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**Caracterização da Expressão
Imunoistoquímica do HER-2 em
Espécimes Cirúrgicos de
Gastrectomia e sua Correlação com
Aspectos Anátomo-Patológicos.**

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Lista de abreviaturas utilizadas

AJCC: *American Joint Committee on Cancer*

CAP: Colégio Americano de Patologia

CISH: Chromogenic *in situ* hybridization

DATASUS: Departamento de Informática do Sistema Único de Saúde do Brasil

EGFR: *epidermal growing factor receptor*

FISH: Fluorescent *in situ* hybridization

HER-2: *human epidermal receptor type 2*

HER-3: *human epidermal receptor type 3*

INCA: Instituto Nacional do Câncer do Brasil

ISCOMPA: Instituto Santa Casa de Misericórdia de Porto Alegre

JEG: junção esôfago gástrica

OMS: Organização Mundial de Saúde

R\$: Reais

SISH: Silver *in situ* hybridization

ToGA: *Trastuzumab for Gastric Cancer Study*

Resumo da Dissertação

Introdução:

Nas estatísticas mundiais, as neoplasias malignas gástricas são a segunda causa de morte relacionada ao câncer e destas, os adenocarcinomas são de longe os mais incidentes.

A baixa eficácia dos esquemas quimioterápicos no tratamento do adenocarcinomas gástrico e da junção esôfago-gástrica motiva pesquisas de fatores prognósticos e terapêuticos alternativos.

Objetivos:

Análise de fatores epidemiológicos e correlação com a expressão imunohistoquímica do HER-2 em espécimes de gastrectomia do Laboratório de Patologia e Citologia do Instituto Santa Casa de Misericórdia de Porto Alegre entre 2002-2007.

Material e Métodos:

A pesquisa consistiu de análise das lâminas e amostras de tecido fixados em parafina, submetidos à reação imunohistoquímica automatizada com o anticorpo monoclonal (4B5), análise microscópica convencional (óptica) utilizando-se os critérios do Colégio Americano de Patologia (CAP).

Resultados:

Do total de 47 amostras selecionadas, 06 (12,8%) localizavam-se no cárdia; 23 (48,9%) no antro gástrico, 10 (21,3%) no corpo, 04 (8,5%) no piloro, 02 (4,3%) no fundo e 02 (4,3%) difusamente.

A idade média ao diagnóstico foi 63,04 anos (32- 98 anos), com prevalência no sexo masculino 32 (68,1%) dos casos e média do maior eixo tumoral de 5,2 cm (1,2-19,0cm).

Quanto à superexpressão do HER-2, 14 (29,8%) de todas as neoplasias analisadas apresentaram superexpressão do HER-2, com 13 (41,93%) dos adenocarcinomas de tipo intestinal apresentando superexpressão, seguidos por 01 (11,1%) do difuso e nenhum do tipo misto.

Não foram encontradas associação entre o número de linfonodos metastáticos e o maior eixo tumoral com a superexpressão do HER-2.

Conclusão:

Adenocarcinomas gástricos e da junção esôfago-gástrica de subtipo intestinal apresentam uma maior chance de superexpressão do gene HER-2. A incorporação do conhecimento do perfil da expressão dos proto-oncogenes da família dos receptores de fator de crescimento epidérmico humano (HER-2, HER-3, EGFR) podem e devem trazer mudanças no tratamento das neoplasias gástricas e junção esôfago-gástrica.

Palavras-chave

Estômago; junção esôfago-gástrica; adenocarcinoma; HER-2; Brasil

1. Introdução

1.1. Epidemiologia dos adenocarcinomas gástricos

Mundialmente, as neoplasias gástricas ainda respondem como segunda causa de morte relacionada ao câncer. No Brasil, as estatísticas estimam em 2014 cerca de 394450 novos casos de neoplasias malignas, excetuando-se as neoplasias de pele não melanoma. Destes, 20390 (5,16%) correspondem à estimativa para as neoplasias primárias gástricas (INCA, 2014).

Informações oficiais do DATASUS, o Brasil teve registro de 3993 óbitos relacionados às neoplasias gástricas, com 21980 internações e gasto total com as mesmas de mais de R\$ 56 milhões.

O tempo médio elevado de internação, o pico de incidência em uma faixa economicamente ativa da população, a baixa sobrevida e o conseqüente impacto econômico motivaram diversos estudos, sejam eles sobre o acréscimo à sobrevida geral garantido pelos diferentes esquemas quimioterápicos, sobre a qualidade da sobrevida e mesmo pelas suas repercussões com gastos de internações hospitalares.

A pesquisa da expressão do HER-2 em neoplasias que não os carcinomas mamários ainda é incipiente, mas há relatos de superexpressão identificada em tumores ovarianos, de glândula salivar, tireóide e mesmo bexiga, podendo ela futuramente impactar também no tratamento de outras neoplasias.

