

Original Research Article

Relationship of expression of HER 2 protein according to histological type tumors by lauren in gastric cancer

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ABSTRACT

Background: Gastric cancer, by the definition of World Health Organization (WHO), is a malignant epithelial tumor of mucosa of the stomach with glandular differentiation. Objective of this Scientific paper was to maintain the relation of expression of HER2 protein and histological type of cancer according to Lauren in gastric cancer.

Methods: In this research, archival samples of tissues of gastric cancer are used from 60 patients that have been obtained after subtotal or total Gastrectomy with a regional lymphadenectomy of lymph nodes. The most representative tissue samples of gastric cancer tissues are selected by the standard hematoxylin-eosin staining method which are cut again by using a microtome and treated by immunohistochemical technique with antibody on the HER2 according to the protocol of the producer and then evaluated by light-microscopic and again evaluated by a modified system of scoring the HER2 positivity of surgical resections. In the data processing, descriptive statistics and nonparametric test of significance respectively. Chi square test and one sample T-test, and also correlation tests respectively Pearson test of correlation.

Results: Statistical analysis of expression of HER2 protein according to histological type of gastric cancer done by chi-square test, does not show significant relation between these two variables ($\chi^2=4,900$). Analysis by using one sample T-test does not show statistical significance ($t=1.1880$), and analysis by using Pearson test of correlation shows negative correlation that is not statistically significant ($r=-0.029$) between these two tested parameters.

Conclusions: Expression of HER2 protein by using an univariate statistical method according to Pearson has shown a negligible negative correlation without statistical significance according to histological type by Lauren.

Keywords: Correlation, Gastric cancer, HER2, Histological type, Lauren

INTRODUCTION

Gastric cancer, by the definition of World Health Organization (WHO), is a malignant epithelial tumor of mucosa of the stomach with glandular differentiation. It is one of the most common tumors and the second leading cause of death of cancer in the world although its incidence has been declining, especially in developed countries, since the 20th century.¹ The incidence of gastric cancer largely depends on the geographic area. It is very common in countries of the Far East, Asian countries of

the former Soviet Union, East-European countries and South Africa. The largest incidence of this type of cancer is in Japan where the number is 80/100,000 inhabitants per year with approximately 100,000 new cases per year and it is eight to ten times more than in West Europe where the number is 10 to 15 new cases per 100,000 inhabitants per year.² The assessment of the stage of cancer is based on basic principles of growth and spreading of cancer. In the beginning phase of the cancer growth it is spreading in the organ where it originated and with the further growth it can directly spread in the

neighboring organs. During the growth of the cancer, cancer cells enter into blood and lymph vessels and then they spread (metastatize) into the lymph nodes and distant organs. Because of that, the most common elements that are used in assessment of tumor stage are as following:

- tumor location in the stomach (there is a special scheme that is used for the assessment of tumor expansion),
- depth of tumor invasion in the wall of the stomach,
- presence of the tumor in lymph nodes and number of affected lymph nodes,
- presence of distant metastases

In the analysis of gastric adenocarcinoma, with the determination of hystological type by Lauren and macroscopic type by Borrmann. It is essential to determine the degree of differentiation and the Goseki grade.³ Hystologically, the best way to classify gastric cancer is by using the current hystological division of gastric adenocarcinoma by Lauren as an intestinal or diffused type and a mixed or unclassified type. The intestinal variant is made of malignant cells which produce neoplastic intestinal lymphs which look like structures that can be seen in colon adenocarcinoma. The diffused variant are made of cells that excrete mucus of gastric type and usually do not create glands. They mostly infiltrate the mucus and the wall in the form of individual signet ring cells or small clusters that corresponds to infiltrative“ type of growth.⁴

Molecular prognostic parameters

Excessive experssion of c-erbB-2 protein in gastric cancer (which appears in approximately 20% of cases of cancer) has shown itself as an indicator of poor prognosis of gastric cancer.⁵ However, these cases of cancer can react conveniently with the combination of chemotherapy and trastuzumab (targeted therapy).⁶

Mentioning protein p53, in one series of research in England and second series of research in Portugal, gastric cancers that express the product of gene TP53 are related with reduced survival rate, but in the research series in Germany such relation is not confirmed.⁷⁻¹⁰ Likewise, increased levels of immunohistochemical detection of cathepsin D are related to poor survival rate of gastric cancer.¹¹ In the same way established, increased experssion of cathepsin B and cathepsin L are related to greater propensity for tumor invasion and metastase.¹²

