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Impacto do Rácio Plaqueta-Linfócito (PLR) no prognóstico de pacientes com cancro gástrico / Impact of Platelet-Lymphocyte Ratio (PLR) in the prognosis of Gastric Cancer patients

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Impacto do Rácio Plaqueta-Linfócito (PLR) no prognóstico de pacientes com cancro gástrico / Impact of Platelet-Lymphocyte Ratio (PLR) in the prognosis of Gastric Cancer patients

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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Impact of Platelet-Lymphocyte Ratio (PLR) in the prognosis of gastric cancer patients

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Faculdade de Medicina da Universidade do Porto, 15/03/2020

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Impact of Platelet-Lymphocyte Ratio (PLR) in the prognosis of Gastric Cancer patients

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Abstract

Background: Cancer-related inflammation is central in tumoral evolution. Elevated platelet-lymphocyte ratio (PLR), an inflammatory biomarker, has been reported as a prognostic predictor in Gastric Cancer (GC). The study's aim was to evaluate the effect of PLR in the prognosis of GC patients submitted to curative-intent resectional surgery.

Methods: A retrospective analysis of a prospective database with 637 GC cases submitted to curative-intent surgery, between January 2010 and December 2017, in an Upper GI Surgery Unit. We analyzed 396 patients that met the inclusion criteria for this study.

Results: In this cohort (n=359), PLR was significantly associated with DFS [HR 1,002; CI95% 1,000-1,004; p=0,015] and OS [HR 1,002; CI95% 1,001-1,004; p=0,004]. Regarding the ROC curve of PLR for OS, the AUC was 0,582 (CI95% 0,521-0,642; p=0,008). Using Youden's method, the optimal PLR cut-off for OS was 160,613. The high PLR (>160,613) group was associated with worse OS [HR 1,676; CI95% 1,221-2,300; p=0,001] and DFS [HR 1,665; CI95% 1,074-2,582; p=0,023]. There was a significant (p=0,043) association between PLR and postoperative complications [18,4% vs 27,5% in low and high PLR groups, respectively; OR 1,673; CI95% 1,015-2,758; p=0,044].

Conclusions: PLR was a prognostic factor in GC patients submitted to curative-intent resectional surgery. PLR>160,613 was associated with worse OS, DFS and more postoperative complications, in this cohort.

Key words: Gastric cancer; Gastrectomy; Platelet-Lymphocyte Ratio; PLR; Prognosis; Survival; Postoperative complications

1 – Introduction

Gastric Cancer (GC) is the third leading cause of cancer death in the world, representing 8,2% of total cancer mortality, and ranks fifth place in terms of incidence. Even though cancer mortality has been declining for several years, its incidence has been increasing across the globe [1]. It's worth noting that Portugal is following this tendency [2], making GC an important healthcare issue.

Nowadays lifestyles encompass numerous risk factors for GC like low fruit intake, excessive alcohol ingestion and tobacco smoking, all of which contribute to the global cancer epidemic [3]. In addition to these habits, the widespread infection with *Helicobacter pylori* contributes to GC carcinogenesis through a chronic inflammatory process, that induces several alterations on the gastric mucosa recurring to several known mechanisms, that include free radical production and interference with DNA repair [4].

It is now widely accepted that inflammation plays a major role in tumorigenesis, from the initiation of the neoplastic process to its dissemination through the organism. This relation contributes to our understanding of GC risk factors, since *H. pylori* infection, tobacco and a variety of dietary variants are all associated with inflammatory processes that contribute to the development of GC [5].

Since these discoveries emerged in the scientific community, several inflammation-associated cells were studied, including lymphocytes and platelets, which seem to play a central role in tumor development [6,7].

High platelet counts are usual findings in cancer patients (10-58%) [7]. These cells are related to tumor development through neoangiogenesis, tumor protection, using a shielding mechanism that protects cancer cells from aggression, and tumor dissemination, by aiding in the metastatic process [7,8]. Several studies have already identified an association between poorer cancer prognosis and thrombocytosis [9,10].

On the other hand, lymphocytes have been found in high numbers within the tumoral tissue, contributing to its development [6]. Despite these local high counts, cancer is associated with an immunosuppressive state, which relates to peripheral lymphopenia, a marker of poor prognosis [11,12].

From these findings, several inflammation-associated indexes were created, with the intent of aiding in the evaluation of cancer progression and prognosis [13-15].

From the numerous indexes related to systemic inflammation, Platelet-Lymphocyte Ratio (PLR) seems to play an important role when approaching GC prognosis, even though results are still controversial [16; 17-20].

The aim of this study was to evaluate the relation between preoperative values of PLR and postoperative outcomes, recurrence and survival of patients with GC submitted to surgery.

2 – Materials and methods

2.1 – Study design and population

A prospective database of GC patients (n=637) who were submitted to gastrectomy in the Upper GI Surgery Unit of São João University Medical Center – Faculty of Medicine, University of Porto (Porto, Portugal), between January 2010 and December 2017, was retrospectively reviewed. The study was approved by the Institutional Review Board (CES 298-12).

For this study, only patients with gastric adenocarcinoma and curative-intent surgery were considered. The exclusion criteria were: non-resectional surgery, palliative gastrectomies, prophylactic gastrectomies, completion gastrectomies (gastric stump cancer cases), atypical resections, post endoscopic resections, pathological stage (pStage) IV carcinomas, histologic types other than adenocarcinoma and R2 resections. Patients lost for follow-up were not included in this analysis. After selecting patients according to the above criteria, a total of 396 cases were analyzed (**Figure 1**).

