

## Multimodal Treatment for Gastric Cancer

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## 1. Introduction

Gastric cancer was until the 1980s the most frequent diagnosed cancer all around the world, and it still remains even nowadays one of the most frequent and aggressive malignant tumors, having the power to cause annually an amazingly high number of deaths and affected people. Even if it went through some difficult phases for more 11 years, the stomach surgery managed to become today quite well defined even if it is not yet fully outlined.

During the last two decades a lot of impressive improvements took place in relation with the diagnosis and treatment of gastric cancer. The improved diagnosis methods can now assure a postoperative survival of over 5 years in 90% of the cases suffering of superficial gastric cancer. Moreover, in our present day's medicine has the possibility to control it very well or even cure it by choosing to apply the radical throughout the therapeutic window.

The treatment of gastric cancer has become in the last decades a complex and individualized one, starting to use a large variety of means and methods that are supposed to be combined and to succeed one another in different well-planned stages and phases. Given these conditions, it can be claimed that it is not only about one single treatment but about a whole therapeutic strategy which cannot be applied anymore by only one doctor as it requires the effort of a multidisciplinary collective, thinking and acting.

Different parameters: demographic, biological, morpho-pathological, and operative parameters were analyzed, the aim being that of emphasizing the possibility of administrating either a curative treatment or a palliative one, depending on the biological and imagistic

particularities of the patients diagnosed with primary gastric neoplasia, as per the results of the histopathological examination.

## 2. Equipment and Methods

Being subject of a retrospective analysis, the data obtained from the patients who went through a surgery was evaluated inside of the General Surgery Clinic II of the Timisoara County Emergency Clinical Hospital "Pius Brinzeu". The activity of data-processing and data-analysis took place between 01.01.2018-01.03.2020, and was performed on a batch of 163 patients, all suffering from different forms and type of gastric malignant tumors.

In order to obtain as accurate as possible data and for the results obtained to be as relevant as possible, at the general batch's level the following selection criteria was established:

- Patients with gastric malignant tumors (adenocarcinomas-ADK, gastrointestinal stromal tumor – GIST, gastric mixed neuroendocrine carcinoma -NEG);
- Patients with esophagogastric malignant junction tumors;
- Patients with gastric malignant tumors at the corporeo-fundic level;
- Patients with gastric malignant tumors identified in the antrax.

In addition to that, the following study methods were used: clinical observation charts, preclinical investigation, analysis of the operative protocols and analysis of the histopathology reports.

All the medical data was introduced in a database where the information was stored in tables created via Microsoft Excel program, the

2019 version. The correlation matrix was obtained with the help of the program Rapid Miner version 9.7, by using the Pearson correlation theory. The statistical significance of the results was also understood based on the value of the coefficient  $r$ . Therefore, there were already created two possible relations between the variables:

- A positive one: where variables are dependent on one another, and they follow the same direction for an  $r$  between 0 and 1. If the value of  $X$  increases then the value of  $Y$  does the same.
- A negative one: where variables follow different paths for the values of an  $r$  between 0 and -1. Therefore, if the value of  $X$  increases, then the value of  $Y$  is decreasing.

The Pearson correlation coefficient  $r$  between 0.7-1 means a strong and very strong correlation. Ranges between 0.5-0.69 determine a medium correlation while those between 0-0.49 are considered weak, respectively very weak correlations. The same interpretation applies to the negative values of  $r$  too.

### 3. Results

The general batch was made up of 163 patients diagnosed with gastric neoplasia, hospitalized between 2016-2019 at the General Surgery Clinic II of the Timisoara County Emergency Clinical Hospital "Pius Brinzeu". The patients had ages between 26 and 87 years old with an average age of 63 years at the moment of being diagnosed. Based on the patients' sex, the general batch was made up of 63.1% males and 39.6% females.

Patients' biological status was also analyzed. To be able to do that, some relevant data for the study was selected, such as preoperative and postoperative hemoglobin values as well as the preoperative albumin values. After performing a statistical correlation between the preoperative hemoglobin values and the re intervention range, it was obtained a Pearson correlation coefficient  $r = -0.547$  with a  $P < 0.05$  which emphasizes a moderate negative correlation statistically significant.