Proved immunohistochemical detection of Cyclin-dependent kinase p27 Kip1 is an indicator of decreased survival rate suffering from gastric cancer.¹³ Preliminary studies show that loss of FHIT protein respectively Bis (5-adenosyl)-triphosphatase is an indicator of poor prognosis of gastric cancer.¹⁴ Expression of T-antigen as a blood precursor of MN system allegedly correlates to the invasion depth and propensity to metastasis of gastric

cancer in distant organs.¹⁵ EBV- positive gastric cancers have better prognosis, probably because of the relation to propensity of activated cytotoxic T-cell infiltrate.^{16,17}

HER2 is a transmembrane glycoprotein essential for transmitting signals of growth factors. HER2 experssion is aslo found in cancer of the colon, bladder, ovary, endometrium, lungs, cervix, head and neck region, esophagus and gastric cancer. Overexpression correlates with clinical outcome, providing poor prognosis, and also presents a predictive factor of a poor result on chemotherapy and endocrine therapy. The largest value of determining the HER2 status is in predicting of response on the therapy HerceptinR-Trastuzumab (HERCEPTIN F. Hoffmann-La Roche Ltd, Basel, Switzerland and Genetech, Inc., South San Francisco, CA), in sense that effectiveness of anti-HER2 therapy correlates with the degree of HER2 positivity, and the Herceptin therapy caused a revolution in treatment of breast cancer.¹⁸⁻²⁰

TNM classification is for now the most important predicting factor for gastric cancer. However, prognosis of different patients with same stage of cancer is not same. Therefore, it is essential, with TNM classification and typical pathological tumor characteristics, to identify biological predicting factors that are usually derived from genetic processes and for which it is considered that they present the crucial step in predicting gastric cancer.

There are opinions that experssion of HER2 has a crucial role in the development of gastric cancer in its progress as well as in metastase. However, little is known about its expression, because research on this topic is limited in the world.²¹ Considering that the largest number of gastric cancer, nowadays, unfortunately, is diagnosed in advanced stage of the disease. It is still not clear if experssion of HER2 protein in this cancer is in relation to some proven predicting factors, and if it can have some potential role on predicting diseases and eventually give directions for therapeutical treatment.

The objective of this research was to determine correlation of experssion of HER2 protein to histological type of tumor by Lauren in gastric cancer.

METHODS

Research that has been done and presented in this study presents the base type of research with an observational method of collecting data that was used in the study.

Data

In this study archive samples of gastric cancer tissues are used and obtained from 60 patients after subtotal and total gastrectomy with regional lymphadenectomy of lymph nodes. Lymph nodes containing adipose tissue display a small and large curvature of the stomach and lymph nodes of the region Tripus celiac and region of

hepatoduodenal ligaments. Pathohistological diagnosis of all samples of gastric cancer that are involved in this study were done at the Department of Pathology at General Hospital Travnik from the beginning of 2010 to the end of 2012. The requirement of the samples in this study is that the patients should have operable tumors with a known status of regional lymph nodes and without evident dissemination in the time of diagnosis. The 60 samples of normal gastric tissue are used as a control group. In the prospective Pathohistological profile of HER2 of amplified gastric cancer is constructed on the basis of retrospective study which was applied in the selection of HER2 protein. To the data related to clinical-pathologic parameter of histologic type of tumor by Lauren of primary tumor came with individual microscopic observation of samples of gastric cancer tissues.

Methods

Pathohistological processing of biopsic data obtained from subtotal and total gastrectomy with regional lymphadenectomy presupposed taking samples of tissues by dissection rules and their standard histochemical process initially in hematoxylin-eosin staining methods as well as special histochemical staining method PAS (periodic acid schiff) for mucin. Microscopic interpretation with these methods of stained tissue samples is obtained from a clinical-pathologic parameter: histologic type of tumor by Lauren. In further procedures, the most representative tissue samples of gastric cancer tissues that are embedded in paraffin blocks are re-cut on the microtome and immunohistochemically stained and treated with antibody to antibody on HER2 according to the protocol of the producer. Finally, light-microscopy evaluated and evaluated by a modified system of scoring HER2 positivity of obtained surgical resection samples.