Atualmente a expressão amplificada do HER-2 é pré-requisito para a incorporação do Trastuzumab (Herceptin®) ao esquema quimioterápico, sendo preconizado e consolidado os benefícios de seu uso no tratamento dos

carcinomas de mama com superexpressão comprovada, sendo seu uso associado a um aumento significativo na sobrevida.

1.2. Tipos Histológicos dos adenocarcinomas gástricos

Baseado em sua origem no epitélio glandular, o adenocarcinoma possui duas classificações amplamente difundidas e utilizadas.

A classificação de Laurén, que leva em consideração a arquitetura glandular relacionada à semelhança com a metaplasia e displasia intestinal, estratificando-as nos dois grandes grupos intestinal e difuso (Lauren, 1965), com suas variáveis mista e não classificável posteriormente consideradas (Fenoglio-Preiser, 2000).

A classificação da OMS que subdivide os adenocarcinomas gástricos em padrão papilar, tubular, mucinoso e pouco coesivo (Bosman et al. 2010)

A classificação de Laurén tem seu destaque por separar as neoplasias gástricas em dois tipos com conhecidas e diferentes etiologias. Tumores com fenótipo intestinal estão mais relacionados a alterações decorrentes de efeitos ambientais, notadamente gastrite crônica e conseqüente metaplasia intestinal e posterior displasia. Já os tumores difusos carregam alterações genéticas germinativas cada vez mais conhecidas e específicas, com uma carga hereditária mais consistente.

1.3. O HER-2

O HER-2 é um oncogene da família das tirosina quinases primeiramente relacionado às neoplasias mamárias ainda durante estudos buscando fatores prognósticos e genéticos do câncer mamário na década de 80 (King, 1985).

Posteriormente, com a determinação do significado prognóstico da sua superexpressão e o desenvolvimento de drogas com intervenção em seu ciclo de proliferação celular, sua pesquisa tornou-se parte da rotina da pesquisa dos fatores prognósticos do câncer mamário (Gutierrez, 2010).

Os mecanismos de atividade do HER-2 integram-se complexamente em conhecidas 3 vias: uma via de membrana, na qual há transmissão de sinais vindos do ambiente extracelular; uma via intracelular de processamento de sinais das proteínas quinases ao núcleo e uma via regulatória de fatores de transcrição gênicos que coordenam várias funções celulares (Citri, 2006).

Imunoistoquimicamente a avaliação que se faz é a pesquisa da superexpressão da proteína HER-2 na membrana celular. Atualmente existem uma grande variedade de anticorpos comercializados, com apresentação monoclonal e policlonal. As duas formas mais difundidas são o HerceptTest (Dako, Glostrup, Denmark) e o anticorpo monoclonal de coelho HER2/*neu* (4B5) (Ventana Medical Systems, Inc, Tucson, Arizona).

Em células normais a proteína do HER-2 possui uma baixa expressão e sua expressão é qualificada de acordo com a intensidade da coloração da membrana das células neoplásicas, com o detalhe da coloração basolateral nas células neoplásicas gástricas.

A confirmação da amplificação do gene HER-2 pode ser feita por métodos moleculares, sendo disponíveis técnicas de SISH, FISH e CISH, todas elas com confirmadas reprodutibilidades (Arnould e cols., 2003); (Gupta e cols.; 2003); (Park e cols., 2003; Francis, 2009).

1.4. Estudos que associaram a quimioterapia convencional associada com Trastuzumab

Diferentemente de outras neoplasias, os esquemas quimioterápicos usuais para os adenocarcinomas gástricos não sofreram grandes mudanças nos últimos anos, sendo valorizada a possibilidade da terapia monoclonal associada à quimioterapia convencional como opção benéfica e que apresenta resultados positivos na literatura cada vez mais consistentes (Moelans e cols., 2011; Sbitti e cols., 2011; Dang e cols., 2012; Choda e cols., 2014).

Grandes estudos vêm sendo realizados em todo o mundo, buscando correlacionar a superexpressão do gene *HER-2/neu* (*Human Epidermal Growth Factor Receptor 2*) um proto-oncogene da família dos receptores de fator de crescimento epidérmico humano com o prognóstico e evolução natural do tumor, sem apresentarem, contudo, resultados suficientemente consistentes na literatura mundial.

Dang, 2012 observou pacientes com metástases hepáticas de adenocarcinoma gástricos, encontrando um pior prognóstico independente naqueles com HER-2 superexpresso.

O primeiro e maior ensaio clínico avaliando o uso do Trastuzumab, ToGA, mostrou resultados animadores em casos de neoplasias localmente avançadas e/ou metastática. A proporção de casos com superexpressão do HER-2 na população da Europa (23,6%), Asia (23,5%) e Japão (27,6%) mostraram-se similares (Bang, 2009). Seguindo essa linha, diversas outras análises foram e estão em andamento.

