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Importance of HER2 status determination in advanced gastric cancer: A case study

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Abstract

Advanced gastric cancer (AGC) is an entity that encompasses two distinct clinical situations: locally advanced unresectable gastric cancer and metastatic disease, with chemotherapy as the standard treatment. HER2 overexpression can occur in 9% to 38% of the cases with this disease and has been the first predictive biomarker used for trastuzumab-targeted therapy in patients with advanced gastric and gastroesophageal tumors. This article presents a patient with AGC and positive HER2 treated with conventional chemotherapy plus trastuzumab as targeted therapy with adequate clinical response.

Keywords

Advanced gastric cancer; Treatment; Trastuzumab; HER2.

INTRODUCTION

Gastric cancer is a public health problem. Every year there are more than 1 million new cases and about 850 000 deaths are caused by it worldwide. According to Globocan 2018, in Colombia it has been estimated that there 7419 new cases per year, being the third most frequent cancer (7.3%) and the most common cause of death from cancer in the country with 5505 deaths (13.7 %) (1). In Western countries, approximately 50 % of the patients with gastric cancer who visit the doctor for the first time are diagnosed with metastatic cancer, and in these cases, the overall survival rate at 5 years is less than 5 % (2).

There are several classifications of stomach cancer. According to one of such classifications, gastric cancer is classified as a localized cancer (stages 0, I, II and III; resectable) and as advanced and metastatic cancer (stage IV, unresectable). The latter (advanced gastric cancer) involves two clinical situations: locally advanced unresectable stomach cancer and metastatic cancer (3).

Chemotherapy based on the combination of platinum agents plus fluoropyrimidines such as 5-fluorouracil (5FU) plus cisplatin (FP) or capecitabine plus cisplatin (XP) (4) is the first-line therapy for advanced gastric cancer. These chemotherapy regimens have been shown to improve overall survival, progression-free survival, and quality of life when compared with best supportive care (3).

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGRF) family that has been associated with increased division, proli-

feration, differentiation, and apoptosis of tumor cells in breast and stomach cancer, as well as in other solid tumors (5).

Several studies have shown that HER2-positive breast carcinomas are more aggressive compared to HER2-negative breast carcinomas and that they are associated with an increased risk of local growth and distant metastasis (6). HER2 is also overexpressed in gastric and gastroesophageal junction carcinomas (6, 7). HER2 overexpression in gastric cancer could result in tumors with an increased proliferative and invasive capacity (6).

Several studies have evaluated the relationship between HER2 status and the prognosis of patients with gastric cancer. Some have shown that having a HER2-positive cancer is associated with a significantly worse prognosis, while others have not found any association; however, overall survival time was longer in patients with HER2-positive cancers compared to those with HER2-negative tumors. Because of this, the relationship between HER2 status and prognosis remains controversial (6).

HER2 is an important predictive biomarker in gastric and gastroesophageal junction tumors. The analysis of HER2 status through immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) techniques using different scoring methods suggest that HER2 overexpression occurs in 7 %-34 % of gastric tumors. Furthermore, the favorable results derived from the ToGA study correlate with the level of HER2 overexpression (8, 9).

After finding out the occurrence of HER2 overexpression in patients with advanced gastric cancer, adding trastuzumab, a first-line therapy anti-HER2 antibody drug that has been shown to improve efficacy outcomes, to chemotherapy has been recommended (7, 10). Currently, result accuracy and standardization in HER2 testing is crucial to identify the target population that can be treated with this drug and benefit from it (11).

The introduction of trastuzumab has allowed the establishment of a new disease: HER2-positive gastric cancer, similar to what happened in the case of HER2-positive breast cancer (6). Currently, knowing HER2 status in patients with stomach cancer is vital to make decisions aimed at ensuring that the patient is given the best possible treatment (6). For this reason, testing HER2 status in all patients with advanced gastric or gastroesophageal junction cancer is important (6).

The objective of this paper is to report the case of a patient with HER2-positive advanced and metastatic gastric cancer treated with chemotherapy plus trastuzumab and in which favorable a clinical response and survival were obtained.

CASE PRESENTATION

This is the clinical case of a 68-year-old male from Putumayo, Colombia, who had experienced dyspepsia, a sense of stomach fullness, hyporexia, nausea, and an approximately 10 kg weight loss during four months. The patient reported having a history of smoking (he had been a heavy smoker and had stopped smoking 25 years before the time of consultation) and a family history (father) of pancreatic cancer. On physical examination an extremely thin and emaciated patient was found; no supraclavicular lymphadenopathy, abdominal masses or ascites were found. An initial esophagogastroduodenoscopy, performed in another health institution, reported a thickening of the folds in the fundus and body of the stomach with decreased distensibility and multiple superficial ulcerated lesions. The histopathology report, made in the institution where the patient was referred from, confirmed he had a 30% intestinal type poorly differentiated, infiltrating and ulcerated adenocarcinoma with mixed histologic pattern, predominantly diffuse with signet ring cells. Furthermore, a contrast-enhanced abdominal CT scan performed in the institution where he was referred from showed an abnormal neoplasm-like thickening of the stomach wall in the fundus and body regions with ulceration, as well as adenomegalies in the gastrohepatic ligament without hepatic or peritoneal involvement. A cT3N1M0 clinical staging was made.