Scoring guide for Hercep test in gastric cancer

Compliance tests or the validity of results between immunohistochemical staining and in situ hybridization pre-ToGA studies, have shown that HER2 IHC test is suitable for gastric cancer cell staining but there appeared to be some differences in relation with the breast cancer, and some changes in the system of scoring for gastric cancer were required. Pre-ToGA and ToGA (Trastuzumab for Gastric Cancer) studies have shown that for the samples of gastric cancer it is required to use a modified system of scoring HER2 positivity.

Statistical analysis of data

After the microscopic analysis of data, the obtained data was entered in MS Excel 2007. We transported the stored data to the software toll SPSS 16.0 for statistical analysis. For data analysis, descriptive statistics was used, nonparameter test of significance, in fact Chi square test and One sample T-test, as well as tests of correlation as the Pearson test of correlation.

RESULTS

After analyzing the histologic type of cancer tissue samples of the experimental group by Lauren, 29 samples or 48.3% of the total number of samples were intestinal type, then 14 samples were diffused type which is 23.3% of the total number of samples of the experimental group, and the remaining 17 samples or 28.4% of the total number of samples of experimental group were mixed type by Lauren, what is numerically presented in the Figure 1.

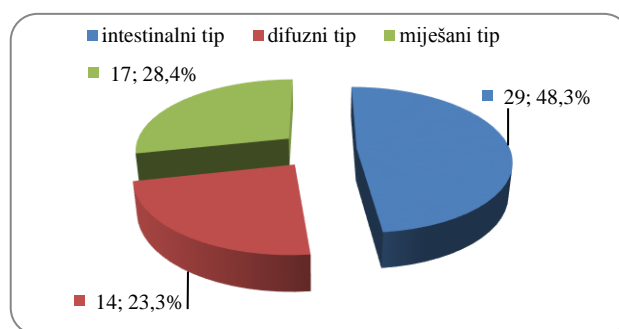


Figure 1: Structure of histologic type of cancer tissues samples of experimental group by Lauren.

After processing and analysing the characteristics of histologic type by Lauren of cancer samples tested on group of patients, immunohistochemical staining is performed and analysis of all samples of experimental and control group of samples. With the performed immunohistochemical analysis of application of herceptest on experimental group of biopsic samples of gastric cancer results are obtained that show that the largest number of gastric cancer shows HER2 negative immunoreactivity, in fact, that the largest number of gastric cancer did not show immunoreactivity in the expression of HER2 protein, and that total from the total of 60 samples, experimental group contains 36 of them, that means that 60% has shown that HER2 negative immunoreactivity (Figure 2).

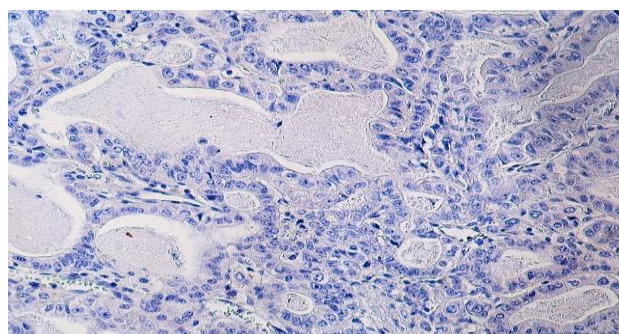


Figure 2: Negative immunoreactivity on HER2 protein (0).

Further, poor or barely visible membrane activity, from which some are just in parts of cell membrane of cancer cells has shown that total 9 samples, in fact 15% from the

total number of samples of experimental group (Figure 3). Ambiguous membrane activity has shown that 8 samples of experimental group or 13.33% of total number of samples of experimental group (Figure 4.) and these samples in further research should be re-tested by the in-situ hybridization method in light-microscopic field (CISH).

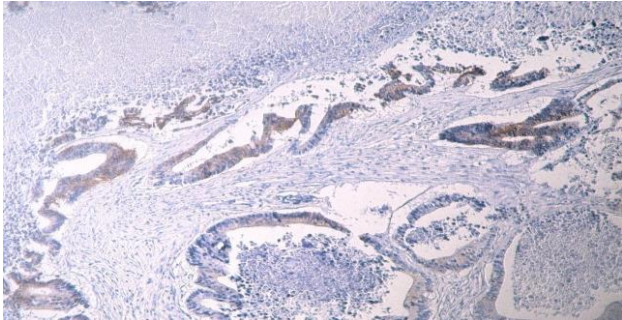


Figure 3: Por HER2 expression (+) (40x), (x40).