Tsuburaya (2009) e Boku (2009), estudando efeitos da quimioterapia neoadjuvante na população japonesa demonstraram um aumento significativo na sobrevida global, com taxas excedendo 1 ano. Nas análises ocidentais, observou-se uma média de 10 meses porém, significativamente maior que o uso da terapia convencional (Van Cutsem, 2006). Frente a isso, o uso de quimioterapia neoadjuvante com a associação do Trastuzumab tem sido proposto por alguns centros, já acumulando relatos de respostas satisfatória com a associação da terapia monoclonal (Sawaki, 2011; Sbitti, 2011).

Inui (2006) descreve um caso de desfecho animador em paciente idoso com neoplasia metastática para fígado que apresentou resposta terapêutica muito satisfatória à associação do anticorpo monoclonal, inclusive sem apresentar os sinais de toxicidade mais frequentes. Desfecho um pouco semelhante foi relatado por Choda (2014), no qual uma mulher de 77 anos com metástases hepáticas múltiplas e peritoniais, apresentando regressão tumoral satisfatória local e das metástases hepáticas após quimioterapia combinada. Diversos outros relatos vão se acumulando a cada dia, a maioria deles com resultados animadores em relação a possíveis mudanças no manejo das neoplasias glandulares gástricas.

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2. Objetivos

2.1. Objetivos gerais

Análise descritiva dos fatores idade, sexo, maior eixo tumoral, metástase linfonodal e classificação de Lauren dos adenocarcinomas gástricos e avaliar a expressão imunohistoquímica do HER-2 em espécimes cirúrgicos de gastrectomia do arquivo do Laboratório de Patologia e Citologia do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre entre os anos de 2002 a 2007.

2.2. Objetivos específicos

Buscar correlação dos achados epidemiológicos com a expressão imunohistoquímica do HER-2.

3. Artigo Científico Redigido em inglês

Immunohistochemistry expression of HER-2 in surgical specimens of gastrectomy and its correlation with pathological features.

Keywords: stomach; esophagogastric junction; adenocarcinoma; HER-2; Brazil

Abstract

Introduction:

Global statistics shows gastric malignancies as second leading cause of cancer-related death and of these adenocarcinomas are by far the most incidents.

The low efficacy of chemotherapy regimens motivates research forecasts and alternative therapeutic factors.

Objectives:

Descriptive analysis of age, gender, anatomic-pathologic features (most neoplastic axis, metastatic lymph nodes, degree of differentiation, Lauren classification and location of gastric adenocarcinoma and esophagogastric junction) and correlation with the immunohistochemical expression of HER-2 in surgical specimens of gastrectomy from Pathology and Cytology Laboratory of Santa Casa de Porto Alegre between 2002-2007.

Methods:

Performed a retrospective analysis of the slides and tissue samples fixed in paraffin. The selected cases and its best samples were subjected to automated Immunohistochemistry using monoclonal antibody (4B5) and further conventional microscopic analysis (optic).

The criteria adopted for characterizing the color of the cell membrane after immunohistochemical reaction will be the same recommended by the American College of Pathology

Results:

Of the 47 selected samples, 06 (12.8%) were located in the cardia; 23 (48.9%) in the antrum, 10 (21.3%) in the body 04 (8.5%) in the pylorus 02 (4.3%) at the bottom and 02 (4.3%) diffusely.

The average age at diagnosis was 63.04 years (32- 98 years), with prevalence among males 32 (68.1%) of cases and mean larger tumor axis of 5.2 cm (1,2-19,0cm).

There was HER-2 overexpression in 14 (29.8%) of all tumors examined; 13 (41.93%) of intestinal type adenocarcinomas showing overexpression, followed by 01 (11.1 %) of diffuse and no mixed type.

Conclusion:

Gastric and esophagogastric junction intestinal subtype adenocarcinomas have a higher chance of overexpression of HER-2 gene. Incorporating the knowledge of these profile, correlated with the prior knowledge of etiology and associated factors can bring better prognosis and changes in the treatment.

Introduction:

Worldwide, gastric cancer still respond as second leading cancer-related cause of death. In Brazil, the statistics estimate in 2014 about 394,450 new cases of malignancies, except for non-melanoma skin cancer. Of these, 20,390 (5.16%) correspond to the estimate for gastric primary neoplasms (INCA, 2014).

Currently, the amplified expression of HER-2 is a prerequisite for the incorporation of Trastuzumab (Herceptin®) to chemotherapy regimen, being promoted and consolidated the benefits of its use in the treatment of breast carcinomas with proven overexpression, and its use is associated with a significant increase in overall survival.

HER-2 is a tyrosine kinase oncogene first related to mammary tumors even for studies seeking prognostic and genetic factors of breast cancer in the 80 (King et al, 1985).

