

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of interest include those contributed in growth regulation like human epidermal growth factor receptor-2 (HER2) and those involved in apoptosis and cell cycle control, like p53[8-12]. Given the advantages of both HER2 and p53 as responders for target therapy and predictors for better outcome in breast cancer, such properties facilitated numerous studies that are intriguing in identifying those markers in gastric adenocarcinoma. On the other hand although overexpression of HER2 and p53 in gastroesophageal adenocarcinomas may increase their dismal outcome with a resistance to the conventional chemotherapy, many ongoing studies conducted in this field are intriguing in that patients get benefit from specific therapy targeting these molecular markers, both for prognostic and therapeutic purposes[9,12].

The current study may provide an insight on the immunohistochemical expression of HER2 and p53 immunomarkers in gastric and esophageal adenocarcinoma in Kurdistan-Iraq. To the best of our knowledge, no previous study was conducted in the same field to evaluate the coexpression of HER2 and p53 in adenocarcinoma of stomach and esophagus in this particular area of Iraq.

MATERIALS AND METHODS

The study was conducted in the Central Laboratory/Directorate of Health, Duhok-Iraq. Specimens were retrieved from histopathologic laboratories in Duhok Region during the period from May 2009 to September 2014. Paraffin embedded, pretreatment (endoscopic biopsy or gastrectomy) specimens were available for 101 patients with newly diagnosed gastric (n=63) and esophageal (n=38) adenocarcinoma. Information pertaining to the patient's age at presentation, gender and type of operation were obtained from patient's request forms.

Four micron-thick tissue sections were taken from the tumor, processed and embedded in paraffin wax, then stained again with Hematoxylin and Eosin (H&E) stains to confirm the diagnosis of adenocarcinoma and for grading purposes. Tumors were classified into 2 types, intestinal and diffuse (signet ring). The intestinal-type adenocarcinomas were further graded, according to the modified WHO classification system, into low grades (well and moderately differentiated) and high grades (poor and undifferentiated). Pathological staging, applied only on gastrectomy specimens (n= 43), was done according to the pathologic TNM tired staging system from I-IV based on the microscopic examination of the primary tumor within organ wall, all available lymph nodes, omentum and any associated structure if available[13].

The immunohistochemical technique applied was streptavidin-biotin system, using monoclonal antibodies manufactured by Ventana Corporation (Ventana, Rocklin, Calif), the chromogen used was 3-3'-diaminobenzidine tetrahydrochloride (DAB) and a standard DAB detection kit (Ventana) was used according to instructions supplied by the manufacturer's (Ventana) and as described previously by Pity et al and Pity and Baizeed[14,15]. Representative tissue sections from the

tumor (without necrosis and little mesenchymal tissue) were selected from the paraffin blocks. Three µm tissue sections were cut with a manual microtome and mounted on poly-l-lysine-coated slides. Sections were placed in oven at 56-60 Cº overnight, then stained with a fully automated immunostaining instrument; Ventana Benchmark (Ventana Medical System Inc., Cell Margue, Ventana, Rocklin, Calif.) where deparaffinzation, dehydration, antigen retrieval in addition to the application of primary and secondary antibodies were achieved. The primary antibodies used included monoclonal antibodies for HER2 (REF-790-2991, Ventana, USA) and for p53 (REF-760-2542, Ventana, USA). Positive controls (strongly positive breast carcinoma for both HER2 and p53) and negative controls (using the same procedure without primary antibodies) were used with each run. Sections were counterstained with Mayer's hematoxylin, dehydrated through graded alcohols to xylen and then mounted with DPX solution and coverslipped.

Positive p53 protein expression was defined as clear nuclear immunostaining in more than 10% of tumor cells16. HER2 staining was evaluated as described by Hofmann et al who addressed 4-graded scales [grade 0 referring to tumors without detectable staining or membrane staining of less than 10%, grade 1+ pertaining to weak staining of greater than 10% of tumor cells, grade 2+ which is defined as weak to moderate staining of the entire cell membrane (thin ring) in more than 10% of tumor cells and grade 3+ reflecting moderate to strong staining of the entire cell membrane (thick ring) in more than 10% of tumor cells]17 . Both (0 and 1+) grade scales are considered negative while grade 2+ and 3+ indicate staining[18].