Based on the preoperative assessment, the patient was taken to surgery with the intention of performing a gastrectomy. During the surgical procedure, a gastric lesion with wall thickening in the body and lesser curvature of the stomach and a matted lymph node in the lesser curvature and multiple metastatic-like liver nodules were found; the lesion was classified as stage IV T3N1M1 cancer. After the surgery was completed, a new computed axial tomography (CT) scan was performed and the surgical findings were confirmed, as multiple 10 mm focal hypodense lesions were observed in segments IV and VI of the liver (**Figure 1A** and **B**), with diffuse stomach wall thickening and a 31 x 17 mm matted lymph node.

Since this was an advanced metastatic stage cancer, chemotherapy with XP (cisplatin + capecitabine) chemotherapy protocol was started and after the first cycle was completed, a liver biopsy report performed in another institution was received in the treating institution informing the following findings: involvement of the liver by a HER2-positive (3+) metastatic gastric adenocarcinoma. For this reason, trastuzumab was added to the established chemotherapy regimen, a combination the patient received for 4 more cycles, when treatment was suspended due to toxicity characterized by asthenia, adynamia, hyporexia, nausea, emesis and diarrhea (up to grade 3 diarrhea). At that time, new chest and abdominal CT scans were performed, showing persistent thickening of the gastric chamber, lymphadenopathy and absence of the liver lesions with apparent complete response of the liver nodules (**Figure 1C**).

Capecitabine plus trastuzumab chemotherapy regimen was continued, but cisplatin administration was suspended. After 2 additional chemotherapy cycles, a laparoscopy was performed and no macroscopic evidence of liver metastases or peritoneal carcinomatosis was found, so the surgical board decided that surgical management with a potentially curative intent was the best treatment option.

Before undergoing the new surgical interventions, the patient was administered two trastuzumab monotherapy doses. Finally, the patient was brought to the operating room on November 27, 2017, 10 months after the initial diagnosis was reached, where a total gastrectomy with D2 lymphadenectomy was performed. The final pathology report of the surgical specimen reported a post-neoadjuvant stage (tumor regression grade 2) mixed-pattern gastric adenocarcinoma with tumor-free resection margins and 3/33 positive lymph nodes for metastasis; a HER2 positive (3+) status was also described (**Figure 2**).

After surgery, the patient was given 4 adjuvant chemotherapy cycles consisting of capecitabine, oxaliplatin and trastuzumab, and 4 more trastuzumab monotherapy cycles, for a total of 18 perioperative trastuzumab cycles.

In a new chest and abdominal CT scan performed 5 months after the surgery (April 11, 2018) the following findings were reported: liver of normal size, morphology, density and contour, without focal lesions and other tumor growth lesions (**Figure 1D**). In subsequent follow-up visits the patient was found to be asymptomatic with mild hearing loss and skin pigmentation changes resulting from chemotherapy. In addition, no tumor-like lesions were observed in a positron emission tomography (PET scan) performed on September 17, 2018 (**Figure 3**). Likewise, according to a MRI performed on October 28, 2018, there was no evidence of suspected malignant lesions at the esophagojejunal anastomosis and of lesions in the liver parenchyma. 18 months after the initial diagnosis, the