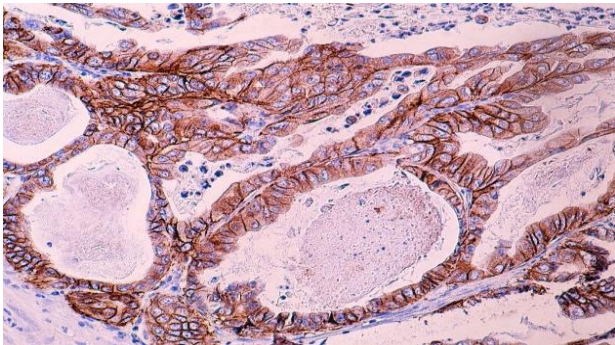


Figure 4: Ambiguous HER2 Positivity (++), (40x).

And on the end, what is most important and because of what the research was conducted, hyperreactivity or basolateral membrane reactivity on expression of HER2 protein has been shown by 7 samples or 11.6% of total number of samples of experimental group (Figure 5).

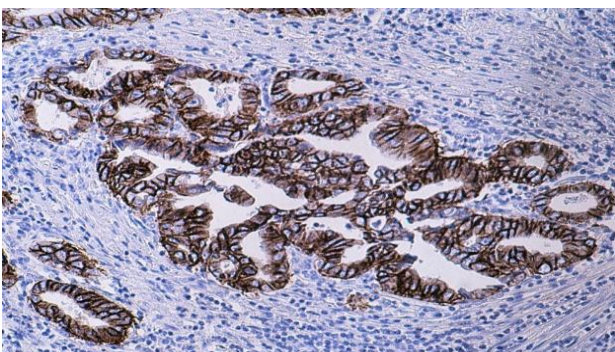


Figure 5: Strng expression of HER2 protein hyperreactivity in expression of HER2 protein (40x).

One sample has shown apical membrane activity, without evident basolateral or lateral membrane activity in expression of HER2 protein and that sample has been

considered as a sample with HER2 negative immunoreactivity (Figure 6).

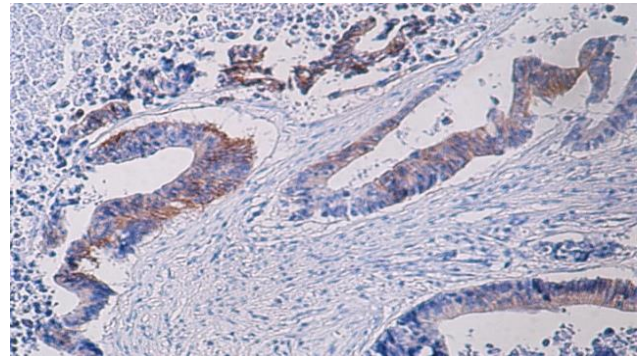


Figure 6: Apical membrane activity in expression of HER2 protein (40x).

All samples of control group samples which presented samples of histologic regular stomach have shown the HER2 negative immunoreactivity (Figure 7).

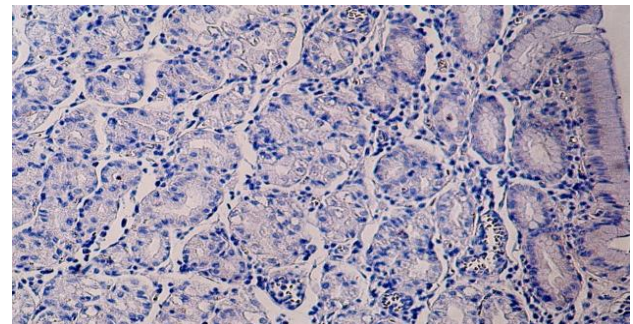


Figure 7: Negative expression of HER2 protein in control samples (40x).

Observing the histological type of gastric cancer of experimental group by Lauren, it is evident that there is almost equal representation of all types in the group, so 29 samples were intestinal type, 14 samples were diffused type and 17 samples were mixed type. By testing the membrane reactivity in expression of HER2 protein it came to the result that the largest number of samples with hyperreactivity were intestinal type, exactly 5 of them or 8.3% of the total number of samples of experimental group.