Statistically, the collected data were organized and tabulated, and descriptive statistics were used to summarize demographic variables. Chi square and Fisher exact tests were used for testing associations between categorical tumor parameters, and differences at the level of $p \leq 0.05$ were considered as statistically significant.

RESULTS

Patient's ages ranged between 28-90 years (mean: 61.7 years). Sixty six patients were males and 35 were females. Gastric specimens (n= 63) included 43 (68.3%) gastrectomy specimens and 20 (31.7%) endoscopic biopsies. All esophageal specimens (n=38) were endoscopic biopsies from the lower esophagus. Histologically, 49 (77.8%) gastric cases were intestinal type and the remaining 14 (22.2%) cases were diffuse type adenocarcinoma whereas all esophageal cancers were intestinal type adenocarcinoma. Thus the total (gastric and esophageal) intestinal type adenocarcinoma formed 87 cases; of these, 41 (47.1%) cases were low-grades and 46 (52.9%) were high-grades. Of the 43 gastrectomy specimens, the tumor (T) status comprised 2 (4.7%) T1, 10 (23.2%) T2, 26 (60.5%) T3 and 5 (11.6%) T4. The lymph node (N) status formed 11 (25.6%) N0, 21 (48.8%) N1, 8 (18.6%) N2 and 3 (7%) N3.

HER2 and p53 Expression

Positive HER2 membranous expression (scores +2 and +3) was demonstrated in 34 (33.7%) cases while p53 nuclear staining was observed in 63 (62.4%) cases. No significant association of any marker was observed with age and gender. The highest frequency of positive {20.8% of HER2 and 36.6% p53} cases was observed among 60-69 year age group (Figure 1), and there was trend toward male gender (Figure 2).

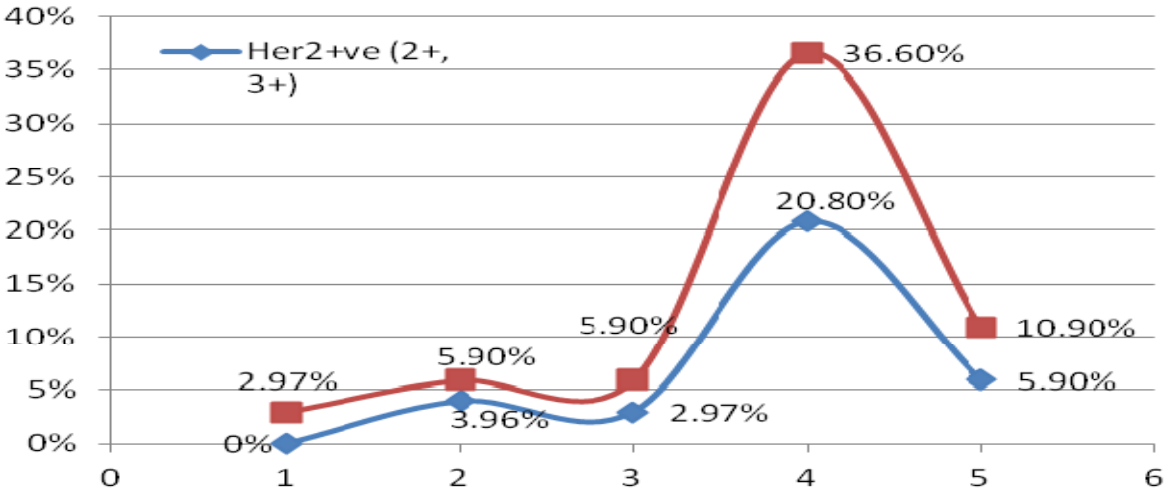


Figure 1. Age distribution for positive HER2 and p53 in gastroesophageal adenocarcinoma cases (Fisher exact test used, p= 0.5 for HER2 and 0.1 for p53).