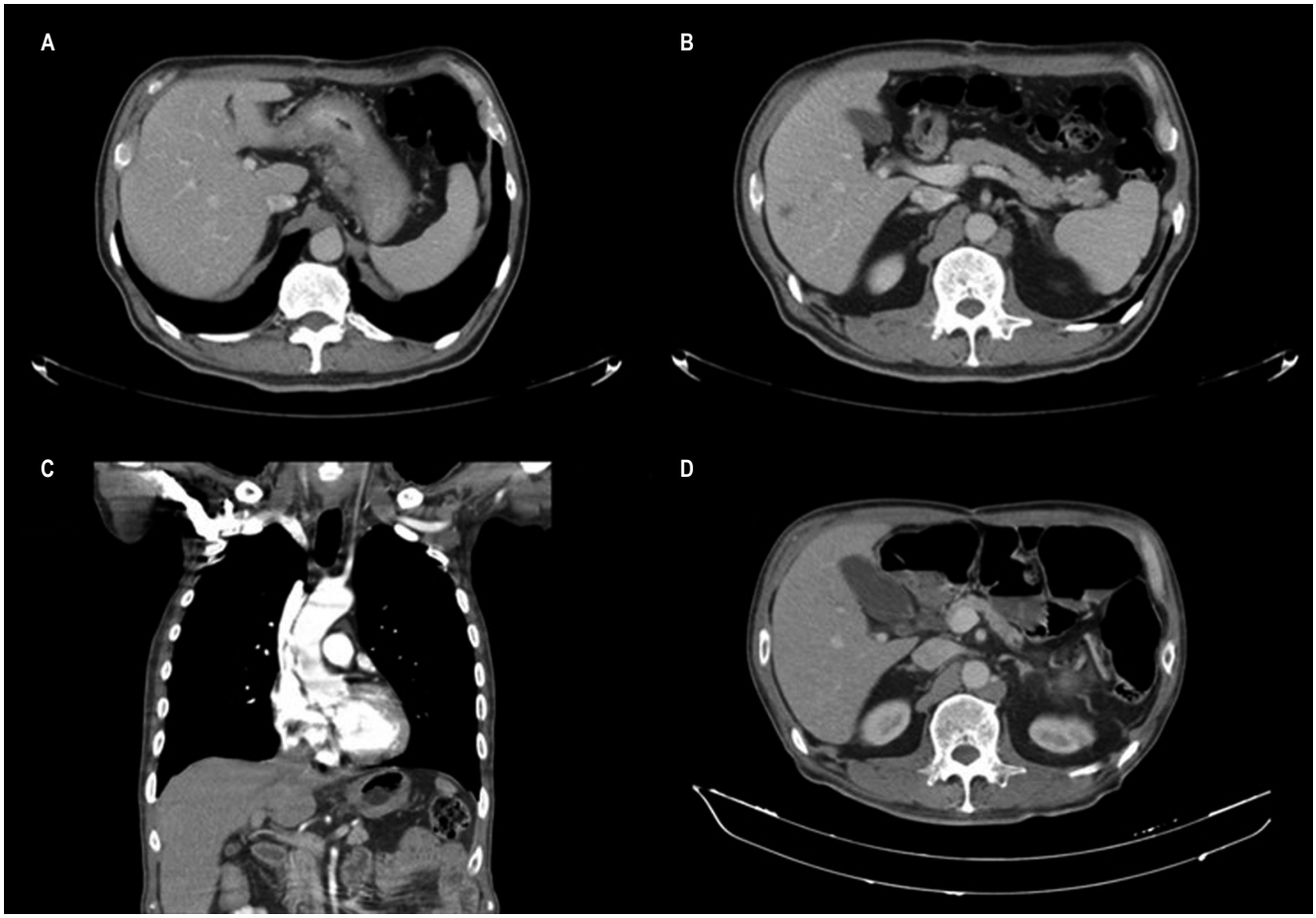


Figure 1. CT scan studies performed for tumor pathology follow-up purposes. **A.** Diffuse stomach wall thickening plus a 31 x 17 mm matted lymph node with extramural extension. **B.** Up to 10 mm focal hypodense hepatic lesions in segments IV and VI of the liver. **C.** Decreased gastric chamber thickening and adenopathies, there are no hepatic nodules or new lesions. **D.** Post gastrectomy changes, normal liver size, morphology, density and contour, without focal lesions or other tumor growth lesions.

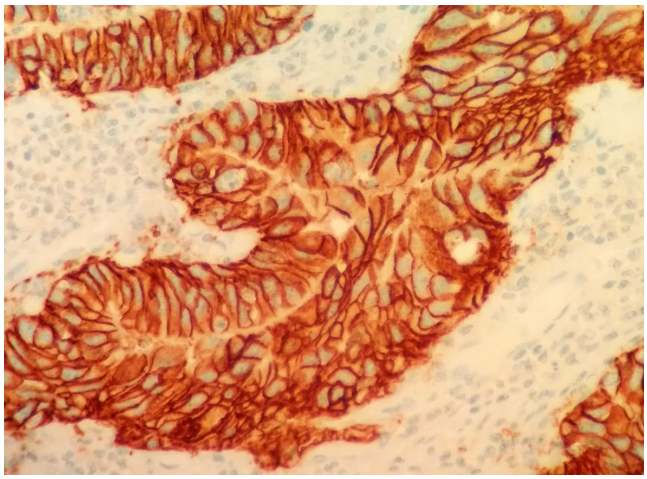


Figure 2. HER2-positive (3+) gastric adenocarcinoma. IHC 40x (in the specimen obtained from the total gastrectomy).

patient is asymptomatic and does not show signs of cancer recurrence. The aforementioned imaging studies, treatment plan and follow-up are shown in **Figure 4**.