From the rest 2 samples with hyperreactivity, 1 sample or 1.7% of total number of samples of experimental group was mixed type, and what is generally a rare finding is that 1 sample of diffused type by Lauren has shown hyperreactivity in expression of HER2 protein. Ambiguous membrane immunoreactivity has been shown in almost equal relation in all three types by Lauren, so that kind of reactivity has been shown by 3 samples of intestinal and 3 samples of mixed type or 5% of total number of samples of experimental group and 2 samples of diffuse type or 3.3% of total number of samples of experimental group, what is numerically presented in the

Figure 8 (a), (b). All samples of the control group were without defined histological type by Lauren and all were without membrane immunoreactivity in expression of HER2 protein.

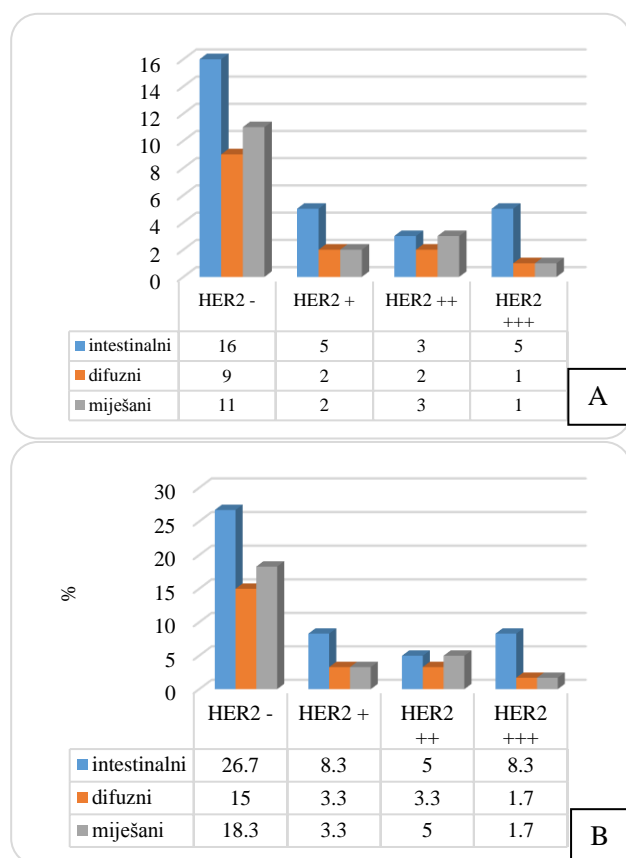


Figure 8 (a) (b): Expression of HER2 protein in relation to histologic type of gastric cancer by Lauren of the tested group.

Statistical analysis of expression of HER2 protein by histologic type of gastric cancer is done by the help of chi-square test does not show statistical significant relation between these two variables ($\chi^2=4.900$; there is a statistical significance relation if $p<0.05$), analysis by sample T-test does not show statistical significant differences ($t=1.880$; difference is not statistical significant if $p>0.05$), and the analysis by Pearson test of correlation shows negative correlation which is not statistically significant ($r=-0.029$) between these two parameters.

DISCUSSION

Research that was conducted had an objective to qualitatively and quantitatively determine the eventual expression of HER2 protein in gastric cancer and testing correlation of expression of HER2 protein with tested clinical-pathologic parameter of gastric cancer or histological type of tumor by Lauren. Before the discussion about the main objectives of this research, We need to discuss the basic characteristics or the clinical-

pathologic parameter of experimental group of research. Analysing the histological group of cancer sample types of experimental group by Lauren, it was found out that 29 samples or 48.3% of total number of samples were intestinal type, then 14 samples or 23.3% of the total number of samples of experimental group were diffused type, and the rest of 17 samples or 28.4% of total number of samples of experimental group were mixed type by Lauren.

