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ORIGINAL ARTICLE

Results of third-generation epirubicin/cisplatin/xeloda adjuvant chemotherapy in patients with radically resected gastric cancer

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Summary

Purpose: *The purpose of this study was to evaluate the efficacy and toxicity of a third-generation chemotherapy regimen in the adjuvant setting to radically operated patients with gastric cancer. This proposed new adjuvant regimen was also compared with a consecutive retrospective cohort of patients treated with the classic McDonald regimen.*

Methods: *Starting in 2006, a non-randomized prospective phase II study was conducted at the Institute of Oncology of Cluj-Napoca on 40 patients with stage IB–IV radically resected gastric adenocarcinoma. These patients were administered a chemotherapy regimen already considered to be standard treatment in the metastatic setting: ECX (epirubicin, cisplatin, xeloda) and were compared to a retrospective control group consisting of 54 patients, treated between 2001 and 2006 according to McDonald's trial.*

Results: *In a previous paper, we reported toxicities and the possible predictive factors for these toxicities; in the present article, we report on the results concerning predictive factors on overall survival (OS) and disease free survival (DFS). The proposed ECX treatment was not less effective than the standard suggested by McDonald's trial. Age was an independent prognostic factor in multivariate analysis. N3 stage was an independent prognostic factor for OS and DFS. N ratio >70% was an independent predictive factor for OS and locoregional disease control. The resection margins were independent prognostic factors for OS and DFS.*

Conclusion: *The proposed treatment is not less effective compared with the McDonald's trial. Age was an independent prognostic factor in multivariate analysis. N3 stage represented an independent prognostic factor and N ratio >70% was a predictive factor for OS and DFS. The resection margins were proven to be independent prognostic factors for OS and DFS.*

Key words: *adjuvant chemotherapy, ECX, gastric cancer, overall survival, predictive factors, toxicity*

Introduction

Given the late symptomatology and its moderate sensitivity to chemotherapy and radiotherapy, gastric cancer is one of the most difficult tumor sites to treat.

According to the latest estimations, its incidence places it among the first 5 tumor sites worldwide (after lung, breast and prostate cancer) [1]. More than 800,000 patients are diagnosed yearly worldwide, approximately 500,000 of whom will have died one year from diagnosis [2]. Gastric cancer ranks second in terms of mortality [3].

Surgical intervention is the only curative treatment in gastric cancer; there is a general consensus regarding its role in the improvement of overall results in this tumor site. Still, how much extensive, surgery does not manage to eliminate

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local relapse. Even in the case of a D2 dissection, the local relapse rate remains high: 5 years after, the risk of local relapse is estimated at 43% for D1 dissections and at 37% for D2 dissections in a Dutch trial [4]. Data provided by autopsy studies reveal even more alarming figures, of up to 80-93% [5]. The overall results concerning the treatment of gastric cancer remain poor in the USA, with 5-year survival rates of 20-30% [5].

The poor overall results in the treatment of gastric cancer convinced the oncological community (surgeons, radiotherapists, medical oncologists) to seek other routes to improve them. Neither adjuvant radiotherapy alone nor adjuvant chemotherapy alone were able to improve these results. Nevertheless, associating them changed the standard therapeutic attitude. In this respect, the largest and most significant study remains the US Intergroup 0116, which demonstrated survival benefit of adjuvant chemotherapy for the first time [6]. The benefit reported then was confirmed almost 10 years later - for all categories of patients, except for those with diffuse adenocarcinoma - in a presentation made at the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting [7].

The purpose of this study conducted at the Institute of Oncology "Prof. Dr. Ion Chiricuta" was to assess the potential benefit of a new postoperative chemotherapy administered to patients having undergone radical resection.

Methods

This was a phase II non-randomized prospective study conducted at the Institute of Oncology "Prof. Dr. Ion Chiricuta" and approved by the Institutional Review Board. All of the patients enrolled in the study required histological confirmation (endoscopic or postoperative) of gastric adenocarcinoma. Only those meeting the criteria for radical resection in accordance with the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines were selected [8]: dissection > D0, R0 or R1 resection. Prior to starting treatment, each patient was required to sign informed consent. Other inclusion criteria were: age >18 years; normal kidney, liver and heart function; normal complete blood count: leukocytes >3,000/mm^3, neutrophils >1,500/mm^3, thrombocytes >100,000/mm^3, hemoglobin >8g/dL; ECOG performance status (PS) 0,1 or 2; TNM stage IB – IV (M0).

Exclusion criteria were: cases unconfirmed histologically; R2 resection; PS >2; deterioration in kidney, liver and heart function; patient's refusal; cytologically-confirmed metastases/peritoneal carcinomatosis; second cancer 5 years from diagnosis, with the exception of basal cell carcinoma or in situ carcinoma of the cervix.

Treatment

The patients enrolled formed the study group – 40 subjects receiving the ECX regimen. In order to compare the ECX results, a control group consisting of 54 patients treated according to the McDonald's regimen [6] between 2001 and 2006 was also selected in a retrospective consecutive manner.