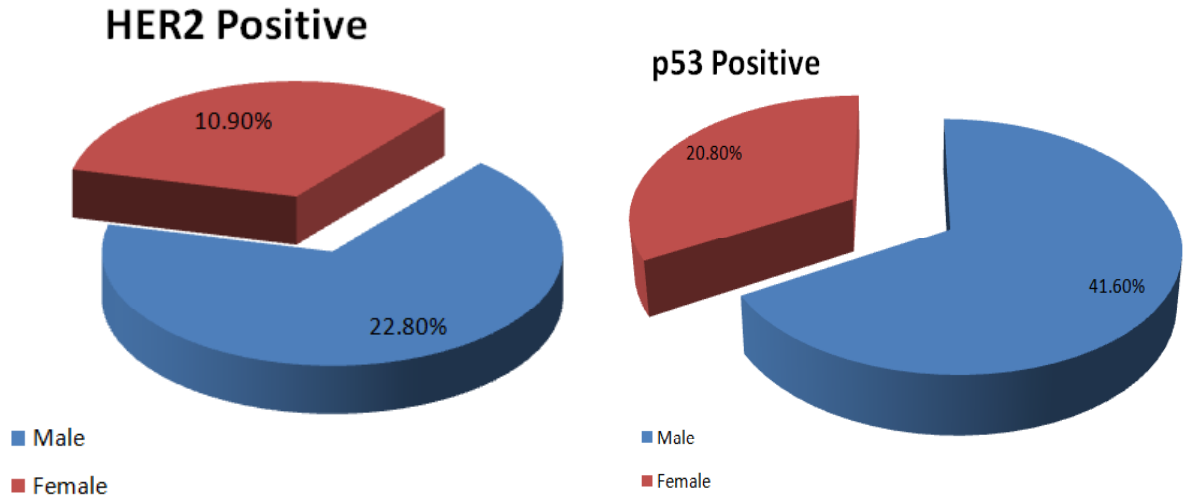


Figure 2. Gender distribution and positive HER2 (p= 0.06) and p53 (p=0.073). X^2 used.

Forty-five gastric and 22 esophageal cancers showed a negative HER2 (0/1+) expression. The remaining positive cases showed a significantly higher dense HER2 (3+) expression among esophageal compared with the gastric cases but lighter density HER2 (2+) was demonstrated only in GC where it was identified in 10.9% of cases (Table 1).

Much higher p53 nuclear expression was demonstrated in gastric 46 (45.6%) compared with the esophageal adenocarcinoma 17 (16.8%), p= 0.06.

Table 1. HER2 scores and site of adenocarcinoma.

	Gastric cancer	Esophageal cancer	Total
HER2			
Negative HER2 (0/+1)	**45 (44.6%)**	**22 (21.8%)**	**67 (66.4%)**
Positive HER2 (+2)	**11 (10.9%)**	**0 (0%)**	**11 (10.9)**
Positive HER2 (+3)	**7 (6.9%)**	**16 (15.8%)**	**23 (22.8%)**
Total*	**63 (62.4%)**	**38 (37.6%)**	**101 (100%)**
P53			
P53 +ve	**46 (45.6%)**	**17 (16.8%)**	**63 (62.4%)**
P53 -ve	**17 (16.9%)**	**21 (20.8%)**	**38 (37.6%)**
Total**	**63 (62.4%)**	**38 (37.6%)**	**101 (100%)**

*: X^2, p= 0.05, **: X^2, p= 0.08

Regarding the histologic type, as shown in figure 3 HER2 immunoexpression was demonstrated only in the intestinal adenocarcinoma. It was completely absent in the diffuse type. In contrast, p53 expression was more obvious in the diffuse (47.5%) than the intestinal type adenocarcinoma (14.9%), but the difference didn't reach the level of significant (p= 0.36).