In this observational study, a comparative analysis was made between patients with high PLR (n=153) and low PLR (n=206).

2.2 – Data collection

For demographic characterization, the following parameters were evaluated: age at time of surgery; gender; presence of comorbidities; American Society of Anesthesiologists (ASA) physical status classification; and body mass index (BMI) score.

To describe the clinicopathological profile, several parameters were used: tumor location, size (cm) and type; macroscopic type; histologic type (Lauren classification) and growth pattern (Ming classification); TNM staging (7^{th} edition, 2010); number of resected lymph nodes (LN); LN ratio; lymphatic, venous and perineural invasions; and pStage.

To characterize the therapeutic approach, type of surgery, resection and lymphadenectomy, and presence of neoadjuvant therapy were also collected.

Concerning the outcomes, we analyzed the presence of post-operative complications (less than 30 days after surgery).

In survival analysis, overall survival (OS) and disease-free survival (DFS) were evaluated. OS was defined as the period between the day of surgery and death of the patient. Patients who had survived until the end of the observation period were censored at their last follow-up visit. DFS was considered the period between the end of primary therapy and the first evidence of disease recurrence. Follow-up (median 75 months, range 0-113 months) was completed for the entire study population in September 2019.

All the data was reviewed by two of the authors (HSS, PV) for identification of data entry errors.

2.3 – Perioperative management and surgical procedure

The procedures used to make the diagnosis of GC were upper endoscopy with biopsy and computerized tomography (CT). The staging of tumor was established according to clinical, radiological (CT) or endoscopic (endoscopic ultrasonography) features, and the staging laparoscopy was used when considered necessary (mostly in local advanced tumors with uncertain resectability).

The preoperative clinical stage of the patient was used to select the surgical approach and the extent of lymphadenectomy. In diffuse and proximally located tumors the total gastrectomy with Roux-en-Y reconstruction was the type of surgery performed. Distally located tumors were resected by a subtotal distal gastrectomy, using Billroth II and sporadically Roux-en-Y reconstructions, according to age and comorbidities presence. The extent of lymphadenectomy was classified based on the third version of Japanese Gastric Treatment Guidelines, 2010.

All the patients went to the post-surgical intensive care unit in the postoperative period to control and for post-operatively early extubation, pain control, vigorous

respiratory therapy, early mobilization and ambulation. Permission for food intake depends on clinical evolution. All patients were followed up by the surgical team at 3-month intervals in the first year after surgery, every 6 months during the second year and annually thereafter.

2.4 – Statistical analysis

Statistical analysis was performed using SPSS® 26.0 for Mac (IBM Co., Armonk, NY, USA). Normal distribution of continuous variables was assessed by visual analysis of histograms, normal Q-Q plots and both Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. Non-parametric test Mann-Whitney U was used to compare means, and chi-square or Fisher's exact test were used to compare proportions, as appropriate. Odds Ratio (OR) and 95% confidence intervals (CI) were calculated by logistic regression.

Regarding the ROC curve of PLR for OS the optimal PLR cut-off was calculated according to the Youden's method. Kaplan-Meier (KM) curves were calculated according to the PLR cut-off and differences between groups were assessed by Log Rank test. Cox regression was used to evaluate the effect of PLR in OS and DFS, and the Hazard ratio (HR) was adjusted to pStage.

Significance was assumed for p values inferior to 0.05. All p values given are results of 2-sided tests.

3 – Results

3.1 – Comparative analysis: High PLR versus Low PLR

In the ROC curve of PLR for OS (**Figure 2**) the AUC was 0,582 (CI95% 0,521 – 0,642; p=0,008). According to the Youden's method, the optimal PLR cut-off for OS was 160,613 (sensitivity 53,2% and specificity 65,4%). In our study, the patients were grouped according to the PLR in High PLR (≥160,613) and Low PLR (<160,613) and population baseline characteristics are described in **Table 1**.

In the High PLR (HPLR) group, the patients were older (70,0 ± 11,1 versus 64,5 ± 12,3; p<0,001). Regarding the clinicopathological profile, the patients in the HPLR group had larger tumors (5,7 ± 3,1 versus 3,4 ± 2,1; p<0,001), higher pT (T1-2 – 39,1% versus 64,0%, T3-4 – 60,9% versus 36,0%; p<0,001), higher pN (pN+ - 52,3% versus 41,3%; p=0,025) and higher LN ratios (>0,2 – 28,8% versus 15,5%; p=0,003). Lymphatic permeation (62,4% versus 45,3%; p=0,002), venous and perineural invasion (48,6% versus 33,5%; p=0,006; and 40,5% versus 28,4%; p=0,022, respectively) and higher pStage (I – 34,6% versus 54,6%, II – 26,8% versus 22,9%, III – 38,6% versus 22,4%; p<0,001) were more frequent in these patients.

In what concerns therapeutic approach, in the HPLR group more open surgeries (61,4% versus 46,6%; p=0,006) and D1 lymphadenectomies (35,3% versus 23,3%; p=0,005) were performed.

3.2 – Survival analysis: Platelet-Lymphocyte Ratio (PLR)

In this study (n=359), PLR median was 142,857 and interquartile range was 102,273 – 207,965 (**Figure 3**).