All study and control group patients received chemoradiotherapy according to the schedule and dosing of McDonald's trial [6]: 50.4 Gy with concomitant chemotherapy consisting of 5-fluorouracil (5-FU) (425 mg/m^2/day) and folinic acid (20 mg/m^2/day), 4 consecutive days at the beginning of radiotherapy and 3 consecutive days at the end of it.

The ECX adjuvant regimen was administered in the study group patients and consisted of epirubicin (50 mg/m^2/day 1), cisplatin (60 mg/m^2/day 1), and xeloda (capecitabine) (1,000/mg/m^2 bid, days 1-14) on 21-day cycles.

In the control group the adjuvant chemotherapy regimen included 5-FU (425 mg /m^2/day, days 1-5) and folinic acid (20 mg/m^2/ day, days 1-5) in 28-day cycles.

In both groups, the first cycle of adjuvant chemotherapy was administered before the start of chemoradiotherapy and 2 more cycles were administered postchemoradiotherapy.

Toxicity

Acute haematological and gastrointestinal toxicities were evaluated according to the CTC V3.0 scale.

Follow-up

The follow-up evaluation consisted of physical examination and of serological and imaging examinations such as chest x-rays and abdominal ultrasound or abdominal and pelvic CT scan at the beginning and the end of treatment, followed by repeat imaging every 3 months for 2 years, every 6 months for 3 years and annually after 5 years.

Survival

OS was calculated from the date of the surgical operation until the patients' death. DFS was calculated from the day of the first chemotherapy cycle until tumor progression (locoregional or metastatic) according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Statistics

For data analysis we used methods for descriptive and inferential statistics. For descriptive statistics we used frequencies tables (for qualitative variables), but also values of parameters of dispersion (standard deviation, range) and centrality (average, median value) for quantifiable variables were used.

Inferential statistics for qualitative variables in-

cluded the calculation of p value through x^2 or Fischer's exact test. A p value<0.05 was considered as statistically significant.

The dynamics of the evolution of different parameters were analyzed with the dynamic curves method. Our options were in favor of percentage recording of values, taken as 100% the initial value (first record of a value of the parameter).

Differences between subgroups were tested with the area under the curve test (AUC) for each subgroup, followed by the non parametric Mann-Whitney U test of the differences between values of the areas. We also investigated the possible correlations between the dynamics of the evolutions of two distinct parameters. This was done using the same percentage exprimation, reported to initial value, for having a uniform exprimation of the units of measurements of the two selected parameters. The testing process was Spearman's correlation coefficient with known interpretation levels:

-0.25 < R< 0.25 – weak correlation or none.

R between -0.5 till -0.25 or more than 0.25 to 0.5- acceptable correlation.

R between -0.7 till -0.5 or more than 0.5 to 0.7 - moderate correlation.

R between -1 till -0.75 or more than 0.75 to 1- good or very good correlation.

For certain numeric parameters we evaluated the prediction power by using receiver operating characteristics (ROC) with AUC (AUROC) calculation (95% CI) and their statistical significance. Global accuracy of each investigational parameter was doubled by the identification of cut-off value, but also by the calculation of sensitivity, specificity, positive and negative predictive values of the identificated value of the parameter.

For data analysis the SPSS 17.0 software (Chicago, Ill) was used. Also Microsoft Office Facility, Excel 2007 for constructing the dynamic curves was used. These curves were represented by using average values for each subgroup for all time intervals taken into considerations.

Results

Patient characteristics

The characteristics of the patients included in both groups were detailed in a previous article, which presented the toxicities encountered during treatment [9]. Several factors which might have a predictive role in the patients' response to treatment and the improvement of the results in connection to OS and DFS were studied. Table 1 shows the characteristics and Table 2 the toxicities reported during treatment.

Table 1. Main patient and disease characteristics

Characteristics	*Control group N (%)*	*Study group N (%)*
Number of patients	51	40
Sex (M/F)	32/19	27/13
Age (mean±SD)	56.4±9.5	55.0±11.0
Localisation of primary tumor		
Distal	24 (47.1)	15 (37.5)
Proximal	27 (52.9)	25 (62.5)
Grade of malignancy		
1	11 (21.6)	3 (7.5)
2	19 (37.3)	14 (35.0)
3	21 (41.2)	23 (57.5)
Histological type		
Intestinal	21 (41.2)	12 (30.0)
Difuse	30 (58.8)	19 (47. 5)
Mixed	0 (0.0)	6 (15.0)
Perineural invasion	21 (41.2)	3 (7.5)
Vascular invasion	13 (25.5)	9 (23.1)
Lymphatic invasion	12 (23.5)	9 (22.5)
T stage		
T1	2 (3.9)	30 (75.0)
T2	20 (39.2)	4 (10)
T3	22 (43.1)	21 (52.5)
T4	7 (13.7)	13 (32.5)
N stage		
N0	8 (15.7)	2 (5.0)
N1	17 (33.3)	10 (25.0)
N2	23 (45.1)	15 (37.5)
N3	3 (5.9)	10 (25.0)
TNM stage		
IA	2 (3.9)	5 (12.5)
IB	2 (3.9)	1 (2.5)
II	8 (15.7)	7 (17.5)
IIIA	21 (41.2)	14 (35.0)
IIIB	10 (19.6)	7 (17.5)
IV	8 (15.7)	5 (12.5)
Type of gastrectomy		
Subtotal	29 (63.0)	6 (15.0)
Total	17 (37.0)	19 (48.7)
Number of resected lymph nodes		
<14	31 (60.8)	20 (51.3)
14-25	17 (33.3)	20 (50.0)
>25	3 (5.9)	15 (37.5)
Death	27 (52.9)	5 (12.5)