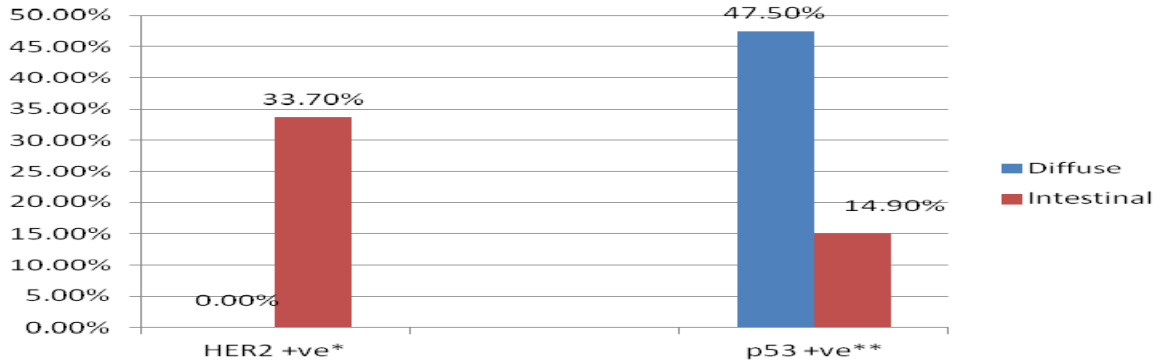
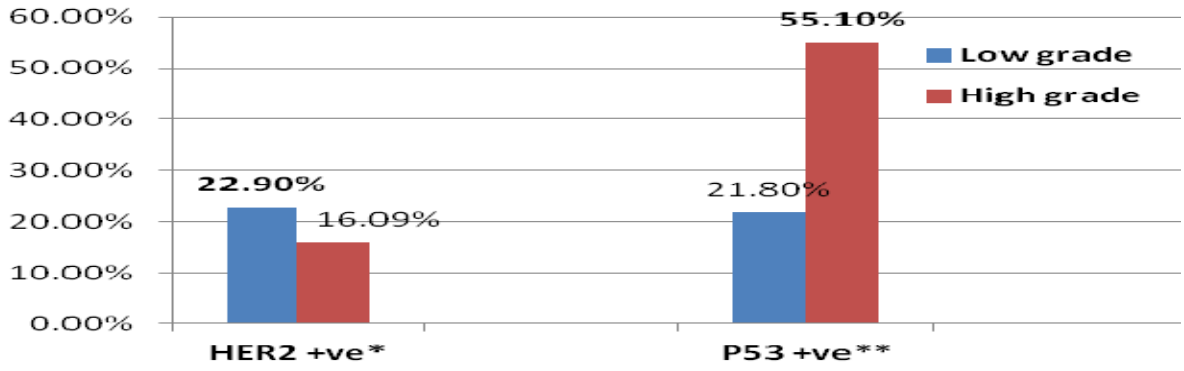


Figure 3. HER2 and p53 immunoexpression and histologic type of adenocarcinoma. (Fisher exact test, p= 0.36).

No statistical significance could be demonstrated between any marker and tumor grade. There was a trend for HER2 toward low grade tumors and p53 toward high grade cancers (Figure 4).



*p= 0.22, **p= 0.09 for p53.

Figure 4. HER2 and p53 immunoexpression and tumor grade.

Considering TNM staging, no significant association was demonstrated between any of HER2 or p53 and T-status despite a trend toward T3 (Figure 5).