According to cox regression (**Table 2**), PLR had a negative effect in OS (HR 1,002; CI95% 1,001 – 1,004; p=0,004) and DFS (HR 1,002; CI95% 1,000 – 1,004; p=0,015). However, when HR was adjusted to pStage, PLR was not significantly associated to OS (HR 1,001; CI95% 1,000 – 1,003; p=0,058) or DFS (HR 1,002; CI95% 0,999 – 1,005; p=0,117).

3.3 – Survival analysis: High PLR versus Low PLR

According to the KM curve (**Figure 4**), the HPLR status had a negative effect in OS (58,579 ± 3,897 versus 75,944 ± 3,444; p=0,001) and in DFS (79,522 ± 4,093 versus 89,661 ± 3,253; p=0,037).

Regarding the cox regression (**Table 3**), HPLR had a negative effect in OS (HR 1,676; CI95% 1,221 – 2,300; p=0,001) and DFS (HR 1,665; CI95% 1,074 – 2,582; p=0,023). However, when HR was adjusted to pStage, the associations with OS (HR 1,308; CI95% 0,946 – 1,810; p=0,105) and DFS (HR 1,096; CI95% 0,703 – 1,709; p=0,686) were no longer statistically significant.

3.4 – Outcome analysis: High PLR versus Low PLR

Regarding the outcomes, the total complication rate was 22,3%. When analyzing the subgroups, it was higher in the HPLR group (27,5% versus 18,4%; p=0,043). PLR was significantly associated with the presence of complications (OR 1,673; CI95% 1,015 – 2,758; p=0,044).

4 – Discussion

Our study's main finding was that High PLR had a negative effect in postoperative outcomes and survival of GC patients undergoing gastrectomy.

According to our results, individuals on the HPLR group had worse OS and DFS. Similar results were found in *Kim et al* study of 1986 consecutive patients who were submitted to curative-intent surgery for GC. In their research, after determining the optimal cut-off levels for PLR, there was a statistically significant association with OS (HR 1,59) and DFS (HR 2,70) [21]. Despite the limitations related to the patient selection method, the study was able to correlate the higher PLR with poorer prognosis in GC patients.

Our results also depicted a significant association between higher PLR and an increase in postoperative complications, a relation described by *Jiang et al.* in their prospective analysis of 377 patients with GC undergoing curative-intent gastrectomy. In this research, PLR was independently associated with postoperative complications (OR 2,273; p=0,09), defined as a drift from normal postsurgical recovery [19]. *Inaoka et al.* described similar results in their retrospective study of 312 patients who underwent potentially curative gastrectomy for GC, with an OR 2,94 (CI95% 1,66-5,35; p<0,001) for postoperative complications in patients with higher PLR, in the univariate analysis [22].

Several studies in this area have evaluated the relation between PLR and the prognosis of GC, reporting similar results, with worse survival and an increased rate of postoperative complications in patients with higher preoperative PLR. *Lian et al.* studied 162 patients with resectable GC and divided them into groups according to median PLR, having described that higher PLR was associated with poorer OS and DFS 5-year survival rates (26,1% and 12,2%, respectively) by comparison to the lower PLR group (48,6% and 25,4%, respectively) [15]. Despite the limitations of the subgroup definition method, the results were supportive of the theory. *Saito et al.* performed a retrospective analysis of 453 GC patients submitted to curative gastrectomy, describing that the higher PLR, defined by the cut-off of 173,3, was associated with worse 5-year survival rates (66,3%) when compared to lower PLR (82,1%) [23]. *Gu et al.* compiled the results

of 14 cohorts, with a total of 6280 patients in a meta-analysis, from which an association between higher PLR and poorer OS emerged (HR 1,3; CI95% 1,1-1,52; p=0,001) [24]. This meta-analysis has a major limitation regarding comparison with our study's results, due to the fact that it included not only patients submitted to curative-intent gastrectomy but also patients submitted to chemotherapy. Nevertheless, the general conclusion is supportive of the hypothesis that higher PLR correlates with worse prognosis.

On the overall view, various research groups have found an association between higher PLR and worse prognosis, but these results remain controversial and studies have refuted this hypothesis and presented opposite findings. *Xu et al.* performed a meta-analysis, using 8 studies (6 retrospective and 2 prospective studies), encompassing 4513 patients with GC, and found that high PLR was not a reliable predictor of OS (HR 0,99; CI95% 0,9-1,1) [18]. *Gunaldi et al.* conducted a research with 245 patients with confirmed diagnosis of GC and found no significant correlation between PLR and survival times [25]. *Gunaldi et al.* results include only patients treated in medical oncology clinics, which is a major limitation in the comparison with our data.

Regarding the postoperative complications, the evidence on the association between PLR and these complications is limited. Despite this lack of evidence, higher platelet counts, and lower lymphocyte counts seem to be associated with an increase in postoperative complications, namely infection, anastomotic leakage, and others [22]. The proposed mechanisms that support this association include: 1 - thrombotic phenomenon on small caliber vessels, due to higher serum platelet counts, which leads to tissue damage; 2 - increased infection progression rates due to the decreased immune cellular response associated with lymphopenia [22].

The first studies reporting an association between GC and inflammation emerged in the 19th century by Rudolf Virchow, due to the identification of leukocytes within the local tumoral environment [5]. Since then, researchers have conducted several studies in order to increase the evidence on these mechanisms. The generally accepted hypothesis links chronic inflammation with initiation, promotion, appearance of mutations that lead to tissue malignancy and invasive

processes [5]. This mechanism explains the increased rate of GC in modern societies, because air pollution, tobacco use, obesity and chronic infections are all risk factors for GC, since they induce an inflammatory state [5].