DISCUSSION

There are several classifications systems used for gastric cancer and they are still under discussion. The classification systems proposed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) are the most frequently used. These systems are based on the staging system, where the penetration of the lesion into the stomach wall (T), lymph node involvement (N) and metastasis (M) are assessed, and stomach cancer is classified as early and advanced (12). Other systems include histopathological classification, such as Lauren's classification (intestinal, diffuse and mixed type adenocarcinoma), Nakamura's classification, the classification by the World Health Organization (WHO), the endoscopic macroscopic classification of the lesion described for both early and advanced gastric cancer (Bormann), and the genomic or molecular classification (2).

On the other hand, unresectable gastric cancer is a term widely used in the clinical setting, however this a concept with highly variable clinical implications, for it does not represent the true extent of the disease.

When the treatment of stomach cancer is defined by its stage, it is classified as localized (stages 0, I, II and III resectable) and as advanced and metastatic cancer (stage IV unresectable). For this reason, the relevant literature describes gastric cancer as disease that involves two different clinical situations: locally advanced unresectable stomach cancer and metastatic cancer (3).

Patients with advanced or metastatic gastric cancer have a very poor prognosis, with a 5-year survival rate <4%. Chemotherapy is the standard treatment in these cases; however, with the emergence of targeted therapies now it is possible to choose the treatment based on the molecular characteristics of the disease (2, 8).

In 1965, Pekka Lauren, based on histopathological criteria, classified stomach cancer into 2 types: intestinal and diffuse. Before the discovery of HER2 and the introduction

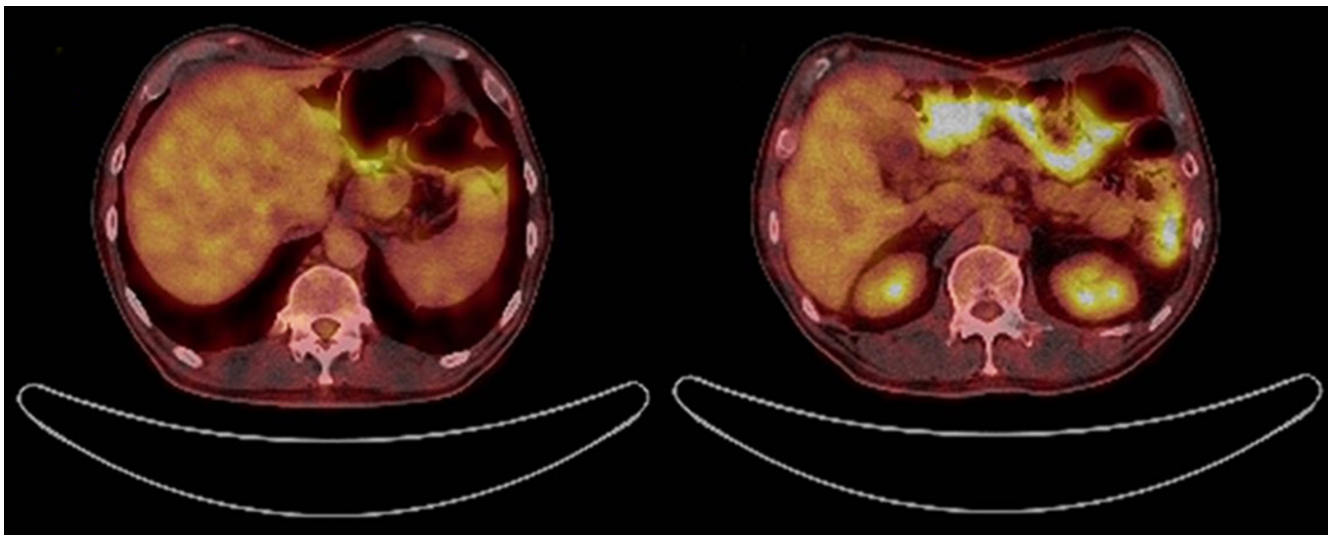
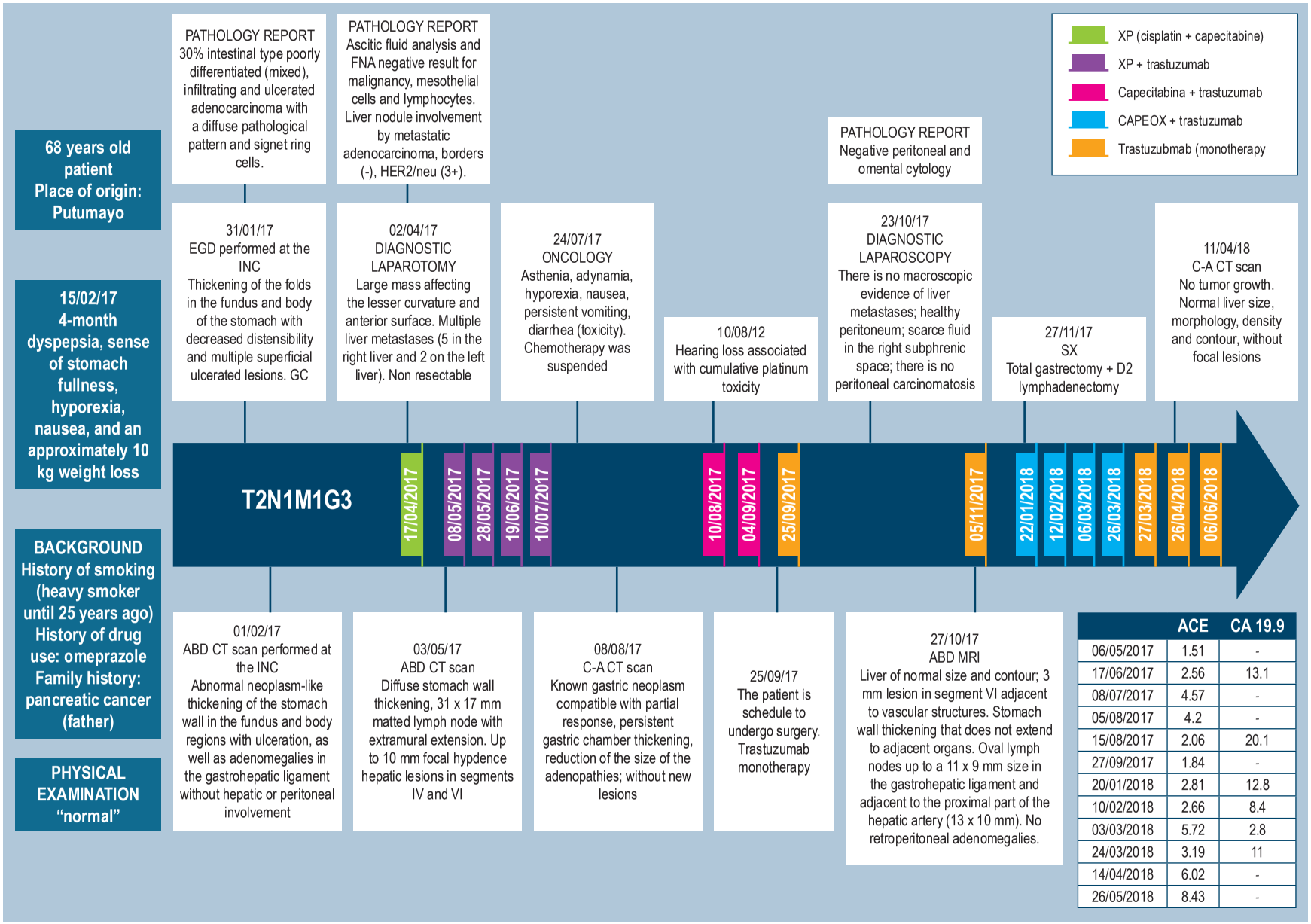