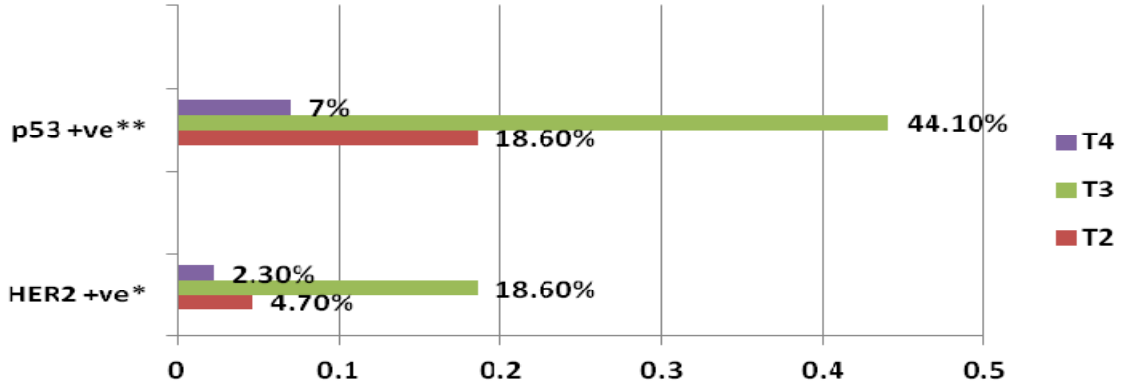


Figure 5. HER2 and p53 expression and T-status.
Fisher exact test used, *: p= 0.93; **: p= 0.14

As shown in figure 6, no statistical differences were observed between any of HER2 or p53 and N-status despite a trend for both markers toward N1.

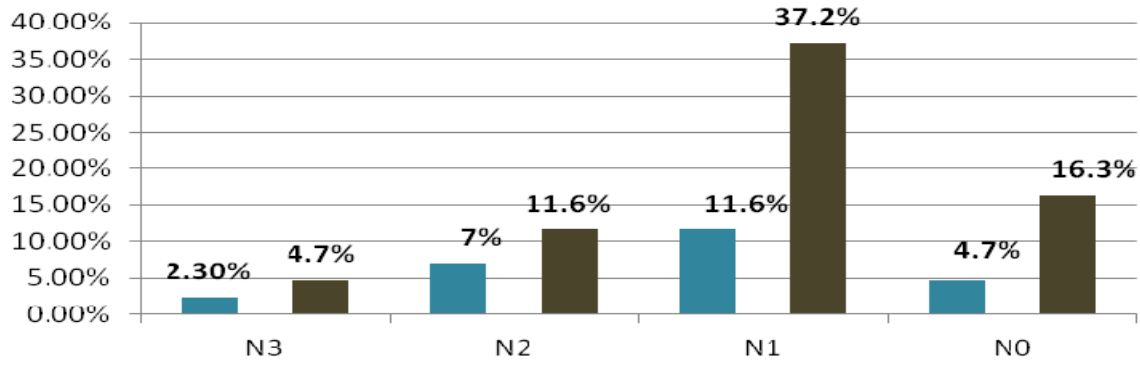


Figure 6. Distribution of gastric cancer cases, according to the the nodal (N) status (n= 43).
Fisher exact test used; *: p= 0.8; **: p= 0.87.

Coexpression of HER2 and p53

Among gastric cancer cases, 19.1% of cases illustrated coexpression of both markers and 53.9% showed negative HER2/positive p53. Lack of both markers was observed in 17.5% of cases, and the remainders (9.5%) showed positive HER2/negative p53. No significant association was found between presence and absence of the 2 markers (Figure 7).

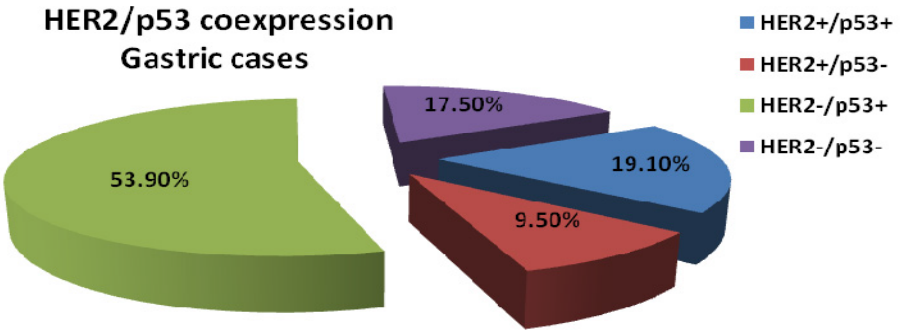


Figure 7. HER2/p53 coexpression in gastric adenocarcinoma, Fisher exact test used, p= 0.67.