The inflammatory response components included on our study are the Lymphocytes and Platelets, which contribute in different ways to cancer progression and influence the patients' overall prognosis.

The lymphocytes are associated to cancer growth and to a systemic immunosuppressive state [6]. Within the tumoral tissue, the lymphocytes release several inflammatory cytokines [6]. These cytokines confer increased survival rates to local abnormal cells, through the activation of several pathways that induce DNA damage, recurring to oxidative mechanisms [6]. This damage ultimately induces mutations that prolong their survivability and resistance [6]. These interactions promote cancer development, and together with tissue remodeling and formation of new blood vessels, favor the appearance of neoplasia [26]. Further studies on this area have identified an association between defective development or function of CD8+ Cytotoxic T Lymphocytes (CTL's), CD4+ Th1 Helper T Cells and Natural Killer (NK) Cells and an increase on tumor incidence and faster tumoral development [12]. It is important to note that, even though lymphocytes have increased number in tumoral tissue, promoting local inflammation, the systemic response to cancer is an immunosuppressive state, with decreased numbers of circulating lymphocytes [6].

This central physiopathological mechanism has led to the design of studies evaluating the lymphocyte blood counts in cancer patients and its association with overall prognosis, due to the importance of this inflammatory component in tumorigenesis and tumor progression. In the study by *Ray-Coquard et al.,* an association between lymphopenia and poorer prognosis of several neoplasms was described [11], supporting the hypothesis linking cancer to an immunosuppressive state and showing the relevance of lymphocytes when approaching inflammatory markers and cancer. Similar findings were found by *Fogar et al.*, relating decreased total lymphocyte counts and poorer prognosis in pancreatic cancer [27]. Corroborating with this hypothesis, *Morgan et al.*

conducted a research project regarding the introduction of genetically modified lymphocytes to raise lymphocyte count, concluding that higher lymphocyte counts are associated with diminished tumor progression and increased tumor regression [28], further increasing the evidence that a lower serum lymphocyte count associates with poorer cancer prognosis.

Platelets are another component of the inflammatory response associated with cancer, contributing to the formation of a procoagulant surface that facilitates the mechanisms related to cancer-associated coagulation [7]. This culminates in a hypercoagulability state, leading to thromboembolic complications, and influence over tumoral cell development [7,8]. Thrombocytosis is directly induced by tumoral cells, that release growth factors and cytokines which stimulate megakaryocytopoiesis, by platelet-derived microparticles and megakaryocyte released factors [7,8].

Another relevant mechanism through which platelets influence tumor progression is their influence over the local angiogenic process, mediated by the stimulation of endothelial cells [7]. These pro-angiogenic signals induce the development of new capillaries, that frequently have a convoluted appearance, are excessive in number, appear distorted and enlarged [12]. This ultimately leads to abnormal blood flow, micro-hemorrhages, altered cell proliferation and cell death [12].

The last studied mechanism by which platelets influence tumorigenesis and tumor progression involves tumor cell shielding [8]. This mechanism involves direct coating processes that protect the tumor cells from blood flow associated aggression within the vessels and from the immune system's response [8].

After the discovery of these mechanisms, research bloomed, leading to the design of several studies that intended to study the relation between serum platelet levels and tumor prognosis, similarly to what happened with the lymphocytes. *Sierko et al.* found that thrombocytosis is a common finding in cancer patients, ranging from 10-57% [7]. *Ikeda et al.* led a study with 369 patients, whose results revealed an association between higher platelet counts and worse 1-year and 3-year survival expectancies [10]. In his series, 1-year survival in patients with and without thrombocytosis was 52,4% and 85,7%, respectively, while 3-year survival in patients with and without thrombocytosis

was 23,4% and 72,9%, respectively. Similar results were found by *Voutsadakis*, who described thrombocytosis as an adverse prognostic factor in a variety of cancers [9]. In his literature review, the author found several associations between elevated platelet counts and a poorer prognosis, mainly worse survival [9].

From these studies on the various hematological inflammatory markers related to cancer, emerged various scores, whose purpose is to aid the clinicians on the evaluation of cancer prognosis. One of these variables is the PLR, computed as the platelet count divided by lymphocyte count [19], which has been studied in various cancers [16]. A meta-analysis, by *Zhou et al.* included 13964 patients from 26 studies, evaluating the effect of PLR in a variety of cancers, including gastric, colorectal, ovarian, pancreatic and others, concluding that PLR was a negative predictor for OS (HR 1,60; CI95% 1,35-1,90) in the globality of the researches [16]. In the specific case of GC, the HR was 1,35 (CI95% 0,80-2,25) [16]. Another meta-analysis, by *Yodying et al.* found similar results when reviewing cases of esophageal cancer, linking higher PLR to worse OS [13]. Similar associations between higher PLR and worse outcomes have been reported in other studies [14-15,20,29-30].

The need to evaluate PLR as a predictor comes from the inexistence of adequate predictors that can be widely used in clinical settings, and from the increasing evidence that systemic inflammatory response could play an important role in the tumorigenic process [5-6,16,26]. Therefore, the combination of circulating platelet and lymphocyte counts, in the form of PLR, emerges as a useful index that is able to reflect the systemic inflammatory state [16]. Although evidence is still controversial, both thrombocytosis and lymphocytopenia correlate with the patient's systemic inflammatory response, making it possible to use PLR as a novel inflammatory marker in the evaluation of cancer prognosis [16].