It could also be observed another statistical correlation between the preoperative hemoglobin values and the intervention time with an  $r = -0.530$  and  $P < 0.05$ . The same pattern was noticed between the postoperative serum levels of hemoglobin, re interventions, and the time duration of the re interventions, this being classified as moderate negative correlation statistically significant with an  $r_1 = -0.562$ ,  $r_2 = -0.541$  and a  $P < 0.05$ . The analysis of the correlations between the serum levels of the albumin and the number of interventions gave as a result a Pearson correlation coefficient  $r = -0.542$  and  $P < 0.05$ , being classified as moderate correlation statistically significant.

After performing an intraoperative and anatomopathological imagistic examination the cases were classified depending on the regions where the tumors were more frequent. Therefore, the majority of them were at the antrum level: 55% out of the whole general batch. The next affected region based on the frequency of the tumors was

the stomach: 32% and the regions with less frequency of the tumors were the cardia tuberosity region and the linitis plastica: 10% and respectively 3%.

On the other hand, based on the Borman classification, the most frequent tumors were proliferative tumors 61.2% and ulcerated tumors 24.3%. The infiltrative tumor, on the contrary, had a low percentage value of only 15.9% compared to the other forms.

According to the WHO classification 38.6% of the cases presented patched ring cell carcinoma. The next group presented tubular forms in proportion of 20.2%, while the mucinous carcinoma was evidenced in a proportion of 18.4%. The papillary and the tubulopapillary forms were less frequent with values of 7.9%, respectively 5.5%.

Moving further, according to the Lauren classification, gastric adenocarcinoma can be divided in 3 subtypes: intestinal, diffuse, and mixed. At the general batch level, the following proportions were registered: intestinal form – 69.9%, diffuse form – 10.4%, mixed form -14.1%. However, due to the extended variety of the tumors, 5.5% of the cases could not be classified in any of the previous three standard forms. It can be observed that the predominant type in the general batch was the intestinal form of gastric neoplasia.

Based on the tumors size, inside our study group 49.9% of the cases were T3, followed by T4 with a percentage value of 34.9%. A lower value out of the total number of the cases was represented by T1 and T2 tumor sizes, with a value of 4.2%, respectively 11.6%, those being represented by tumors at the muscle level. Patients with this later condition were in an incipient stage, therefore, without any metastasis and loco-regional dissemination, it made possible for the doctors to apply a multimodal treatment with curative purpose.

After achieving a correlation between the tumoral dimensions (pT) and the disease stage (TNM), the following Pearson correlation coefficient was obtained:  $r = 0.803$  with a  $P < 0.05$ , which is high significant from a statistical point of view.

By taking into consideration the primary tumor, the following correlations were also obtained:

- Primary tumor sizes (pT) and number of invaded lymph nodes,  $r = 0.430$
- Primary tumor sizes (pT) and tumoral degree,  $r = 0.424$
- Primary tumor sizes (pT) and lymphovascular invasion,  $r = 0.370$ .

The following chart aims to highlight the distribution of the patients according to the number of invaded lymph nodes. Inside the general batch, a significant value of 28.8% represents those patients that belong to the N1 group with a low number of humoral nodes [1-2]. This group is followed by the N0 one, which represents 28.2% of the general batch. These two aspects emphasize an increase of the patients' recovery chances.

The other two groups N2 and N3 had lower percentages of 23.3%

and 19.6%. All cases inside these two groups are characterized by the invasion of a high number of lymph nodes (<7 for N3 and between 3-6 for N2) and present a pathological stage above phase II.

Moving further with the study, it was considered useful to realize a correlation between the number of invaded lymph nodes (N) and the disease stages. The value of the Pearson correlation coefficient obtained was of 0.657% with  $P < 0.05$ , aspect that emphasizes the existence of a moderate correlation statistically significant.