Table 2. Main toxicities in the two patient groups

Kinds of toxicity	*Grade of toxicity*	*Control group*	*Study group*
Number of chemo cycles		*153*	*120*
Type of toxicity		*Number of patients (%)*	*Number of patients (%)*
Gastrointestinal	1	3 (5.88)	18 (45)
Nausea	0	41 (80.39)	16 (40)
Vomiting	2	7 (13.72)	4 (10)
	3	0 (0)	2 (5)
Diarrhea	0	48 (94.11)	20 (50)
	1	2 (3.92)	13 (32.5)
	2	1 (1.96)	5 (12.5)
	3	0 (0)	2 (5)
Hematologic			
White blood cells	0	47 (92.15)	24 (60)
	1	1 (1.96)	5 (12.5)
	2	2 (3.92)	5 (12.5)
	3	1 (1.96)	6 (15)
Hb	0	50 (98.03)	25 (62.5)
	1	1 (1.97)	9 (22.5)
	2	0 (0)	5 (12.5)
	3	0 (0)	1 (2.5)
Platelets	0	48 (94.11)	35 (87.5)
	1	3 (5.88)	0 (0)
	2	0 (0)	4 (10)
	3	0 (0)	1 (2.5)
Hand-foot syndrome			
	0	49 (96.07)	24 (60)
	1	1 (1.97)	7 (17.5)
	2	1 (1.97)	8 (20)
	3	0 (0)	1 (2.5)

Overall survival

The control and the study group included 91 patients (51 and 40, respectively), for whom the 2-year overall survival rate was of 60.4% (Figure 1).

Taken separately, the control group had a higher overall survival rate (62.7 vs 57.5%) compared with the study group; however, this difference was not statistically significant (p= 0.494) (Figure 2).

Disease-free survival

The 2-year DFS of the control and study group was 58.2% (Figure 3).

Assessed separately, the control group had better DFS (60.8 vs 55%), but without statistical significance (p=0.431) (Figure 4).

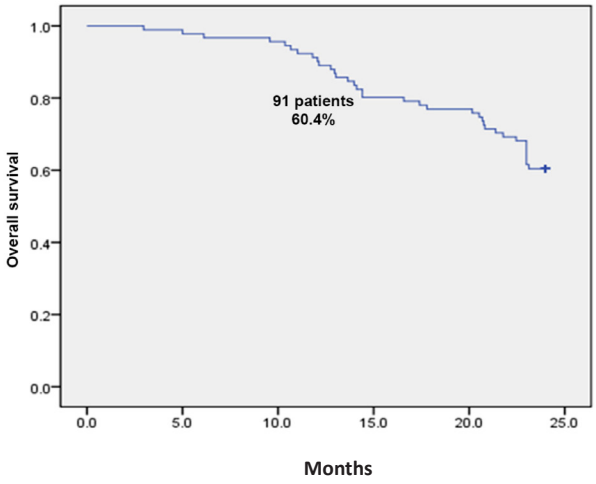

Figure 1. Global overall survival.

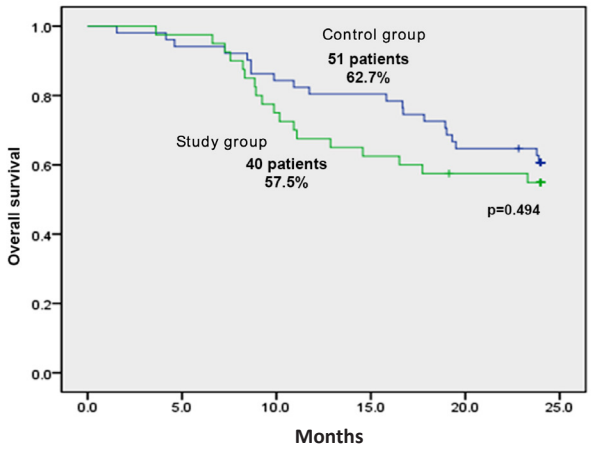

Figure 2. Overall survival in the control group and the study group.