The clinical use of PLR may not be limited to evaluating prognosis, since its reflection of the inflammatory state may useful in the selection of pharmacological targets to intervene, improving OS and overall prognosis of GC patients. Some studies have emerged in this regard, evaluating the possible use of Glycoprotein IIb-IIIa inhibitors, which affect peripheral platelet counts, influencing tumor

associated angiogenesis and tumor promoting interactions [7]. In some types of cancer, namely non-small cell lung cancer and breast cancer, the use of aspirin was also tested, with promising results regarding increases in survival [8]. These results remain, however, controversial with variations between various types of cancer.

The use of anti-inflammatory drugs was also hypothesized, mainly in the limitation of cancer progression [5], but evidence of its use is still limited. The use of aspirin, and other non-steroidal anti-inflammatory drugs (NSAID's), such as naproxen or ibuprofen, have been shown to lower the risk of GC [31], disrupting the inflammatory pathways that lead to the development of neoplasms. These drugs could be used to protect against GC development but are not yet recommended due to its complications, such as bleeding, and lack of supporting evidence [31].

The limitations of the present research include its retrospective nature; analysis of a limited number of patients (n=396) belonging only to one hospital; the selected hospital is a tertiary center, receiving patients in poorer health conditions, and may not be representative of the general population; and only patients submitted to curative intent surgery were included in the study.

Although there are some studies evaluating the association between PLR and the prognosis of GC patients after gastrectomy, and despite the fact that the evidence regarding the mechanisms by which inflammatory components influence cancer is increasing, a consensus has not yet been found in both matters. Therefore, further investigation has to be made in order to uncover more data that supports these correlations, and our results. In addition, there are no studies in the Portuguese population, even though Portugal has high incidence and mortality rates associated with GC [2], increasing this study's potential benefits in the approach of GC patients, ultimately improving survival and reducing postoperative outcomes of GC.

5 – Conclusion

This study has shown that PLR was a prognostic factor in GC patients submitted to curative-intent resectional surgery. PLR>160,613 was associated with worse OS, DFS and an increased rate of postoperative complications, so strategies to reduce preoperative inflammatory parameters should be studied and implemented.

Disclosures

The authors have no conflict of interest or financial ties to disclosure.

References

[1] Bray, F.*, et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68, 394-424 (2018).

[2] Morais, S.*, et al.* Trends in gastric cancer mortality and in the prevalence of Helicobacter pylori infection in Portugal. *Eur J Cancer Prev* 25, 275-281 (2016).

[3] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and Stomach Cancer 2018.*

[4] Herrera, V. & Parsonnet, J. Helicobacter pylori and gastric adenocarcinoma. *Clin Microbiol Infect* 15, 971-976 (2009).

[5] Grivennikov, S.I., Greten, F.R. & Karin, M. Immunity, inflammation, and cancer. *Cell* 140, 883-899 (2010).

[6] Balkwill, F. & Mantovani, A. Inflammation and cancer: back to Virchow? *Lancet* 357, 539-545 (2001).

[7] Sierko, E. & Wojtukiewicz, M.Z. Platelets and angiogenesis in malignancy. *Semin Thromb Hemost* 30, 95-108 (2004).

[8] Bambace, N.M. & Holmes, C.E. The platelet contribution to cancer progression. *J Thromb Haemost* 9, 237-249 (2011).

[9] Voutsadakis, I.A. Thrombocytosis as a prognostic marker in gastrointestinal cancers. *World J Gastrointest Oncol* 6, 34-40 (2014).

[10] Ikeda, M.*, et al.* Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Annals of Surgical Oncology* 9, 287-291 (2002).

[11] Ray-Coquard, I.*, et al.* Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res* 69, 5383-5391 (2009).

[12] Hanahan, D. & Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell* 144, 646-674 (2011).

[13] Yodying, H.*, et al.* Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 23, 646-654 (2016).

[14] Chen, L.*, et al.* Peripheral Venous Blood Platelet-to-Lymphocyte Ratio (PLR) for Predicting the Survival of Patients with Gastric Cancer Treated With SOX or XELOX Regimen Neoadjuvant Chemotherapy. *Technol Cancer Res Treat* 18, 1533033819829485

[15] Lian, L.*, et al.* Application of platelet/lymphocyte and neutrophil/lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. *Cancer Biomark* 15, 899-907 (2015).

[16] Zhou, X.*, et al.* Prognostic value of PLR in various cancers: a meta-analysis. *PLoS One* 9, e101119 (2014).

[17] Xin-Ji, Z.*, et al.* The prognostic role of neutrophils to lymphocytes ratio and platelet count in gastric cancer: A meta-analysis. *Int J Surg* 21, 84-91 (2015).

[18] Xu, Z.*, et al.* The Prognostic Role of the Platelet-Lymphocytes Ratio in Gastric Cancer: A Meta-Analysis. *PLoS One* 11, e0163719 (2016).

[19] Jiang, N.*, et al.* The role of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after radical resection for gastric cancer. *Biomarkers* 19, 444-451 (2014).

[20] Wen, J.*, et al.* The value of inflammation based prognostic scores in patients undergoing surgical resection for oesophageal and gastric carcinoma. *J Surg Oncol* 117, 1697-1707 (2018).

[21] Kim, E.Y., Lee, J.W., Yoo, H.M., Park, C.H. & Song, K.Y. The Platelet-to-Lymphocyte Ratio Versus Neutrophil-to-Lymphocyte Ratio: Which is Better as a Prognostic Factor in Gastric Cancer? *Ann Surg Oncol* 22, 4363-4370 (2015).