Regarding the lymph vascular invasion, the majority of the patients of the study group presented an invasion inside the lymphatic and blood vessels that were in the nearest proximity to the primary tumoral affection. Over 74.2% of the cases were classified as LV1, thing that indicates a higher probability of having postoperative recurrence. On the other hand, only 25.7% of the patients received a histopathological result that was classified as LV0, this being also accompanied by a positive diagnosis.

From a tumor grade point of view, it could be observed, statistically, a high number of G3 cases (79 out of 160), while 48.4% reflected a lower range of tumor differentiation and a higher range of mitosis, followed by an accelerated tendency to spread. The result of the correlation between the tumor grade and the disease stage resulted an  $r = 0.555$  and  $P < 0.05$ , therefore in this case it was emphasized a correlation which was moderate positive statistically significant.

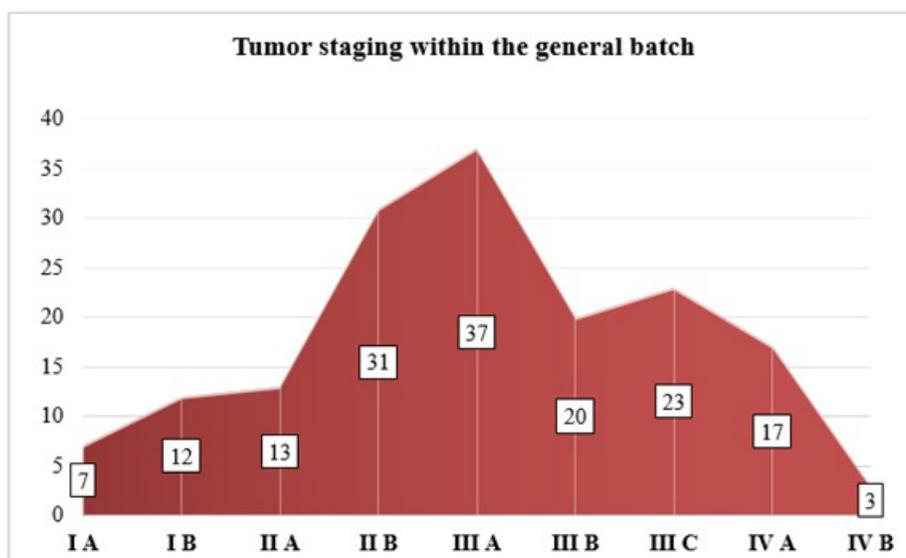
While performing a classification of the disease stages (Figure 1), it was noticed that a great number of cases (80%) fell under the medium and advanced stages, starting from IIb, IIIa, IIIb, IIIc, IVa up to IVb. It was also remarked the fact that “the peak of the iceberg”

were those patients in stage IIIa with lymphonodular metastasis (N1; N2; N3), thing that necessarily required a multimodal treatment to be applied (chemotherapy, radiotherapy, surgery). Out of 163 patients from the initial batch, only 7 were diagnosed in stage Ia, the equivalent of a percentage of 4.2%. This is thought to be the result of an endoscopic mucosal resection. On the other hand, 20 out of 163 patients were diagnosed in stage IV with distant metastasis and therefore needed palliative treatment (chemotherapy, immunotherapy, and/or surgery).