Later, with the determination of prognostic significance of their overexpression and drug development with intervention on your cell proliferation cycle, your search has become part of the routine search of prognostic factors of breast cancer (Gutierrez, 2010).

HER-2 activity mechanisms is complexly part in 3 known ways: one way membrane, which is no transmission of signals from the extracellular environment; via an intracellular signal processing of the core protein kinases, and a regulatory pathway gene transcription factors that coordinate various cellular functions (Citri, 2006).

Immunohistochemically, the evaluation consist to search the overexpression of HER-2 protein in the cell membrane. There are a variety of commercialized antibodies, monoclonal and polyclonal presentation. The two most widespread forms are HercepTest (Dako, Glostrup, Denmark) and rabbit monoclonal antibody HER2 / *neu* (4B5) (Ventana Medical Systems, Inc., Tucson, Arizona).

At normal cells, HER-2 protein has a low expression, and its expression is qualified according to the intensity of staining of the membrane of cancer cells, with the detail of the lateral or basolateral staining in gastric cancer cells.

Confirmation of amplification of the HER-2 gene can be made by molecular methods and techniques available SISH, FISH and CISH, all of which have confirmed

reproducibility (Arnould et al, 2003) (Gupta et al, 2003) (Park et al, 2003) and (Francis, 2009).

Large studies have been conducted around the world, trying to correlate the overexpression of HER-2 / *neu* gene (*Human Epidermal Growth Factor Receptor 2*) a proto-oncogene family of human epidermal growth factor receptor with prognosis and natural evolution of tumor, without showing, however, sufficiently consistent results in the literature.

Objectives:

To correlate the data from age, sex and pathologic features of gastric adenocarcinoma and esophagogastric junction with the immunohistochemical expression of HER-2 in surgical specimens of gastrectomy from Pathology and Cytology Laboratory of Santa Casa de Misericórdia de Porto Alegre between the years 2002 and 2007 in order to determine their expression status.

Methods:

This is a retrospective analysis study of the slides and tissue samples fixed in paraffin, from the Pathology and Cytology Laboratory of Santa Casa de Misericórdia de Porto Alegre.

Samples from products of partial or total gastrectomy with the pathological diagnosis of gastric adenocarcinoma and esophagogastric junction were included between the years 2002 and 2007.

From the samples were microscopically analyzed the histological classification according to the Laurén's criteria (intestinal, mixed or diffuse) and HER-2 expression in a tumor area after automated immunohistochemistry process.

Immunohistochemistry was prepared using rabbit monoclonal antibody HER2 / *neu* (4B5) and specific determinations of automated platform (Ventana Medical Systems, Inc.,

Tucson, Arizona). The information about sex, age at diagnosis and greater tumor axis were obtained from laboratory database.

Microscopic analysis was performed on histological sections with blades (3-4 μ m) filed tissue in paraffin, stained with hematoxylin and eosin and analyzed in two stages: only by the researcher and another time by the researcher along with your advisor - *expert* in order to determine whether or not case fill the study protocol, the degree of differentiation and Lauren classification. If there is disagreement in the analysis, a new joint analysis was performed at another time, trying to obtain a consensus between the parties.

After the selection of cases and their best samples, they were subjected to automated immunohistochemistry, followed by microscopic analysis (optical), following the same guidelines of the histological analysis.

The characterization of the staining of the cell membrane after immunohistochemistry followed the recommended parameters by the CAP:

- Negative (score 0): no reactivity or membranous reactivity in < 10% of cancer cells;
- Weak positive (score +1): faint or barely perceptible membranous reactivity in \geq 10% of cancer cells; cells are reactive only in part of their membrane;
- Positive intermediate (score +2): weak to moderate complete, basolateral or lateral membranous reactivity in >10% of tumor cells;
- Strong positive (score +3): strong complete, basolateral or lateral membranous reactivity in \geq 10% of cancer cells.

Neoplasms presenting overexpression of HER-2 in immunohistochemical evaluation should present a +3 score (strong positive). The other scores were considered as not overexpressed. Positive control was performed on each test individually, using a gastric cancer control with amplification previously confirmed by SISH.

All cases selected with the respective data were listed in mirror document and filed for analysis. There was no identification of patients or materials during the study or at its

conclusion.

Inclusion criteria

We included all patients diagnosed with gastric adenocarcinoma or esophagogastric junction of Pathology and Cytology Laboratory of the Hospital Santa Casa de Misericordia de Porto Alegre between 2002-2007.

Exclusion criteria

The study excluded patients with previous diagnosis of cancer of any other site registered in the laboratory database, in which samples were found significant autolysis of the sampled tissue (by analysis of histological slides stained with hematoxylin and eosin), samples that had some the paraffin blocks taken from the patient and laboratory samples with cracks or irregularities in the parafinized material which may have affected the tissue structures, compromising the result of immunohistochemistry.

Statistical analysis

The data were described and statistical analyzes performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

Quantitative variables were arranged in means, proportions, variances and absolute numbers by your relevance.