[22] Inaoka, K.*, et al.* Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer. *World J Gastroenterol* 23, 2519-2526 (2017).

[23] Saito, H.*, et al.* Prognostic Significance of Platelet-Based Inflammatory Indicators in Patients with Gastric Cancer. *World J Surg* 42, 2542-2550 (2018).

[24] Gu, X.*, et al.* Clinicopathological and prognostic significance of platelet to lymphocyte ratio in patients with gastric cancer. *Oncotarget* 7, 49878-49887 (2016).

[25] Gunaldi, M.*, et al.* Prognostic impact of platelet/lymphocyte and neutrophil/lymphocyte ratios in patients with gastric cancer: a multicenter study. *Int J Clin Exp Med* 8, 5937-5942 (2015).

[26] Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. *Nature* 454, 436-444 (2008).

[27] Fogar, P.*, et al.* Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. *Pancreas* 32, 22-28 (2006).

[28] Morgan, R.A.*, et al.* Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 314, 126-129 (2006).

[29] Aldemir, M.N.*, et al.* Prognostic Value of Baseline Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios in Local and Advanced Gastric Cancer Patients. *Asian Pac J Cancer Prev* 16, 5933-5937 (2015).

[30] Deng, Q.*, et al.* Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl Med* 13, 66-66 (2015).

[31] Rawla, P. & Barsouk, A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol* 14, 26-38 (2019).

	LPLR (n=206)	HPLR (n=153)	Total (n=359)	p value
Demographics				
Age at surgery (years), mean ± SD	64,5 ± 12,3	70,0 ± 11,1	66,8 ± 11,9	**<0.001***
Gender, n (%)				0,668
Male	115 (55,8)	89 (58,2)	204 (56,8)	
Female	91 (44,2)	64 (41,8)	155 (43,2)	
Comorbidities, n (%)				0,382
Presence	170 (82,5)	132 (86,3)	302 (84,1)	
Absence	36 (17,5)	21 (13,7)	57 (15,9)	
ASA score, n (%)				0,162
I	23 (11,2)	17 (11,1)	40 (11,1)	
II	116 (56,3)	70 (45,8)	186 (51,8)	
III	64 (31,1)	61 (39,9)	125 (34,8)	
IV	3 (1,5)	5 (3,3)	8 (2,2)	
BMI (Kg/m^2) mean ± SD	26,0 ± 3,8	25,8 ± 6,0	25,9 ± 4,2	0,510*
Clinicopathological profile				
Tumor location, n (%)				0,308
Fundus	142 (69,3)	103 (67,3)	245 (68,4)	
Body	57 (27,8)	42 (27,5)	99 (27,7)	
Antrum	3 (1,5)	1 (0,7)	4 (1,1)	
Extensive	3 (1,5)	7 (4,6)	10 (2,8)	
Tumor size (cm), mean ± SD	3,4 ± 2,1	5,7 ± 3,1	4,3 ± 2,8	**<0,001***
Macroscopic type, n (%)				**0,001**
Fungating	30 (15,8)	26 (18,6)	56 (17,0)	
Ulcerated	67 (35,3)	41 (29,3)	108 (32,7)	
Infiltrative	31 (16,3)	6 (4,3)	37 (11,2)	
Ulcero-fungating	15 (7,9)	24 (17,1)	39 (11,8)	
Ulcero-infiltrative	47 (24,7)	43 (30,7)	90 (27,3)	
Histologic type (Lauren), n (%)				0,153
Intestinal	93 (46,5)	71 (47,7)	164 (47,0)	
Diffuse	29 (14,5)	15 (10,1)	44 (12,6)	
Unclassified of solid structure	2 (1,0)	7 (4,7)	9 (2,6)	
Unclassified of mixed structure	57 (28,5)	38 (25,5)	95 (27,2)	
Unclassified NOS	19 (9,5)	18 (12,1)	37 (10,6)	
Growth pattern (Ming), n (%)				0,358
Expansive	41 (20,4)	40 (26,8)	81 (23,1)	
Infiltrative	147 (73,1)	101 (67,8)	248 (70,9)	
Unclassified	13 (6,5)	8 (5,4)	21 (6,0)	
pT (7th ed, 2010, simplified), n (%)				**<0,001**
T1-2	130 (64,0)	59 (39,1)	189 (53,4)	