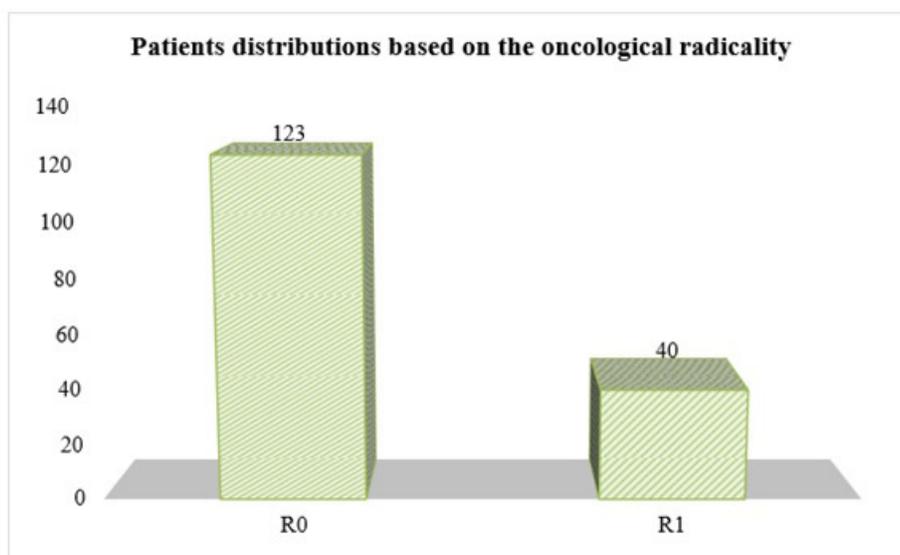
After analyzing and studying the data from the histopathology reports it was obtained a distribution of the patients according to the presence or absence of the remaining tissue on the resection sides of the retained piece (Figure 2). This aspect, which characterized most of the patients R0 - 75.4%, highlights the success of the operative procedure, all the pieces extracted lacking any tumoral leftovers on the tissues situated within the neoplasia proximity.

It was also observed, however in some cases a low percentage (24.5%) of neoplasia at the resection margins level. This is associated with a higher probability of local or distant recurrence and at the same time with a sadder diagnosis.

Based on the tumor cell biology, the mitotic index Ki-67 had within the general group of study a medium value of 39.57%, a minimum value of 10% and a maximum value of 80%. The lack of any correlation between the mitotic index Ki-67 and the tumor grading could be considered a unique particularity of this study, as it was in contradiction with the scholarly literature which demonstrated multiple correlations between these 2 parameters responsible for tumor biology [14].



**Figure 1:** Patients distribution based on the disease stage



**Figure 2:** Patients distribution based on the oncological radicality

Regarding the type of the surgical interventions performed (Figure 3), the most frequent one was the subtotal gastrectomy which was applied to 36.8% of the patients. As for the full gastrectomy, it was applied to 25.1% throughout the entire study period. In order to extract the proximal gastric neoplasia, 13.4% of patients needed superior polar gastrectomy, while the next most frequent interventions were as it follows: exploratory laparotomy – 10.4%, exploratory laparoscopy 8.5% and other procedures.

By analyzing the percentage of the curative interventions (75.4%) versus the percentage of the palliative interventions (24.5%) it can be remarked that the number of palliatives interventions was still significant. The goal from a surgery point of view, that of performing a radical surgery was achieved on a quite high percentage which, however, could still be perfectionated.

Throughout the study, the surgical teams have performed D3 lymphadenectomy in 4.2% of the cases, 62.5% have benefitted from a lymphadenectomy D1 and the 33.1% from D2 lymphadenectomy (Figure 4). As for the time duration of the surgical intervention, curative or palliative, the shortest intervention was of 146 minutes and the longest was of 254 minutes with an average of 199 minutes.

There was also performed an analysis of the postoperative complications. Therefore, for 9.2% of the cases an anastomotic fistula was noticed, other 3.6% of the cases went through bleeding complications and 2.4% were diagnosed with duodenal fistula.

It was also considered necessary to create some correlations between these complications and the number of re interventions needed. The result of this analysis was a Pearson correlation coefficient  $r = 0.839$  with  $P < 0.05$ , therefore highlighting a statistically high significant correlation.

Another correlation type was established between the postoperative

complications and the time of the re interventions with a Pearson correlation coefficient  $r = 0.784$  and  $P < 0.05$ , which was considered a statistically high significant correlation too. The third correlation was between the postoperative complications and the number of days the patients were hospitalized, obtaining an  $r = 0.527$  and a  $P < 0.05$ , which emphasizes a moderate positive correlation statistically significant.

The minimum number of hospitalization days for the patients diagnosed with gastric cancer, patients that went through a surgical intervention with either curative or palliative purpose was of 8 days, the maximum number was of 33 days and the average number of hospitalization days was of [13].