Qualitative associations of proportion as to whether or not overexpression of HER-2 and as tumors higher than 3.0 cm, higher than 5.0 and intestinal subtypes and non-intestinal were analyzed using Fisher's exact test and considered the statistical value of $p < 0.05$ to invalidate the null hypothesis.

Results:

Listed in the registry of Pathology and Cytology Laboratory of the Hospital Santa Casa de Misericórdia de Porto Alegre between the years 2002 to 2007, 102 cases of gastric and esophagogastric junction adenocarcinoma operated, of which 47 were selected for this study. The most cases exclusion factor was unsatisfactory fixation of surgical specimens.

The average age at diagnosis of cancer was 63.04 years (32- 98 years). Males had 32 (68.1%) cases and 17 female (31.9%) and the mean of larger tumor axis was 5.2 cm (1.2 to 19.0 cm).

As to tumor location, 06 (12.8%) were located in the cardia; 23 (48.9%) in the antrum, 10 (21.3%) in the body 04 (8.5%) in the pylorus, 02 (4.3%) at fundus and 02 (4.3%) diffusely.

The HER-2 status of tumors are summarized in Table 1 according to the Lauren classification, and of the total of gastric cancer and esophagogastric junction analyzed, 29.8% showed overexpression of HER-2.

Stratifying the findings based on Laurén's classification, 13 cases (41.93%) of intestinal type adenocarcinomas showed overexpression, followed by 01 (11.1%) of the diffuse and no mixed type presenting overexpression.

Comparing overexpression of HER-2 with the intestinal type, a positive correlation was observed ($p < 0.05$) between intestinal type and overexpression. When done with analysis of neoplasms superficial extension (greater than 3.0 cm or 5.0 cm and larger) correlation is not observed with overexpression of HER-2 ($p = 0.410$ and $p = 0.528$ respectively).

The lymph node status for the presence or absence of metastasis and correlation with overexpression of HER-2 also showed no association ($p = 0.204$).

Discussion:

Official information from DATASUS, Brazil, had record 3993 deaths related to gastric cancer, with 21,980 hospitalizations and total spend with them more than R\$ 56 million (over U\$ 21 million).

The research of HER-2 expression in cancers other than breast carcinomas is still incipient, but there are reports that identified overexpression in ovarian tumors of salivary gland, thyroid and even bladder, it may also impact the future treatment of other malignancies.

Based on its origin in the glandular epithelium, adenocarcinoma has two widely disseminated and used classifications. The Laurén's classification, which takes into account the glandular architecture related to the similarity to the intestinal metaplasia and dysplasia, stratifying them in two large intestinal and diffuse groups, with its mixed variables and unclassifiable subsequently considered.

WHO classification subdivides the gastric adenocarcinomas in standard papillary, tubular, mucinous and little cohesive.

The Lauren's classification has its highlighted by separate gastric cancer in two types of known and different etiologies. Tumors with intestinal phenotype are more related to changes due to environmental effects, especially chronic gastritis and intestinal metaplasia and consequent later dysplasia. Since diffuse tumors carry genetic alterations known and increasingly specific germ, with a more consistent heredity.

Unlike other cancers, the usual chemotherapy regimens for gastric adenocarcinomas have not undergone major changes in recent years, with the possibility of valued monoclonal therapy combined with conventional chemotherapy to be a beneficial option and shows positive results.

The first and largest clinical trial evaluating the use of Trastuzumab, ToGA, showed encouraging results in cases of locally advanced tumors and / or metastatic. The proportion of cases with overexpression of HER-2 in Europe's population (23.6%), Asia (23.5%) and Japan (27.6%) were similar (Bang, 2009). Following this line, several other analyzes have been and are ongoing.

Dang (2012) observed patients with liver metastases of gastric adenocarcinoma, finding a worse independent prognostic those with HER-2 overexpression. Tsuburaya (2009) and Boku (2009) studied effects of neoadjuvant chemotherapy in the Japanese population demonstrated a significant increase in overall survival, with rates exceeding one year. In the Western analysis showed an average 10-month however, significantly greater than the use of conventional therapy (Van Cutsem, 2006). Due to it, the use of neoadjuvant chemotherapy with the combination of trastuzumab has been proposed by some centers, already accumulating reports of satisfactory answers to the association of monoclonal therapy (Sawaki, 2011; Sbitti, 2011).

Inui (2006) describes a case of encouraging outcome in elderly patients with metastatic to the liver that showed very satisfactory therapeutic response to the association of monoclonal antibody, including without presenting the most frequent signs of toxicity. Somewhat similar outcome was reported by Choda (2014), in which a woman aged 77 with multiple liver metastases, and peritoneal, with satisfactory tumor regression and location of liver metastases after combination chemotherapy.