Figure 3. PET scan performed after gastrectomy and where the absence of tumor-like lesions is evidenced.



	ACE	CA 19.9
06/05/2017	1.51	-
17/06/2017	2.56	13.1
08/07/2017	4.57	-
05/08/2017	4.2	-
15/08/2017	2.06	20.1
27/09/2017	1.84	-
20/01/2018	2.81	12.8
10/02/2018	2.66	8.4
03/03/2018	5.72	2.8
24/03/2018	3.19	11
14/04/2018	6.02	-
26/05/2018	8.43	-

Figure 4. Timeline of the clinical case in which the initial management approach, the studies performed, the treatment the patient was given and follow-up of the patient are outlined. ABD: abdominal; FNA: fine needle aspiration; CEA: carcinoembryonic antigen tumor marker; CA 19-9: cancer antigen 19-9 tumor marker; SX: surgery; EGD: esophagogastroduodenoscopy or upper gastrointestinal endoscopy; GC: gastric cancer; INC: Instituto Nacional de Cancerología (National Cancer Institute of Colombia); MRI: magnetic resonance imaging; C-A: chest and abdomen.

of trastuzumab into clinical practice, there were no predictive biomarkers that allowed guiding the treatment of this type of cancer (7).

HER2 is a receptor tyrosine kinase that belongs to the EFGR family and that is encoded by the ERBB2 proto-oncogene located in chromosome 17, which plays a very important role in cell differentiation, survival, apoptosis and proliferation (6). There has been an increasing interest in this epidermal growth factor receptor 2, also known as HER2/neu, HER2, c-er-B2 and ErbB2 (13, 14).