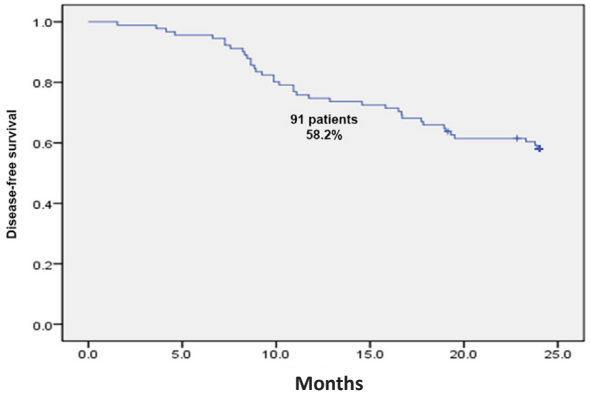

Figure 3. Global disease free survival.

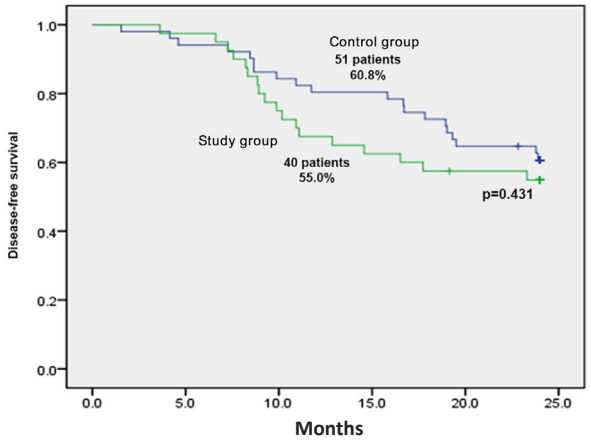

Figure 4. Disease-free survival per group.

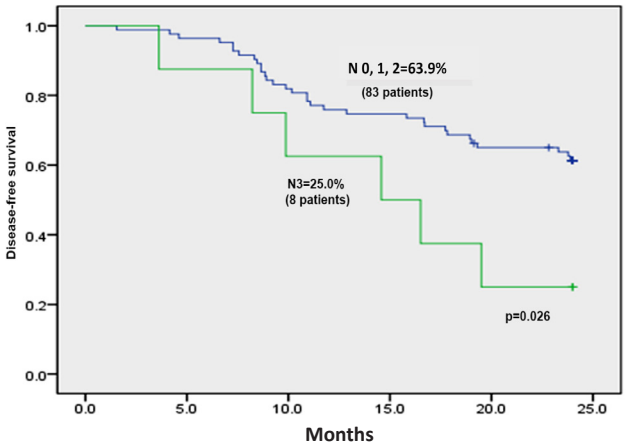

Figure 5. Disease-free survival in N3 stage vs other N stages.

Predictive or prognostic factors

The following factors were assessed:

Clinical factors: gender distribution and the influence of gender on OS and DFS; average age; median age; stage distribution; presence of alarming symptoms.

Histological factors: cancer site; histopathological type (diffuse, intestinal, mixed), tumor grade; presence of lymphatic, vascular, perineural invasion on the resection specimen; number of patients who underwent optimal lymphadenectomy; type of resection (R0, R1 or R2).

Treatment-related factors: type of surgery (total or subtotal gastrectomy)

In what follows, only the items that are statistically relevant will be detailed.

1. N category

Studied separately, for each of the groups, the N category did not have any statistically significant impact on OS or DFS. It is noteworthy that the percentage of N3 stage patients was 5.88% in the control group, whereas in the study group it was twice as high (12.5%), with an extremely low survival rate (0%). Given the preliminary statistical results and the reserved prognostic significance of the N3 stage, its influence on OS and DFS was assessed. Separate group assessment did not provide any statistically significant results (it should be reminded that the percentage of stage N3 patients was twice as high in the study group as compared to the control group).

The overall assessment showed that the impact of the N3 stage on DFS was statistically significant (Figure 5).

The impact of the N3 stage on OS was main-

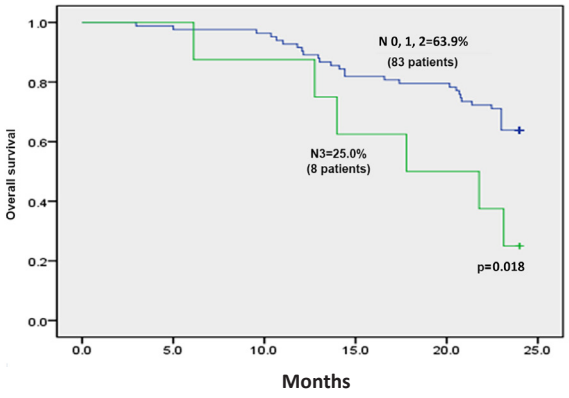

Figure 6. Overall survival in N3 stage vs other N stages.