Analyzing the findings of the study, compared to the world stage of gastric tumors, we see general agreement with the findings relating to the distribution by sex, age and late diagnosis, the latter based on the large number of extensive tumors responsible for the intensity of the social impact that this diagnosis brings. It was observed also a tendency of similarities with the characteristics of the oriental populations in the histological question (Laurén subtypes) and, consequently, the immunophenotypic finding of HER-2. It must to the fact development mechanisms of cancer with intestinal differentiation have strong relationship with the eating habits of the population. Not that the cuisine of these populations are similar, but the sample population (Southern Brazil) has habits involving similar ingredients in its basic constitution, considerable amounts of protein, spices, sausages, and a diet low in fresh fruits and vegetables.

The sample selection process went through a bias to use old materials stored in paraffin at the expense of downtime and inoperability of obtaining the consent forms for use. Undesirable events experience were reduced by the use of immunohistochemistry

confirmed positive control on each slide and the exclusion of samples filled in the exclusion criteria.

Positively, the use of a complete histologic section from neoplastic material available on the paraffin block helped to lessen the possibility of an incorrect characterization of gene expression due to possible intratumoral heterogeneity. That is, the larger area covered neoplastic increases the possibility of an trully representation of the sample immunophenotype. Representation of this was the fact that mixed types of cancer (diffuse and intestinal), two of them presented indeterminate result (score 2+) and two others were negative (score 1+). Possibly the research by molecular methods could reveal that some of these cases were to be cancer with gene amplification of the HER-2 but with dubious and heterogeneous immunostaining.

The authors feel then that research HER-2 expression by immunohistochemistry in gastric cancer and esophagogastric junction, especially those with intestinal and mixed histological subtypes of Lauren has practical low technical and operational cost and answers an important question that can generate changes in therapeutic approach and even prognosis of affected people. The latter, prognosis, not by direct and independent association, but further limit the alternatives of chemotherapy regimens available.

Conclusion:

Epidemiologically, the study findings are consistent with previous investigations of Western countries, with a predominance of males, preferential distribution in the age group above 50 years and relatively extense tumors at diagnosis.

Overexpression of HER-2 demonstrably higher in intestinal type of Lauren, and your preferred location in the gastric antrum also corroborate findings from other studies.

Despite the different forms of histological characterization, to non-standard interpretations of immunohistochemical results and the presence of some contradictory results regarding the HER-2 in gastric cancer, the construction of knowledge about its importance and significance is developing good steps. Keeping up the search for answers

and associations, to improve the quality of life, the patient survival and dissemination of better diagnostic methods, the picture the treatment of gastric adenocarcinomas and esophagogastric junction takes is of good changes and better perspectives to those affected for such unwanted disease.

Fact of these changes was the suggestion of HER-2 survey in the patients by immunohistochemistry in the Brazilian Consensus of Gastric Cancer of 2013.

The authors emphasize that the determination of whether or not the monoclonal therapy combined with chemotherapy is the best choice go beyond simply determining the overexpression of the gene for tumor or its metastases. There are still involved important and also financial clinical factors that should be analyzed primarily within the context of the possibilities of society when it comes to public governmental actions. The authors also argue that knowledge should be consolidated each study; that it should be diffused, applied and given the access to all those who obtain conditions for such.

Competing interests: The authors declares not to have competing interests.

Provenance and peer review: Not commissioned; internally peer reviewed.

Table I - Histologic type of gastric adenocarcinomas and HER-2 expression

Lauren's type	Score 0	Score 1+	Score 2+	Score 3+	Total
Intestinal	12	3	3	14	32
Difuse	5	1	1	1	8
Mixed	0	2	2	0	4
Non classified	3	0	0	0	3
Total	20	6	6	15	47

Table II - Topography of gastric adenocarcinomas

Topography	Frequency	%
Cardia	6	12,8
Corpus	10	21,3
Antrun	23	48,9
Fundus	2	4,3
Difuse	2	4,3
Pyloro	4	8,5
Total	47	100,0

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A presente dissertação será enviada para o Brazilian Journal of Pathology
and Laboratory Medicine

Jornal Brasileiro de Patologia e Medicina Laboratorial (JBPML), a continuation of Jornal Brasileiro de Patologia, which is published bimonthly (February, April, June, August, October and December), is an official organ of Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial (SBPC/ML), Sociedade Brasileira de Patologia (SBP) and Sociedade Brasileira de Citopatologia, indexed at Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), at Periódica and at Chemical Abstracts. It is also a member of the Scientific Electronic Library Online (ScieELO) database. It is aimed at the publication of scientific papers that contribute to the development of Laboratory Medicine and it accepts the following text categories: original, review, and experimental articles; case reports, brief communications and letters to the editor. The papers may be submitted in Portuguese, English or Spanish.

Analysis of the articles

The received manuscript will be sent to at least two independent evaluators, well-known scientific pairs with expertise in the area discussed in the article. After their analysis, the chief editor of JBPML will contact the main author to inform the steps to be followed for publication or its ultimate rejection.