HER2, being a co-receptor, does not have a ligand, as the other members of the EGRF family do (**Figure 5**). Homodimerization causes a conformational change of the receptor that stimulates HER2-coupled intracellular signaling pathways that occur either through the mitogen-activated protein kinase (MAPK) pathway, which is associated with tumor proliferation, migration, differentiation or angiogenesis, or through the PI3K-AKT-mTOR pathway, related to tumor survival and anti-apoptotic signaling (**Figure 5**) (13, 15).

HER2 is overexpressed in different classes of tumors that promote cell proliferation, tumor progression and metastasis. HER2 overexpression was first detected in gastric cancer by Fukushige et al. in 1986 (16). The frequency of HER2 overexpression in stomach cancer varies considerably in different studies from 6% to 30% (6). In an attempt to measure this variability, the researchers responsible for the TOGA study carried out a validation study to measure HER2 status in people with advanced gastric cancer using IHC and FISH techniques. Bearing this in mind, tissue samples from 3807 patients were collected in 24 countries and then analyzed using IHC and FISH. HER2 status was defined as positive (IHC 3+, or FISH+) based on cell membrane staining patterns or gene amplification in surgical specimens or biopsy samples, respectively (6). HER2 overexpression (HER2 positive status) was associated with being male and having well- and moderately-differentiated intestinal-type tumors (6).

The criteria for defining HER2 overexpression differ between breast and stomach cancer due to tumor biology inherent differences and to differences in the expression pattern (6, 9). Compared to breast cancer, stomach cancer exhibits different staining characteristics such as high incidence of tumor heterogeneity (defined as > 10% positive staining of

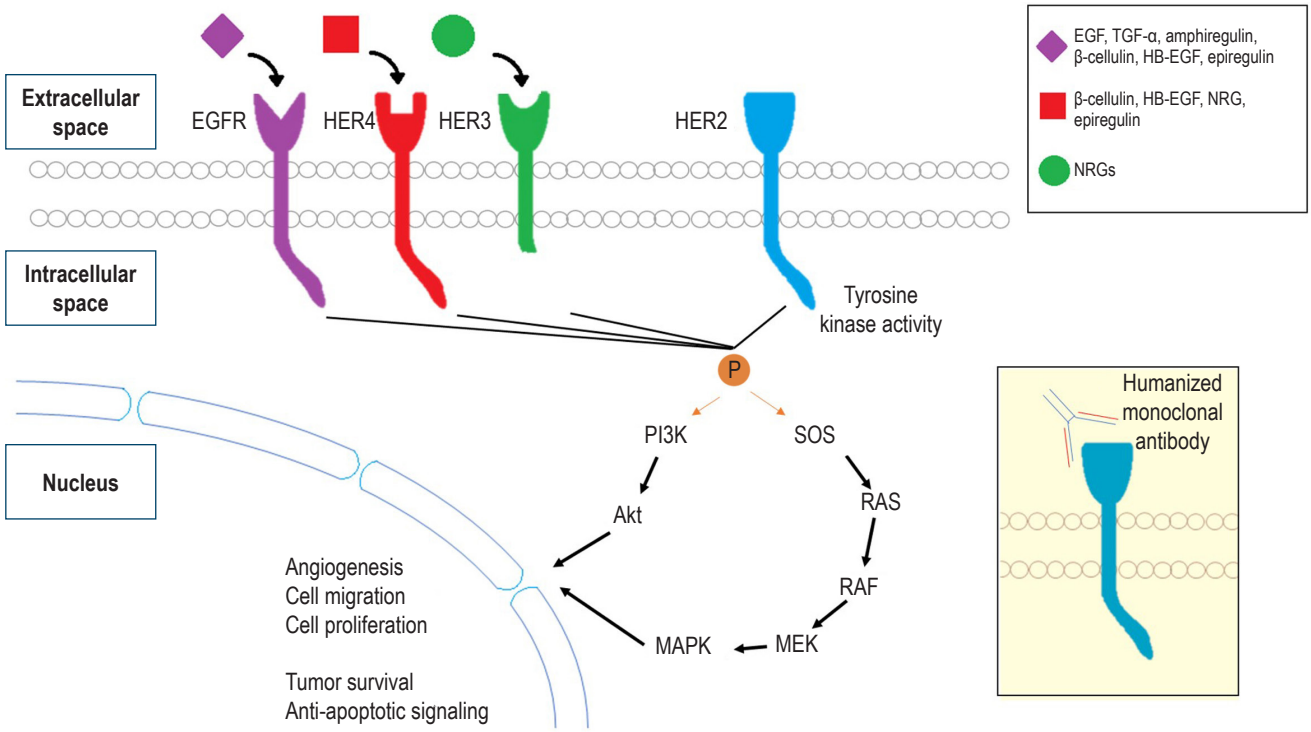


Figure 5. Interaction between receptors with tyrosine kinase activity. The different receptors are outlined and the different ligands that are related to each receptor are listed in the upper right corner. HER2 does not have specific ligands, so it must bind to the other receptors to trigger the intracellular signaling pathways that will act on tumor proliferation and survival. Trastuzumab inhibits the interaction between HER2 and the other members of the receptor family. Tka: tyrosine kinase activity; HB-EGF: heparin-binding epidermal growth factor; NRG: neuregulin; PI3K: phosphatidylinositol-3-kinase; TGF-α: transforming growth factor-alpha. Made by the authors.