On the other hand, all esophageal adenocarcinoma showed either absent HER2, p53 or both markers. No coexpression of both markers was demonstrated among esophageal cases. The difference was statistically significant (Figure 8).

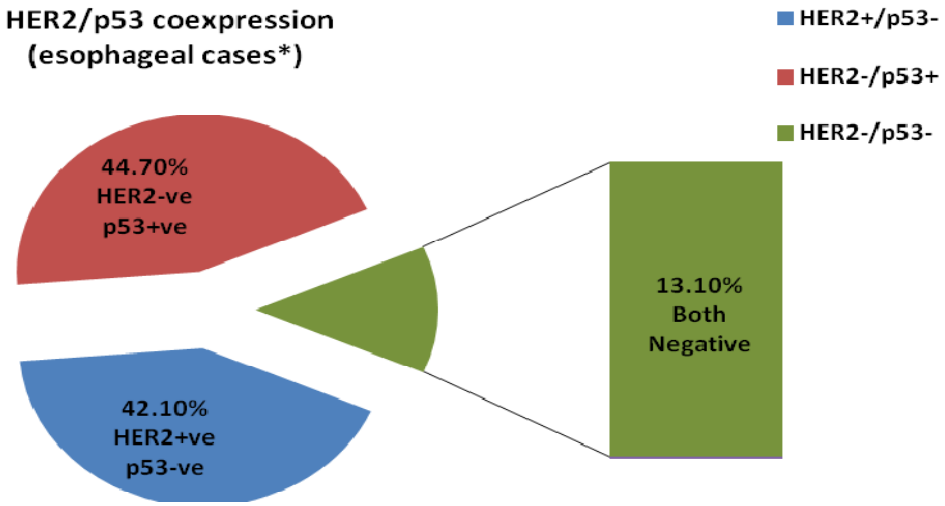


Figure 8. HER2/p53 coexpression in esophageal adenocarcinoma, *Fisher exact test, p= 0.034.

DISCUSSION

Overall, this study demonstrated a relatively high HER2 positivity (33.7%) in gastric and esophageal adenocarcinoma compared with what was previously reported by Kunz et al and Kataoka et al among Americans and Japanese with gastric cancer (8.5% to 10.3%)[19,20]. By a sequence analysis done in 122 centers out of 24 countries with gastric and esophageal cancers, the Trastuzumab anti-HER2 target therapy for Gastric Cancer (ToGA) trial demonstrated 10.4% to 22.1% HER2 positivity[9]. Barros-Silva et al, in their study among Portugal's population, observed a wider HER2 positivity range (5.2%-22.6%) but still lower than the current frequency21. The relatively higher expression of HER2 among our series is probably the result of combining HER2 (2+ and 3+) immunoexpression despite the fact that there is a high concordance between IHC and in situ hybridization for HER2 2+ demonstrated by Hofmann et al and Dowsett et al in their study of HER2 in both gastric and breast cancers[17,22].

It is worth mentioning that HER2-positivity differed by its staining intensity among our series. A strikingly high HER2 (3+) expression was observed among esophageal cancers compared with its gastric counterpart. In contrast, HER2 (2+) was completely absent among esophageal cancer cases. Tanner et al also demonstrated higher HER2 positivity in gastroesophageal junction cancer than GC (24% versus 12%) on their study among Finland population23. However, different results have been observed by many other studies9,16,18. The technique applied for HER2 detection with a further subcategrization of HER2 (2+) into positive or negative according to the in situ hybridization reading may influence the detection rate ranges[17,21,22].

Concerning p53 nuclear immunoexpression, in the course of this experiment we faced an exciting finding

that it was strikingly high in gastric adenocarcinoma compared with its esophageal counterpart (45.6% versus 16.8%). Wide p53 range rates for both gastric and esophageal adenocarcinoma have been documented in the literature (19% to 90%)[27-32]. The conflicting data demonstrated by different studies probably reside in the differences of geographic populations studied with heterogeneous socioeconomic sample sets studied and dietary habits as well as differences in their personal behaviors[2]. However, variation in the methods applied for evaluation of mutated p53 and the anti-p53 antibodies used may also contribute to such wide range rates[31].