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Ethics

Studies carried out with human beings, including organs and/or isolated tissues as well as clinical records, must be according to the standards 196/96 of the National Health Council (<http://www.bioetica.ufrgs.br/res19696.htm>). Papers to be published shall be accompanied by the ethics committee certificate from the institution where research has been carried out, in accordance with the Helsinki Declaration, 1989 (<http://www.bioetica.ufrgs.br/helsin4.htm>). In the experimental investigations involving animals, the ethical principles of animal experiments stated by Colégio Brasileiro de Experimentação Animal (COBEA) and the standards established by the Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, Washington, DC, 1996) must be respected. The drugs and chemical substances used in the research must be precisely identified. Names or patient's initials, business names, companies and hospital records must not be used.

Abstracts and key words

Regardless of the language in which the article was written, there must be two abstracts: one in Portuguese and another one in English. The abstracts must identify the objectives, procedures and conclusions of the research (maximum of 250 words for original, review and update articles; and maximum of 100 words for case reports and brief communications). If the article is in Spanish, there should also be an abstract in Spanish. The key words, which represent the subject discussed in the article, must be within three to six, using controlled vocabulary Descritores em Ciências da Saúde (DeCS) of BIREME, with other terms when necessary. They must be presented in Portuguese and English. If the article is written in Spanish, the key words should also be in that language.

Structure of the text

Original articles

They are intended to report the original unpublished research results that may be replicated and generalized. The articles may have a maximum of 4 thousand words. The formal structure must follow the presentation structure of this kind of article: Introduction, Objectives, Material and Method, Results, Discussion, Conclusions and References. The use of subtitles is recommended, particularly in Discussion. Clinical implications and study limitations must be clearly stated. The

topic Material and Method should be thoroughly detailed. In these articles, the presentation of a structured abstract in Portuguese and English is required with the formal presentation of the article: Introduction, Objectives, Material and Method, Results, Discussion, Conclusions and References. The abstract in English must be preceded by the title in English. The references must be at the end of the text according to the following standards.

Brief communications

They are short reports that must present: 1) preliminary study data with suggestive findings that guarantee a more definite investigation; 2) replication studies; and 3) negative studies of important topics. These articles must have a maximum of 1,500 words, including non-structured abstract, one table or image at most, as well as the References.

Review articles

Review articles will be accepted by means of an invitation. They are systematized critical evaluation of the literature about a certain topic, which must state conclusions and have up to 5 thousand words. The organization of the article is up to the author, apart from Introduction, Discussion and Conclusion. A structured abstract of the text in its original language and another one in English are required. An extensive list of references must appear at the end of the text.

Update articles

They are descriptive and interpretative texts based on the recent literature about the global situation in which a certain topic is found. It must have a maximum of 3 thousand words. The structure of the text is decided by the author, but it must contain a non-structured abstract in the original language and another one in English, as well as the references.

Case reports

They are original clinical-laboratory observations followed by analysis and discussion. They must have up to 1,500 words. The structure must present at least the following topics: Introduction, Case reports, and Discussion. Include a non-structured abstract in the original language and another one in English.

Letters to the Editor

They are letters that aim at discussing the recent articles published in the magazine or reporting original research or relevant scientific findings. Brief letters with a maximum of 500 words (including bibliography, no tables and pictures) will be considered if the sentence "for publication" is explicit.

4. Considerações finais

Epidemiologicamente, os achados do estudo são concordantes com investigações prévias de países ocidentais, apresentando predileção pelo sexo masculino, distribuição preferencial na faixa etária acima dos 50 anos e neoplasias relativamente extensas ao diagnóstico.

A superexpressão do HER-2 comprovadamente maior nos tipos intestinal de Lauren, e sua localização preferencial no antro gástrico também corroboram achados de outros estudos.

Apesar das diferentes formas de caracterização histológica, da não uniformização das interpretações dos resultados imunoistoquímicos e da presença de alguns resultados contraditórios quanto ao HER-2 nas neoplasias gástricas, a construção do conhecimento sobre sua importância e significado está se desenvolvendo a bons passos. Mantendo-se a busca por respostas e associações, pela melhoria da qualidade de vida, pela sobrevivência dos pacientes e divulgação de métodos diagnósticos, o panorama que se vê ao tratamento dos adenocarcinomas gástricos e da junção gastroesofágica é de boas mudanças e melhores perspectivas aos acometidos por tão indesejada moléstia.

Fato comprovante dessas mudanças foi a sugestão da pesquisa do HER-2 em pacientes candidatos a quimioterapia no Consenso Brasileiro sobre Câncer Gástrico de 2013.