cells or only focal staining of tumor cells in groups of more than 5 cells) in up to 30% of HER2-positive cases. Another key difference with breast cancer is that in HER2-positive gastric carcinomas are usually found in the intestinal-type glands and may show incomplete, basolateral or lateral staining, and all these are considered as positive results when using IHC. For this reason, specific protocols for HER2 testing in gastric cancer have been developed and standardized, and following these recommendations is imperative (2, 9).

Given these differences in terms of expression between breast and stomach cancer, an appropriate scoring system was developed exclusively for gastric tumors. This system, proposed by Hofmann et al., has been adopted and is specific for both gastric tumors and surgical specimen biopsies (2, 17).

Intratumoral heterogeneity also appears to have contradictory results regarding HER2 expression in primary tumor and metastatic lesions specimens. Previous studies have found significant differences when HER2 expression is analyzed in whole tissue sections and in small tissue samples. Thus, analyzing HER2 expression in more than one sample or in all available specimens and, if possible, in metastatic lesions specimens, is recommended. Taking this into account, surgical specimens in patients with HER2-negative biopsy results should be also analyzed in order to increase the possibility of finding HER2-positive tumors (17). Several gastric tissue biopsies must be performed, ideally between 6 and 8 fragments. In this regard, the German guidelines recommend a minimum of 8 samples (6, 18, 19). IHC test must be performed as the initial test, while molecular tests such as FISH (CISH or DISH) must be used to reevaluate 2+ or equivocal IHC test results (2, 6, 9).

Based on the results of the TOGA study, trastuzumab use was approved to treat HER2-positive gastric cancer, which is defined as IHC 3+ or FISH positive in the United States and Japan. In contrast, in Europe, HER2-positive gastric cancer is defined as IHC 3+ or as IHC 2+ plus FISH-positive (6).

The guidelines for HER2 status testing developed by the Japanese Society of Pathology recommend performing HER2 testing routinely in patients with metastatic or recurrent gastric cancer at the time of diagnosis (6, 9).

The algorithm of the test developed to determine HER2 status includes performing the IHC test first and then the FISH test in case of patients with a IHC 2+ result (**Figure 6**) (17).

Trastuzumab is a humanized monoclonal antibody that selectively binds to HER2. It is indicated for the treatment of HER2-positive breast and gastric tumors (11). In 2010 the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved its use based on the overall survival benefit it offers to patients with metastatic gastric cancer or gastroesophageal junction cancer and in which HER2 overexpression has been determined by means of an accurate and validated measurement (9, 11).

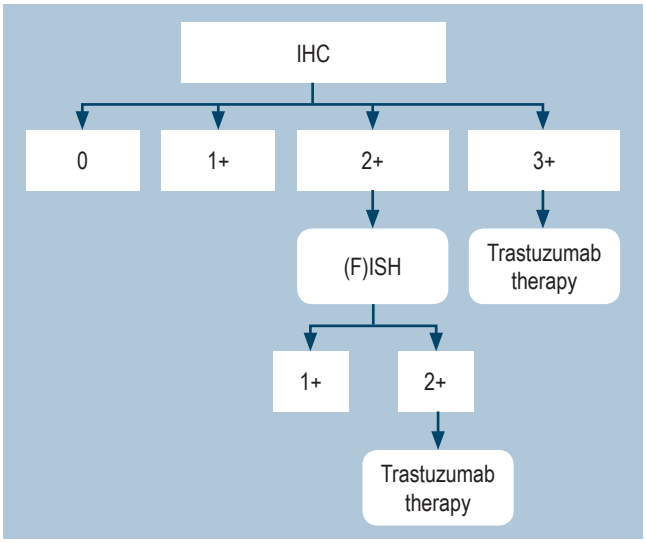


Figure 6. Histopathological algorithm to determine HER2 overexpression (18). Taken from: Lordick F et al. J Cancer Res Clin Oncol. 2017;143(5):835-841.