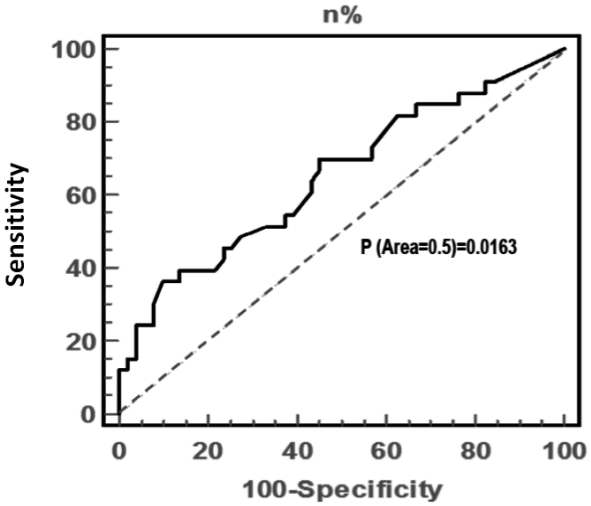

Figure 7. Sensitivity and specificity of N ratio in predicting overall survival. Area under the ROC curve=0.650; Standard error=0.063; 95% confidence interval=0.539-0.751.

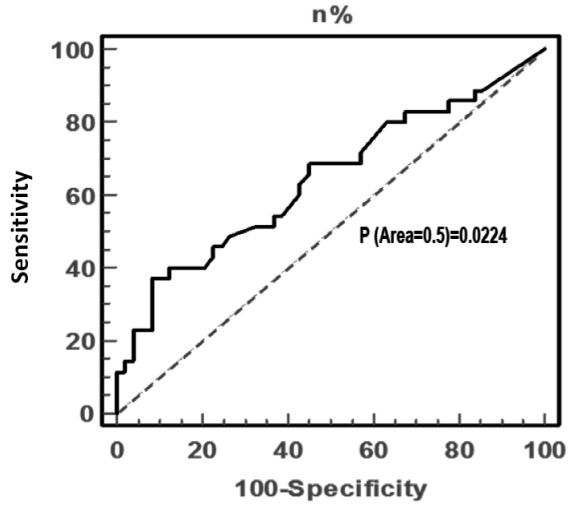

Figure 8. Sensitivity and specificity of N ratio in predicting relapse. Area under the ROC curve=0.642; Standard error=0.062; 95% confidence interval=0.530-0.743.

tained, as in the case of DFS (Figure 6).

In the study group, the N3 stage was an independent prognostic factor for both OS and DFS. In the control group, it was of borderline statistical significance.

2. N Ratio

Given the fact that, in clinical practice, having patients with optimal lymphadenectomy is not always the case, the literature available analyses the ratio between positive lymph nodes and the total number excised i.e. the *N ratio*. A first data interpretation was done according to a first division: N ratio 0, 0%; N ratio 1, 1-9%; N ratio 2, 10-25%; N ratio 3, >25%, which was not statistically significant. By contrast, the "N ratio parameter" had high potential in predicting relapse (AUROC=0.642, p=0.022). Thus, at cut-off values of over 70%, the N ratio presented a sensitivity=37.1% and specificity=91.8% in predicting future relapse or death of the patient (Figures 7 and 8).

Predictive factors of positive adenopathy such as T category, grade of malignancy, histological type, tumor site, age and lymphatic invasion as predictive factors in clinically positive N stage patients were studied. The calculations did not reveal any statistically significant correlation.

Part of the TNM staging system, the N category was not statistically significant when correlated with OS or DFS in the groups studied.

The following factors were not statistically significant either: grade of malignancy (p=0.934), histological type (p=0.093) - the diffuse type being the most frequently associated with positive adenopathies - , age group (p=0.883), tumor site (p=0.547) and presence of lymphatic invasion (p=0.315).

3. Resection margins

a) Overall survival

Patients in the control group who underwent incomplete resection (R1-microscopic residual tumor) accounted for 15.68% of all cases and had an OS rate much lower (25%) than those with R0 resection (69.8%). The correlation between the resection margins and OS was statistically significant, as shown in Figure 9.

Likewise, resection margins had a statistically significant impact on patients' survival in the study group (Figure 10).

b) Disease-free survival

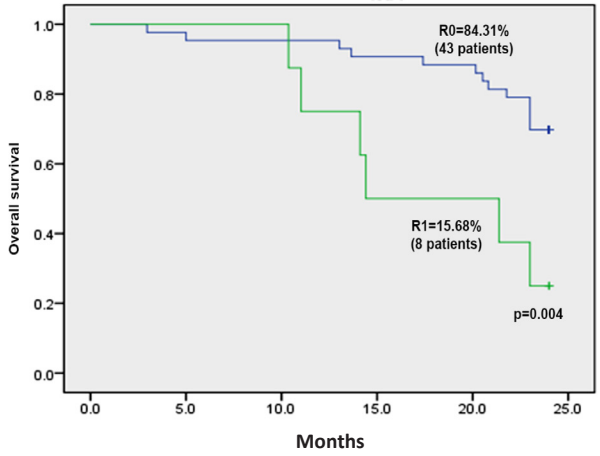

Figure 9. Overall survival in the control group according to the resection margins.