Os autores reforçam que a determinação do uso ou não da terapia monoclonal associada à quimioterapia vai além da simples determinação da superexpressão do gene pela neoplasia ou sua metástase. Estão envolvidos ainda fatores clínicos

importantes e também financeiros que devem ser analisados principalmente dentro do contexto das possibilidades da sociedade quando se trata de atuações publico-governamentais. Os autores ainda advogam que o conhecimento deve ser consolidado a cada estudo; que o mesmo deve ser difundido, aplicado e que seja proporcionado acesso a todos aqueles que obtiverem condições para tal.

5. Anexos

5.1. Parecer do Comitê de Ética da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA).

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CARACTERIZAÇÃO DA EXPRESSÃO IMUNOISTOQUÍMICA DO HER-2 (RECEPTOR 2 DO FATOR DE CRESCIMENTO EPIDÉRMICO HUMANO) EM ESPÉCIMES CIRÚRGICOS DE GASTRECTOMIA E SUA CORRELAÇÃO COM ASPECTOS ANÁTOMO-PATOLÓGICOS

Pesquisador: Claudio Galleano Zettler

Área Temática:

Versão: 3

CAAE: 18235413.0.3001.5345

Instituição Proponente: Irmandade da Santa Casa de Misericórdia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 621.468

Data da Relatoria: 17/04/2014

Apresentação do Projeto:

Trata-se de um projeto de mestrado em Patologia sobre a análise retrospectiva de lâminas e amostras de tecido fixados em parafina provenientes do Laboratório de Patologia e Citologia do Hospital Santa Rita do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre. O projeto já passou pelo CEP da Santa Casa com parecer aprovado.

Objetivo da Pesquisa:

Correlacionar os tipos histológicos (intestinal, misto, difuso e células em anel de sinete) e o grau de diferenciação (bem diferenciado, moderadamente e pouco diferenciado) dos adenocarcinomas gástricos com a expressão/supereexpressão da proteína transmembrana HER2.

Relacionar os tipos histológicos (intestinal, misto, difuso e células em anel de sinete) e grau de diferenciação (bem diferenciado, moderadamente ou

pouco diferenciado) dos adenocarcinomas gástricos com os fatores sexo e idade no período de 2002 a 2007. Correlacionar os fatores sexo e idade com a expressão ou supereexpressão da proteína transmembrana HER2 através de reação imunoistoquímica automatizada em uma amostra de cada caso selecionado.

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Bairro:

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Município: PORTO ALEGRE

Telefone: (513)303 -8804

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Continuação do Parecer: 621.468

Avaliação dos Riscos e Benefícios:

Não há riscos envolvidos. Os benefícios relacionam-se ao avanço das possibilidades de tratamento de neoplasias gástricas.

Comentários e Considerações sobre a Pesquisa:

Projeto com embasamento teórico apropriado e metodologia adequada.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta aprovação do CEP da Instituição proponente. Não apresenta: Folha de rosto; Folha de encaminhamento CEP-UFCSPA; Termo de compromisso de entrega de relatório; Lattes da equipe.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

Verificar a documentação exigida pelo CEP-CEUA.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Término do projeto 08/2014.

PORTO ALEGRE, 22 de Abril de 2014

Assinador por:
José Geraldo Vernet Taborda
(Coordenador)

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5.2. Parecer do Comitê de Ética da Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCOMPA).

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CARACTERIZAÇÃO DA EXPRESSÃO IMUNOISTOQUÍMICA DO HER-2 (RECEPTOR 2 DO FATOR DE CRESCIMENTO EPIDÉRMICO HUMANO) EM ESPÉCIMES CIRÚRGICOS DE GASTRECTOMIA E SUA CORRELAÇÃO COM ASPECTOS ANÁTOMO-PATOLÓGICOS

Pesquisador: Claudio Galleano Zettler

Área Temática:

Versão: 3

CAAE: 18235413.0.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericórdia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 546.258

Data da Relatoria: 05/03/2014

Apresentação do Projeto:

Descrita e aprovada conforme parecer substanciado.

Objetivo da Pesquisa:

De acordo.

Avaliação dos Riscos e Benefícios:

De acordo.

Comentários e Considerações sobre a Pesquisa:

Pesquisa aprovada por este CEP.

Considerações sobre os Termos de apresentação obrigatória:

De acordo.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

Foi solicitada a alteração da área temática pela CONEP, solicitação atendida pelo pesquisador. Portanto, o projeto de pesquisa segue aprovado por este CEP.

Endereço: R. Profº Annes Dias, 285 Hosp. Dom Vicente Scherer

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IRMANDADE DA SANTA CASA
DE MISERICORDIA DE PORTO
ALEGRE - ISCMPA



Continuação do Parecer: 546.258

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Após avaliação das alterações efetuadas no estudo acima descrito, o presente Comitê não encontrou óbices quanto à implementação das mesmas.

PORTO ALEGRE, 05 de Março de 2014

Assinador por:
Claudio Teloken
(Coordenador)

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