In the current study, HER2 positivity was limited to the intestinal adenocarcinoma in both gastric and esophageal tumors; it was completely negative in the diffuse type. Interestingly, this finding is in agreement with numerous prior studies conducted in this field among American and European populations[9,17]. In addition to the fact that mutated HER2 is already low in the diffuse type, lack of HER2 immunoexpression among our diffuse cases is at least partly related to the small sample size of the present study. In contrary to HER2 expression, p53 nuclear expression was found to be expressed in both intestinal and diffuse adenocarcinoma with no significant difference between the two. This finding is comparable to what was observed by Pinto *et al* among Portugal's population[30]. However, contradictory findings were observed by Zheng et al and Lee et al among Japanese and Koreans where nuclear p53 overexpression was much more frequent in intestinal than the diffuse type adenocarcinoma[24,34].

As far as the grade is concerned, we failed to demonstrate any significant association between any of HER2 and p53 positivity and grading despite a trend toward low grade tumor for HER2 and toward high grade for p53. Divergent results have been demonstrated by many other studies conducted among different geographic populations 24-26 although similar results have been reported in a study done by Gleeson *et al* on gastroesophageal adenocarcinoma[35].

The already high T3 and N1 frequencies among our series may explain the predominance of HER2 and p53 positivity among both categories. However, the differences didn't reach the level of significance. Similarly, Kataoka et al denied any correlation between pathological stage and HER2 overexpression[20].

Moreover, despite a trend toward elderly and male gender neither HER2 nor p53 immunoexpression was significantly associated with any of age groups or gender in the current study. Honda et al, in their study among Japanese, have observed a significantly lower p53-immunoreactivity among young patients 36. However, our finding is in sharp contrast to the negative correlation between HER2 with both age and gender that was previously reported by Chen et al among Chinese population and the remarkable predominance of mutated p53 among the Romanian male gender[16,37].

Another important finding in this study is that no significant difference or association between both markers was demonstrated. Cases lacking HER2 with or without p53 among GC cases were more frequent than those expressing both markers together and all esophageal cancers were negative for at least one marker if not both. Such observation is in sharp contrast to what was previously described by Kataoka et al who suggested a possible role of p53 perturbation in the development of HER2-positive gastric cancer[20].

Moreover, the information obtained in this experiment provided a clinicopathological analysis of only 63 patients with GC and 38 patients with esophageal cancer, which is relatively small sample size. As well, we did not perform an in situ hybridization recommended to determine the real HER2 status particularly in equivocal cases, i.e. IHC (2+). These might subject our data to selection bias. More ad hoc-designed studies are needed to clarify these aspects and to ascertain whether HER2 and p53 immunoexpression really reflects their gene mutations and whether alterations of the genes themselves or their pathways have an intercommunicating role in gastric and esophageal adenocarcinoma.

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پوختە

لێنێرینا HER2 وp53 ل پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ

پێشەکی و ئارمانج: پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ دمینیت ئێك ژ نەخوشیێن کوژەك دگەل زێدەبوونا رێژا توشبوونێ. نیشاندەرێن گرێدای پەنجەشێرێڤە ئەوێن نوی هاتینە دیارکرن وەکی HER2 وp53 دهاریکارن بو بلەزکرنا بەرسڤدانێ بو چارەسەریا بەری نشتەرگەریێ و ب گشتی ژیانێ باشتر لێدکەن. ئارمانجا ڤێ ڤەکولینێ دیارکرنا خونیشاندانا پارێزکرنێ یا HER2 وp53 ل پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ و دەستنیشانکرنا هەڤبەندییێ دناڤبەرا هەردووا دگەل پیڤەرێن کلینیکی و تاقیگەهی.