By testing membrane reactivity in expression of HER2 protein findings showed that the largest number of cancer samples with hyperreactivity of HER2 protein was intestinal type, exactly 5 of them or 8.3% of total number of samples of experimental group. From the remaining samples, 2 were hyperreactivity, 1 sample was mixed type or 1.7% of total number of samples of experimental group. What is generally a rare finding being that 1 sample of diffused type by Lauren has shown hyperreactivity in expression of HER2 protein. Ambiguous membrane immunoreactivity has been shown in almost equal relation in all three types by Lauren, so that kind of reactivity has been shown by 3 samples of intestinal and 3 samples of mixed type or 5% of total number of samples of experimental group and 2 samples of diffuse type or 3.3% of total number of samples of experimental group. Poor membrane activity in expression of HER2 protein had 5 samples of cancer that was intestinal type or 8.3% of the total number of samples, and 2 samples of diffuse and 2 samples of mixed type of cancer what is 3.3% of total number of samples of experimental group. On the other side, the largest number of samples has shown negative HER2 immunoreactivity, so a reaction such this one had 16 samples of intestinal type of cancer which is 15% of total number of samples and 11 samples of mixed type of cancer or 18.3% of total number of samples of experimental group. Statistical analysis of expression of HER2 protein by histological type of gastric cancer was done by chi-square test that did not show statistically significant relation between these two variables ($\chi^2=4.900$; there is statistical significant relation if $p<0.05$), analysis by sample T-test does not show a statistically significant difference ($t=1.880$; difference is not statistically significant if $p>0.05$), and the analysis by Pearson test of correlation shows negative correlation which is not statistically significant ($r=-0.029$) between these two parameters.

In the largest study ever done on this topic that was conducted by Guan Zhen Yu et al, the frequency of expression of HER2 protein is significantly combined with the morphology of gastric cancer. According to Lauren, only the intestinal type of adenocarcinoma of stomach had HER2 positivity. Our study also shows that the largest number of gastric cancer samples with hyperexpression of HER2 protein do not belong to intestinal type by Lauren, but our study shows that the hyperexpression of HER2 protein does not belong exclusively to intestinal type of cancer, so this kind of

membrane activity in present study has been obtained and characterized into one sample of diffused cancer and one sample of mixed cancer by Lauren.

Expression of HER2 protein with an univariant statistical method by Pearson displayed a negligible negative correlation without statistical significance to the histological type by Lauren. Hyperexpression of HER2 protein was obtained with 71.43% of intestinal types of gastric cancer of all samples with hyperexpression of HER2 proteins, and which coincides with the percentage of samples which show hyperexpression of HER2 protein, which had pT3 stage. Similar to present results, Ferlay J et al in his study noticed that hyperexpression of HER2 protein was significantly present in intestinal type of cancer than in diffused or mixed type of cancer.²²

Also, the same results are obtained by Tanner et al after the study was done.²³ The high correlation between expression of HER2 and intestinal histological type of gastric cancer was reported by several authors.^{24,25} In a Finnish study, a strong expression of HER2 protein has been related to poor prognosis of gastric cancer that is specifically visible in the subgroup of intestinal type of cancer ($p=0.0019$), and what is considered to be more favorable in predicting than that of adenocarcinoma of stomach of diffuse type.²⁶ Gastric cancers of intestinal type have also shown higher rates of expression of HER2 protein than gastric cancer of diffused type ($p<0,05$) in one Korean study.²⁷ In the published studies it is determined that proximal gastric cancers with intestinal phenotype have higher existence of HER2 expression than distal diffused gastric cancers (Table 1).²⁸

Table 1: Results of different studies.

Author	Population	n	Histologic Type		
			Intestinal (%)	Diffuse (%)	Mixed (%)
Tanner	Finland	231	21.5	2	5
Gravalos	Spain	166	16	7	14
Lordick	International	1527	34	6	20
Matsubara	Japan	87	32.5	6	
Park	Korea	161	8	1	

Before it came to the knowledge of existence of prognostic factors on molecular level, clinical-pathological parameters were the only one known predictive and prognostic factors until then. To the recent proven prognostic variables belong the tumor stage, histological gradus, tumor size, localization, existence of lymphovascular invasion, age and gender of the patient, and molecular tumor markers p53, E-cadherin, CD-34, c-ErbB2, CA 72-4, CEA which recently gained popularity as potential prognostic indicators for predicting the tumor behavior.²⁹

CONCLUSION

Expression of HER2 protein by using an univariate statistical method according to Pearson has shown a negligible negative correlation without statistical significance according to histological type by Lauren.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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