Another correlation was created between the hospitalization days and the need of re interventions which resulted in a Pearson coefficient  $r = 0.670$  and a  $P < 0.05$ , moderate correlation statistically significant. Along with an increase in the number of the hospitalization days it was observed an increase in the re intervention range this emphasizing the fact a direct proportional relation was built between these two criteria. In other words, the longer the intervention lasted, the longer the hospitalization period, and that is due to the necessity of providing additional and particular care to each individual case. For this correlation it was obtained an  $r = 0.696$  with a  $P < 0.05$ , value situated on a thin line between a medium statistical power ( $0.5 < r < 0.69$ ) and a higher one ( $r > 0.7$ ).

Moving even further, another analysis was performed with regards to the number of hospitalization days and the preoperative, respectively postoperative hemoglobin values. In this situation, the results highlighted a Pearson correlation coefficient  $r = -0.537$  for preoperative hemoglobin level and an  $r = -0.511$  for the postoperative one. Therefore, the correlation established between these two criteria was a moderate negative statistically significant one.

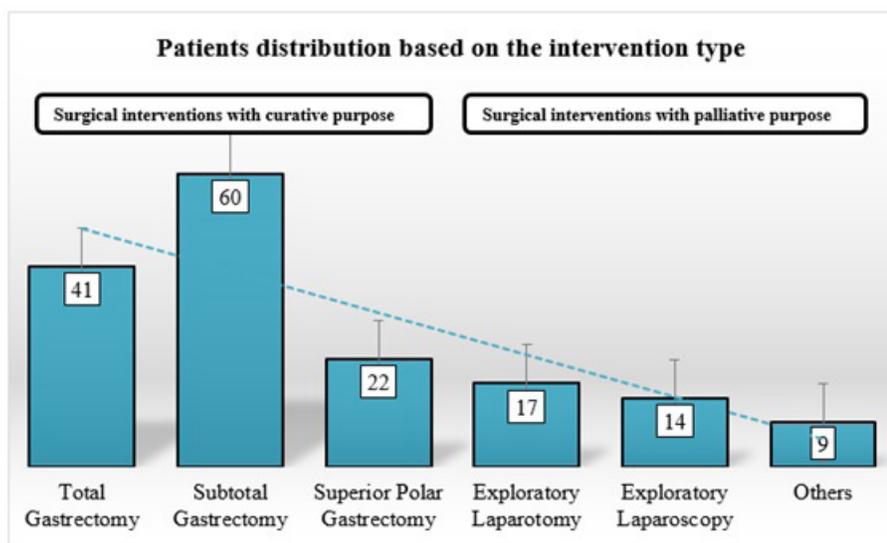


Figure 3: Patients distribution based on the intervention type

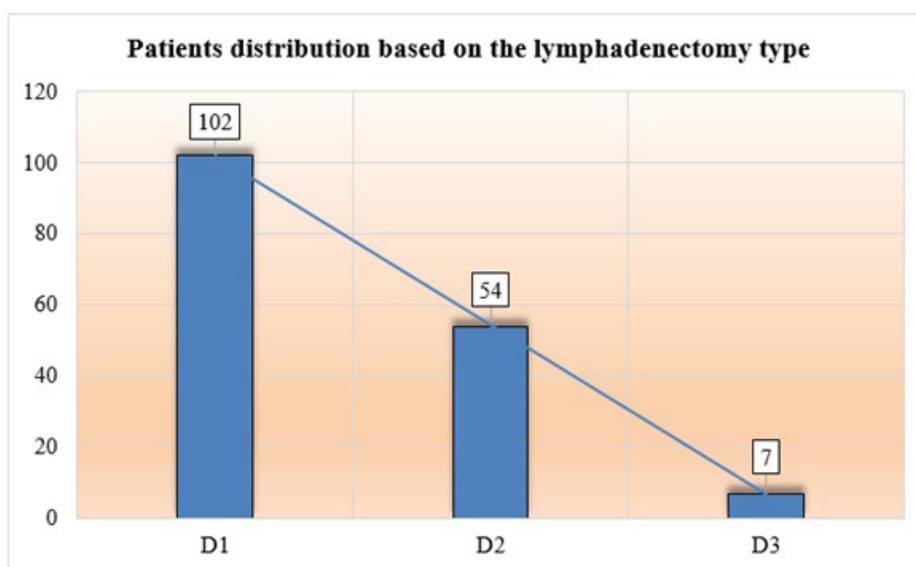


Figure 4: Surgical intervention structure based on the lymphadenectomy type performed