ڕێکێن ڤەکولینێ: ئەڤ ڤەکولینە هاتە ئەنجامدان ل تاقیگەها مەلبەندییا ڕێڤەبەریا ساخلەمیا دهوکێ – عیراق دناڤبەرا گولانا ٢٠٠٩یێ و ئیلونا ٢٠١٤ لسەر ١٠١ حالەتێن پەنجەشێرا گلاندییا گەدێ و بوریکا خوارنێ بکارئینانا دژەلەشێن ئێك جور دژی وەرگرێن HER2 و پروتینێ ناوەکێ یێ p53 سلاید هاتنە رەنگکرن ب ئامیرێ فول ئوتوماتیکێ رەنگکرنێ (Ventana Benchmark).

ئەنجام: سەرجەمێ خونیشاندانا پوزەتیڤ یا HER2 ب پیڤانا (+٢/ +٣) هاتە دیارکرن ل ٣٢,٧٪ ژحالەتان و بشێوەکێ بەرچاڤ +٣ پتر بوو ل پەنجەشێرا بوریکا خوارنێ ببەراوردی دگەل پەنجەشێرا گەدێ، و بەروڤاژی +٢ هەر هیچ دیارنەبوو ل پەنجەشێرا بوریکا خوارنێ. رەنگدانەڤەیا p53 هاتە دیتن ل ٦٢,٤٪ ژ حالەتان و بشێوەکێ بەرچاڤ پتر بوو ل پەنجەشێرا گەدێ ژ پەنجەشێرا بوریکا خوارنێ.

دەرئەنجام: HER2 ب تنێ ل جورێ ڕویڤیکی هاتە دیتن لێ p53 لهەردوو جورێن ڕویڤیکی و بەربەلاڤ هاتە دیتن. چ خونیشاندانێن بهەڤا بێن HER2 وp53 نەهاتنە دیتن لهەردوو پەنجەشێرێن گەدێ و بوریکا خوارنێ.

الخلاصة

معاينة HER2 و p53 في السرطان الغدي للمعدة والمرئ

الخلفية وأهداف البحث: تبقى السرطانات الغدية للمعدة والمرئ أمراض مميتة مع ارتفاع نسبة الإصابة بها، أما العلامات الجينية المتعلقة بالأورام أو المكتشفة حديثاً مثل HER2 و p53 تساعد على تسهيل كل من الاستجابة للعلاج قبل الجراحة وتحسين البقاء على قيد الحياة بشكل عام.

تم تصميم هذه الدراسة لتقييم التعبير المناعي لكل من HER2 و p53 في السرطانات الغدية للمعدة والمرئ ولإيجاد الارتباط بين HER2 و p53 مع الأنماط السريرية.

طرق البحث: أجريت الدراسة في المختبر المركزي للمديرية العامة لصحة محافظة دهوك، وتم البحث على عينات نسيجية (منظارية أو مستئصلة جراحياً) مأخوذة من مائة وواحد شخصاً مصاباً بسرطان الغدي للمعدة والمرئ، كما تم صبغ الشرائح بجهاز الصبغ الكيميائي المناعي الآلي (Ventana Benchmark) باستخدام أجسام مضادة أحادية السلالة لمستقبلات الـHER2 و p53.

النتائج: أظهرت النتائج الإيجابية للمعاينة الكيميائية المناعية لـ(HER2+2/+3) بنسبة ٢٣.٧% لدى المرضى المصابين بسرطان الغدي للمعدة والمرئ مع ارتفاع ملحوظ لـ(HEFR2+3) لدى المصابين بأورام المرئ مقارنة بنظائرها في المعدة، والعكس صحيح بالنسبة للمعاينة المناعية (p53) في ٦٢.٤% من الحالات، مع ارتفاع ملحوظ في الأورام الغدية للمعدة مقارنة بالمرئ. وفيما يتعلق بالنوع النسيجي فقد كان HER2 مقتصراً على النوع المعوي لسرطان المعدة في حين ظهر p53 في كلا النوعين المعوي والمنتشر على الرغم من تغلبه باتجاه النوع المعوي.

الاستنتاج: اقتصرت معاينة الـHER2 على النوع النسيجي المعوي لسرطان الغدي للمعدة، ولم يكن هناك أي ربط بين HER2 و p53 في هذه الأورام ولاسيما أورام المرئ.