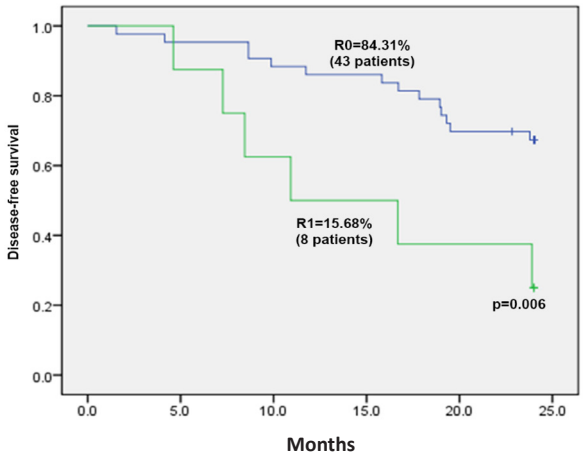

Figure 11. Disease-free survival in the control group according to the resection margins.

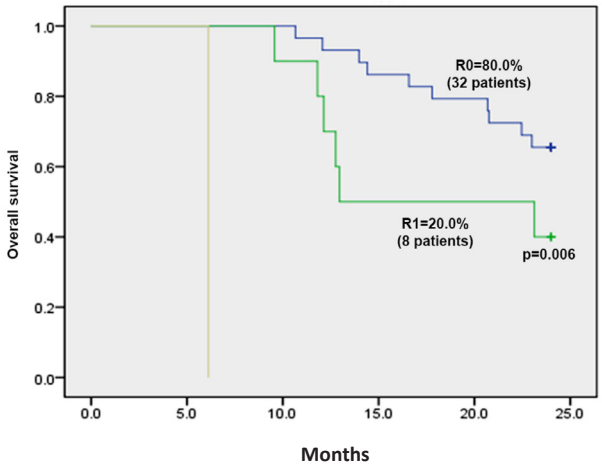

Figure 10. Overall survival in the study group according to the resection margins.

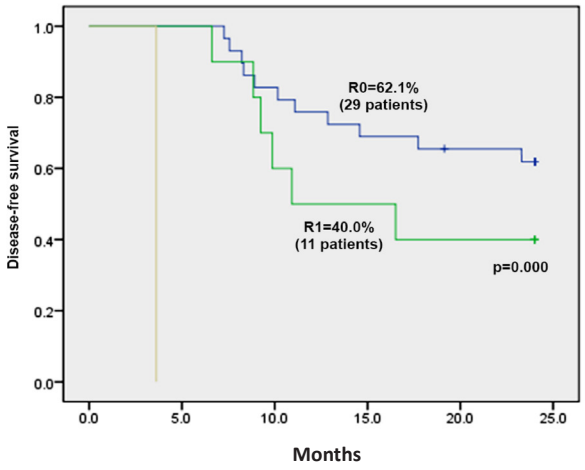

Figure 12. Disease-free survival in the study group according to the resection margins.

In the control group, DFS was influenced by the resection margins, being 25% for R0 resections vs 67.4% for R1 resections. Of the patients, 15.68% underwent R1 resection and this difference was statistically significant (Figure 11). The percentage of patients with invaded margins in the study group was higher (27.5%), with a lower DFS rate (40%), than patients who underwent a R0 resection (62.1%) (Figure 12). The correlation between the status of the resection margins and DFS was statistically significant for the study group as well.

In multivariate analysis, the status of the resection margins was proved as independent prognostic factor for OS and DFS in both groups – those who had invaded margins had poorer prognosis as compared to those who underwent a R0 resection (p=0.000 and 0.032, respectively).

4. Histology

The diffuse type had a more severe evolution, with lower OS and DFS rates than the intestinal type, without reaching the threshold for statistical significance (p=0.282 and 0.205, respectively). Multivariate analysis revealed that the histological type was not an independent prognostic factor for the groups under study.

5. Grade of malignancy

In multivariate analysis, the grade of malignancy was statistically significant in the control

group and of borderline statistical significance in the study group. It was an independent prognostic factor for OS but not for DFS (p=0.038 and 0.052, respectively).

6. Lymphatic, vascular, perineural invasion

In multivariate analysis, lymphatic invasion (p=0.198 and 0.447, respectively), vascular invasion (p=0.147 and 0.426, respectively), perineural invasion (p=0.198 and 0.447, respectively) were not independent prognostic factors for OS or DFS.

7. Type of lymphadenectomy (optimal=15 lymph nodes or recommended=25 lymph nodes)

Lymphadenectomy did not influence DFS or OS in any of the groups studied (p=0).