T3-4	73 (36,0)	92 (60,9)	165 (46,6)	
pN (7th ed, 2010, simplified), n (%)				**0,025**
pN-	121 (58,7)	73 (47,7)	194 (54,0)	
pN+	85 (41,3)	80 (52,3)	165 (46,0)	
Nr of resected LN, mean ± SD	27,3 ± 12,7	27,0 ± 13,4	27,4 ± 13,1	0,719*
LN ratio, n (%)				**0,003**
≤0,2	174 (84,5)	109 (71,2)	283 (78,8)	
>0,2	32 (15,5)	44 (28,8)	76 (21,2)	
Lymphatic permeation, n (%)				**0,002**
Presence	92 (45,3)	93 (62,4)	185 (52,6)	
Absence	111 (54,7)	56 (37,6)	167 (47,4)	
Venous invasion, n (%)				**0,006**
Presence	68 (33,5)	72 (48,6)	140 (39,9)	
Absence	135 (66,5)	76 (51,4)	211 (60,1)	
Perineural invasion, n (%)				**0,022**
Presence	58 (28,4)	60 (40,5)	118 (33,5)	
Absence	146 (71,6)	88 (59,5)	234 (66,5)	
Pathological stage, n (%)				**<0,001**
I	112 (54,6)	53 (34,6)	165 (46,1)	
II	47 (22,9)	41 (26,8)	88 (24,6)	
III	46 (22,4)	59 (38,6)	105 (29,3)	
Therapeutic approach				
Type of surgery approach, n (%)				**0,006**
Open	96 (46,6)	94 (61,4)	190 (52,9)	
Laparoscopic	110 (53,4)	59 (38,6)	169 (47,1)	
Type of resection, n (%)				0,183
Total gastrectomy	76 (36,9)	56 (36,6)	132 (36,8)	
Distal gastrectomy, Billroth II	114 (55,3)	92 (60,1)	206 (57,4)	
Distal gastrectomy, Roux-en-Y	16 (7,8)	5 (3,3)	21 (5,8)	
Type of lymphadenectomy, n (%)				**0,005**
D1	48 (23,3)	54 (35,3)	102 (28,4)	
D1+	69 (33,5)	57 (37,3)	126 (35,1)	
D2	89 (43,2)	42 (27,5)	131 (36,5)	
Neoadjuvant therapy, n (%)				0,059
Presence	34 (16,5)	14 (9,2)	48 (13,4)	
Absence	172 (83,5)	139 (90,8)	311 (86,6)	

Table 1: Comparative analysis LPLR versus HPLR: Baseline characteristics.

LPLR, low platelet-lymphocyte ratio; HPLR, high platelet-lymphocyte ratio; SD, standard deviation; ASA, American Society of Anesthesiologists; BMI, body mass index; NOS, none other specification; LN, lymph nodes

*Nonparametric test Mann Whitney U

Are highlighted in bold significant p values (<0,05)

	Crude HR	CI 95%	p value	Adjusted HR	CI 95%	p value
OS	1,002	1,001 – 1,004	**0,004**	1,001	1,000 – 1,003	0,058
DFS	1,002	1,000 – 1,004	**0,015**	1,002	0,999 – 1,005	0,117

Table 2: Survival analysis: Cox regression - PLR (Crude HR and Adjusted HR for pStage).

OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval

Are highlighted in bold significant p values (<0,05)

Overall Survival (OS)						
	Crude HR	**CI 95%**	**p value**	**Adjusted HR**	**CI 95%**	**p value**
PLR						
LPLR	1			1		
HPLR	1,676	1,221 – 2,300	**0,001**	1,308	0,946 – 1,810	0,105
Disease Free Survival (DFS)						
	Crude HR	**CI 95%**	**p value**	**Adjusted HR**	**CI 95%**	**p value**
PLR						
LPLR	1			1		
HPLR	1,665	1,074 – 2,582	**0,023**	1,096	0,703 – 1,709	0,686

Table 3: Survival analysis: Cox regression – HPLR versus LPLR (Crude HR and Adjusted HR for pStage).

PLR, platelet-lymphocyte ratio; LPLR, low platelet-lymphocyte ratio; HPLR, high platelet-lymphocyte ratio; HR, hazard ratio; CI, confidence interval

Are highlighted in bold significant p values (<0,05)