#### 4. Discussion

Gastric cancer is known to be a considerable health issue at the world level, and it represents one of the main death causes associated to cancer. In the USA, gastric malignant tumors are only 2% of the total number of the oncological cases reported annually compared to South Korea where things are totally different, this being on the top of the pyramid, leading the world nations with a value of 20.8%. A multi-centric study that had randomly evaluated the survival rate after 5 years from a subtotal gastrectomy versus 5 years from a total gastrectomy, concluded that there was remarked a better nutritional status and a more qualitative lifestyle in the case of the former one. Based on this study it was claimed that the procedure of subtotal gastrectomy should become the first chosen procedure, with the condition that the proximate margin to be attached to a healthy tissue.

Regarding this aspect, it can be observed that within our group of study the most frequent intervention with curative purpose was the subtotal gastrectomy [24].

One of the main aspects that could become subject to future studies and analysis would be the fact that the occurrence of postoperative complications could determine the progress of neoplasia. The results of the meta-analysis showed a few possible physio-pathological scenarios that could be the reasoning of this phenomena. For example: the trauma during a major surgical intervention could activate a certain range of systemic inflammatory response (SIRS), including the freedom of inflammatory or anti-inflammatory cytokines such as IL-1b, IL-6, TNF- $\alpha$ , IL-102 and TGF- $\beta$ , that could contribute to the overgrowth of the malignant cells and the advancement of the metastasis. Moreover, excessive catecholamine release could negatively affect the immune system, contribute to the advancement of

the metastasis and to the survival dropping rate.

## 5. Conclusions

As a first conclusion, this study aimed to offer, on one hand, an overall image on the main demographical, biological, morpho-pathological, and operative characteristics of the gastric cancer, and on the other hand it also aimed to highlight how different types of correlations were created between the analyzed criteria.

From the positioning point of view, many tumors were located at the gastric antrum level, their frequency decreasing from a distant to a proximal region. These were followed by those at the stomach level representing 33% of the total number, and only 10% were situated in the near proximity. This histopathologic pattern was predominant throughout the other group as well.

Patients registered with low values of hemoglobin and albumin tended to have a higher risk of dealing with postoperative complications, therefore going through re interventions in order to take care of them. The previously mentioned low values also have an impact on the time duration of the re intervention being able to increase them.

Additionally, the number of hospitalization days and the time duration of the re intervention have an indirectly proportional relation with the preoperative and postoperative hemoglobin values.

The stage of the disease was strongly influenced by the dimensions of the initial tumor (T) and slightly influenced by the number of lymph nodes and the tumor grading. Almost half of the cases (49.9%) were T3 tumors. Ki-67 index had various values, indicating different grading of cell overgrowth, while the average value throughout this batch was of 39.57%, value which indicates that the cell overgrowth had a moderate grading inside this group of study.

Regarding the surgical treatment performed, the most frequent intervention was the subtotal gastrectomy (36.8%) with a rate of 15.3% of postoperative complications whose number is correlated with the number of re interventions performed and the duration time for them. Hospitalization period was directly proportional with the complication rate, respectively the re intervention rate.

The high number of patients (75.5%) that went through a curative intervention are the real proof of the necessity of early diagnosis and the success of the medical methods used. However, there is still a percentage of 24.5% that went through a palliative intervention, this being because of the late diagnosis. In this case, the patients presented themselves tardily to the doctor when their tumors were already in an advanced phase. Therefore, it is very important to remember that in order to improve the results, early diagnosis is the best and should be seen as the main choice.

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