8. Age

The patients' age did not have any impact on OS in the control group; in the study group, the lowest survival rate was recorded in patients in the 2nd and 6th decades. The correlation between age and DFS was not statistically significant. In multivariate analysis, age between the 2nd and 6th decades seemed to be an independent prognostic factor for OS and DFS only in the study group (p=0.000 vs 0.187 in the control group).

9. Gender

In multivariate analysis, gender was not an independent prognostic factor for OS or DFS but it was of borderline statistical significance in women, especially if they were in their 2nd decade of life (p=0.064 in the control group vs 0.114 in the study group).

10. Alarm symptoms

"Alarm" symptoms such as dysphagia, hemorrhage or weight loss were studied. In multivariate analysis, the number of symptoms, as well as each symptom taken separately were not proven to be independent prognostic factors for OS or DFS.

11. Type of surgery

The correlation between the type of surgical procedure and DFS was not statistically significant for the groups studied.

Discussion

Given the short follow-up period, the data of this study were reported at a fortuitous 2-year interval.

Overall survival and disease-free survival

In our study, the 2-year OS rate was 60.4% and the 2-year DFS rate assessed globally, for the two groups, was of 58.2%.

When assessed separately, a higher OS rate was noted for the control group (62.7 vs 57.5% in the study group); the same trend characterized DFS, with 60.8 vs 50%. However, the difference was not statistically significant, which denotes that the treatment administered (ECX) was not less effective than the standard treatment in McDonald's trial. The results are comparable to those of McDonald's trial [6], who obtained a 3-year OS rate of 50% and a 3-year DFS rate of 48%.

The poor results of our study were mainly the consequence of the fact that patients are diagnosed in advanced stages, only 25 to 40% of them being detected while cancer is still localized [4].

Predictive factors for overall survival and disease-free survival

Surgery practically involves two stages: one concerns the primary gastric tumor (gastrectomy), the other the excision of the perigastric lymph nodes (lymphadenectomy). The final aim is to perform a R0 resection.

Gastrectomy can be total or subtotal, classic or laparoscopic. Of the patients, 39.21% in the control group underwent total gastrectomy, as opposed to 52.5% of the patients in the study group. The correlation between the type of gastrectomy performed and OS or DFS was not statistically significant in any of the groups studied.

Patients in the control group who underwent incomplete resection (R1-microscopic residual tumor) and who accounted for 15.68% of the cases, had a lower OS rate (25%) compared to those who underwent R0 resection (84.32%). In the study group, 27.5% of the patients underwent R1 resections. Surgical resection margins represented key elements, which had a statistically significant impact on OS and DFS in both groups. In multivariate analysis, the status of the resection margins represented an independent prognostic factor for OS and DFS in both groups; patients with invaded margins had a poorer prognosis than patients with R0 resection.

Surgery represents the only curative treatment available for gastric cancer [10]. For this rea-

son, achieving a R0 resection (resection margins with no microscopic residual tumor) is mandatory and is the strongest prognostic factor in gastric cancer [11,12]. One of the biggest issues was to define R0 resection. According to most surgeons, a R0 resection involves a distance of at least 6 cm from the top of the tumor and a safety margin of at least 1 cm under the pylorus [13]. Abiding by this principle calls into question the need to perform total gastrectomy, despite some authors' belief that it is only this type of gastrectomy (and not subtotal gastrectomy) that can provide reasonable safety margins [14,15].

On the other hand, the effort of obtaining a resection optimal from an oncologic standpoint is worth making, irrespective of the patient's age; a study conducted in Germany [16] showed that the resectability of gastric cancer is not age-dependent, but that postoperative morbidity tends to be higher in seniors, due to associated comorbidities. An important study proved that in T4 stage patients [17], the resection of two or several organs, especially after the age of 70, is encumbered by mortality and additional morbidity. The Japanese [18] also suggest the survival benefit of curative R0 resections in T4 stage patients. Aging is the most important factor that contributes to the increasing incidence of cancer. Advanced age is accompanied with various comorbidities and metabolic changes, making cancer treatment more difficult. However, every effort should be done to administer an optimal anticancer treatment since this is connected with improved survival [19]. Younger patients (under 40) seems to have more undifferentiated and more aggressive gastric cancer [20]. Given the increase in morbidity and perioperative mortality in advanced locoregional stages, patient selection is essential – only those in whom R0 resection may be achieved are to undergo multiorgan resection; N3 stage cancels the potential benefit of aggressive surgery [21].

The presence of microscopically positive margins significantly alters survival, especially in incipient stages I-II; its impact in advanced stages III and IV is not statistically significant [22].

The presence of positive perigastric lymph nodes is the strongest prognostic factor for gastric cancer after R0 resection [23]. The predictive factors for lymph node invasion are the T stage and the lymphatic vessel or submucosal invasion.

The extent of lymphadenectomy is still an extremely debated topic. The only consensus is that a D0 dissection (no excised lymph nodes) is suboptimal from an oncological point of view.