The TOGA study (20), published in 2010, was a prospective phase III study where patients with HER2-positive advanced gastric or gastroesophageal junction cancer were randomized into two groups: trastuzumab plus chemotherapy and chemotherapy alone. The chemotherapy regimen consisted of 6 cycles administered every 3 weeks. Trastuzumab was administered at a dose of 8 mg/kg on day 1 of the first cycle and then it was administered at a 6 mg/kg dose every 3 weeks until disease progression, unacceptable toxicity, or consented withdrawal. A total of 3803 patients were considered for being included in the study. The characteristics of both the patients allocated to the trastuzumab plus chemotherapy (n = 294) and chemotherapy alone (n = 290) groups were similar, including age, sex, chemotherapy regimens, tumor site (stomach and gastroesophageal junction). Furthermore, in both groups, 97% of patients had metastatic cancer and slightly less than half were classified as FISH + /IHC 3+ cancer (45% vs. 43%).

Overall survival, which was the primary outcome considered by the study, was significantly longer in patients in the trastuzumab plus chemotherapy group compared to those in the chemotherapy alone group, with a 2.7-month increase (13.8 months vs. 11 months). Progression-free survival was also longer in the trastuzumab plus chemotherapy group (6.7 months vs. 5.5 months). A 47% overall response rate was observed in the trastuzumab plus chemotherapy group (complete response 5%, partial response 42%). Likewise, response duration was longer in the trastuzumab plus chemotherapy group (6.9 months vs. 4.8 months) (20).

Patient subgroup analysis also showed that overall survival was longer in patients with high HER2 expression, as determined by IHC and FISH (IHC 3+ or IHC 2+ plus FISH positive) than in those with low HER2 expression (IHC 0 or 1+ plus FISH positive) (6, 20). According to these results, trastuzumab therapy is recommended for patients with IHC 3+ or IHC 2+ plus FISH positive (high HER2 expression) cancer (6).

The results of this study show that the combination of chemotherapy plus trastuzumab significantly improves overall survival in patients with HER2-positive advanced gastric or gastroesophageal junction cancer compared to chemotherapy alone, and that said improvement was particularly significant in patients with high HER2 expression. It is worth noting that trastuzumab administration did not increase the incidence of adverse events associated with chemotherapy, and that the frequency of cardiac events was low (20).

In addition, several case reports have shown favorable outcomes associated with trastuzumab when it has been used as part of perioperative chemotherapy in gastric cancer (16, 21). Some patients have experienced pathologic complete response.

In the case reported here, the patient was diagnosed with HER2-positive overexpression based on the biopsy report of the specimen taken from the liver metastatic lesion by means of laparotomy. The patient's gastric pathology report sent from the institution where he was referred from did not provide any information regarding HER2 status, and since this was an advanced stage cancer case due to gastric lesion with liver metastases, the patient was given standard chemotherapy with capecitabine plus cisplatin; however, once his HER2 status was known, trastuzumab was added to the treatment plan. This drug (trastuzumab) combined with chemotherapy (fluoropyrimidine and platinum) prolongs overall survival in patients with unresectable HER2-positive gastric cancer (2, 20).

Given the favorable response of the patient to the treatment consisting of the disappearance of the liver lesions, which was confirmed through imaging studies and a laparoscopy, a curative-intent total gastrectomy with D2 lymphadenectomy was performed. HER2 overexpression result was positive in the surgical specimen biopsy. After the surgery, the patient also received trastuzumab monotherapy and the disease was controlled for 18 months from the initial diagnosis, as a negative result was reported in the PET scan.

This allows understanding the importance of determining HER2 status in patients with advanced gastric cancer; also, the fact that the introduction of trastuzumab allowed the establishment of a new disease (HER2-positive gastric cancer), similar to the case of HER2-positive breast cancer, stands out (4, 5). Patients with advanced cancer with HER2 overexpression benefit from anti-HER2 therapy with trastuzumab (2).

In Colombia, the morbidity and mortality burden of gastric cancer is high, and more than one decade has passed since targeted therapies were developed. However, studies addressing this specific field of action in the country are scarce. One of such studies, conducted in the city of Bucaramanga and published in 2013, reported that the frequency of HER2 expression in patients with gastric adenocarcinoma was 11.2 % (22), which is higher than the frequency reported in other Latin American countries such as Brazil, Peru and Mexico (10.5 %, 9 % and 6.5 %, respectively) (23).

In conclusion, chemotherapy (FP) plus trastuzumab is the standard treatment for patients with HER2-positive metastatic advanced gastric cancer or gastroesophageal junction cancer. All of these cancers must be screened for HER2 status in paraffin blocks or biopsy specimens taken from the primary tumor or metastases at the time of initial diagnosis. Likewise, multiple gastric biopsies by endoscopy must be performed. IHC must be the initial test. Equivocal or incomplete tumors with IHC 2+ must be analyzed with FISH for confirmation. HER2 status testing and scoring must follow the specific recommendations for gastric cancer and must be performed in a laboratory experienced in doing so (2, 9). The perspectives are the evaluation of trastuzumab use for the treatment of patients with HER2-positive advanced gastric cancer in the perioperative and adjuvant setting.

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