The correlation between OS or DFS and standard lymphadenectomy – 15 lymph nodes, according to the ESMO and ASCO guidelines in place or optimal lymphadenectomy > 25 lymph nodes, was not statistically significant in our study. The great advocates of extended lymphadenectomy are the Japanese: a D2 dissection is considered to be the standard procedure in Japan – many of the very satisfactory results that have been published being obtained for retrospective groups [13]. The trials conducted in Europe did not manage to achieve the same results. The relative morbidity and mortality risk increases significantly when splenectomy and pancreatectomy are performed during a D2 dissection and when patients are over 70, age at which the potential benefit is canceled by excess morbidity and mortality [13]. Splenectomy contributes to morbidity with a relative risk of 2.16 and pancreatectomy with a relative risk of 3.34 [13]; this is why they are to be avoided if the intraoperative status allows it.

An extremely interesting American study has shown that, for every 10 excised lymph nodes, survival improves by 7.6% [24]. There are studies which have proved that extended lymphadenectomy is the most important prognostic factor for overall survival and recurrence, especially for stage III gastric cancer patients [25].

The question arose as to whether it was the site or rather the number of positive lymph nodes that was more important. In order to answer this question, several studies have been conducted. Some suggest that the site of the positive lymph nodes (especially if we refer to the cardia) is not an independent prognostic factor – in other words, site matters [26]. Other studies have found a lesser impact on the prognosis for a lower number of pathologically positive lymph nodes (pN1 and pN2) with a possible influence of the site; by contrast, pN3 seems to be a reserved prognostic factor that is not site-dependent [27]. Our study points to the same direction.

Given the fact that not all patients undergo optimal lymphadenectomy which, according to the ESMO Clinical Practice Guidelines, means at least 14 excised lymph nodes (25 is the optimal number) [8], the question as to whether or not the N ratio (the ratio between positive lymph nodes and the total number of lymph nodes excised) reflects better the prognosis of patients, especially of those with less than 14 excised lymph nodes. In a study which included 1850 patients initially divided according to the number of the lymph nodes excised (under or over 15) and, subsequently, ac-

cording to the following scheme: N ratio 0, 0%; N ratio 1, 1-9%; N ratio 2, 10-25%; N ratio 3, >25%, it was noted that, in both groups, the N ratio was an independent prognostic factor which also allowed the ordering of the patients who underwent insufficient lymphadenectomy [23].

Some still doubt that the excision of as many lymph nodes as possible is the best solution [23]. As a matter of fact, trials concerning the extent of the surgical intervention (D2,D3) in gastric cancer revealed that, despite the excision of a large number of lymph nodes, no significant improvement was recorded in survival rates. The increase in the number of excised lymph nodes does not seem to be an aim in itself to achieve better results. It is rather a way of "measuring" the quality of the surgical procedure [23]. Nonetheless, an increasing number of studies talks, apart from "stage migration", of a potential curative benefit of enlarged lymphadenectomy [24]. Of course, this benefit seems small but, for certain subgroups of patients, it can be a survival benefit, especially now, when it is unanimously accepted that a D3 dissection can be done in specialized centers with minimal morbidity and mortality risk.

We restate the fact that, to date, there is neither irrefutable proof nor an international consensus regarding the way in which lymphadenectomy should be performed and regarding its curative role in gastric cancer. In our study, the N ratio >70% was a predictive factor for relapse and gastric cancer-related death.

The site of the primary tumor – even if the proximal tumor is coupled with a reserved prognosis and its incidence was increasing – was not proven to statistically correlate with OS or DFS in this study. The histological type and the grade of malignancy do not have a statistically significant impact, even though previously published studies granted them an uncertain prognostic significance [18]. In the case of R0 resection, the impact of the grade of malignancy on survival decreases significantly [18]. According to some studies, lymphatic or vascular invasion is an independent prognostic factor [27].

Nonetheless, the timing of administration of adjuvant treatment is also extremely important as several authors underline that a delay more than 45 days could impair the survival of these patients [28].

The "alarm symptoms" - weight loss, dysphagia and palpable tumor mass in the epigastrium seem to be correlated with patient survival. Their accumulation is associated with higher mortality risk [29]. Emergency surgery in gastric cancer (hemorrhage, perforation) alters the prognosis, but to a lower extent, if R0 is achieved.

Conclusions

1. OS and DFS were similar in both groups (the proposed treatment is not less effective than the standard imposed by McDonald's trial).

2. Patients from extreme age groups (adolescents/2nd decade and seniors/6th decade) have the most reserved prognosis. Age is an independent prognostic factor in multivariate analysis, for OS as well as for DFS.

3. N3 stage represented an independent prognostic factor for OS and DFS in multivariate analysis. The percentage of N3 stage patients was double in the study group as compared to the control group.

4. N ratio >70% represents a predictive factor with a 37% sensitivity and 95% specificity for OS and locoregional control in gastric cancer.

5. Positive resection margins were represented to a larger extent in the study group than in the control group (27.5 vs 15.68%). The resection margins were proven to be independent prognostic factors for OS and DFS.

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