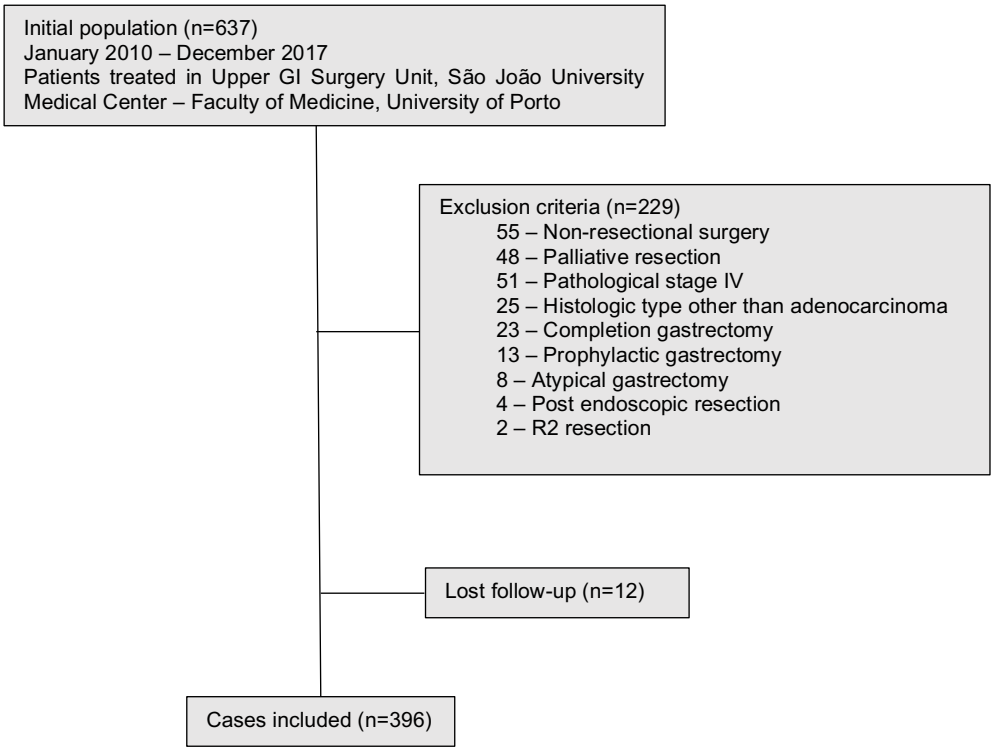


Figure 1: Flow chart of the study design

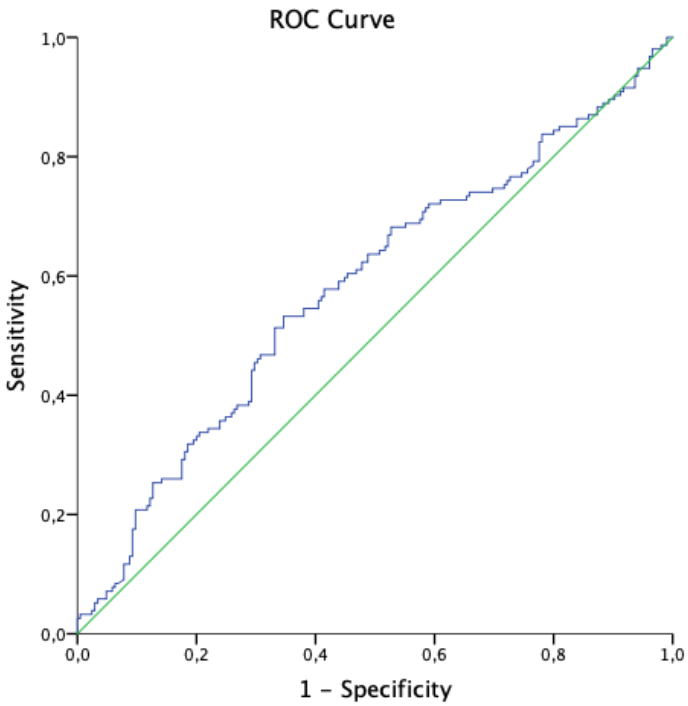


Figure 2: ROC Curve of PLR for OS

PLR, platelet-lymphocyte ratio; OS, overall survival

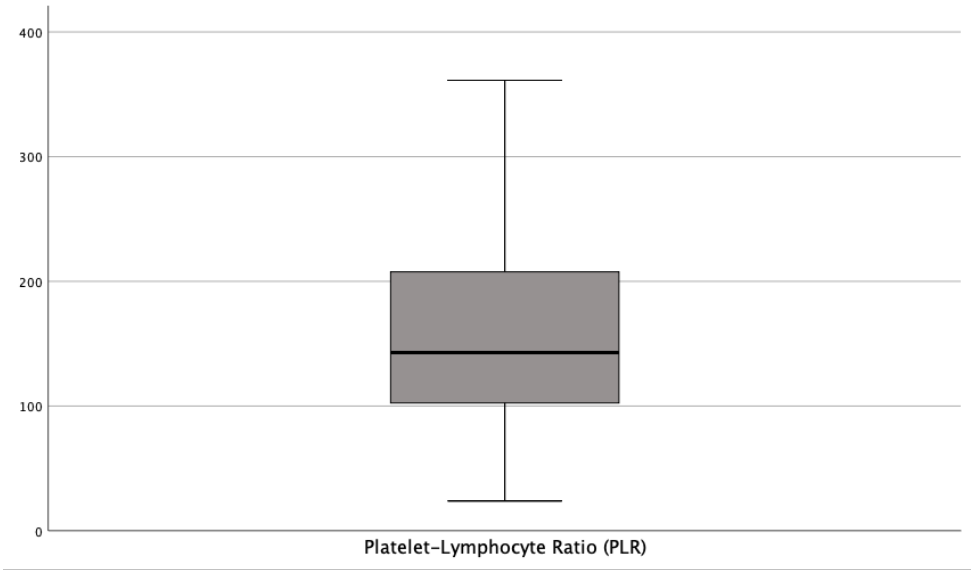
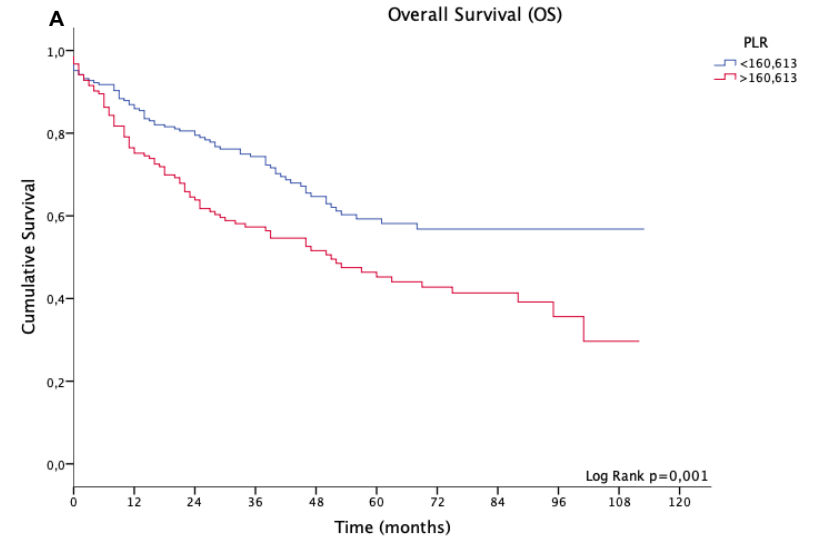


Figure 3: Boxplot of PLR distribution

PLR, platelet-lymphocyte ratio



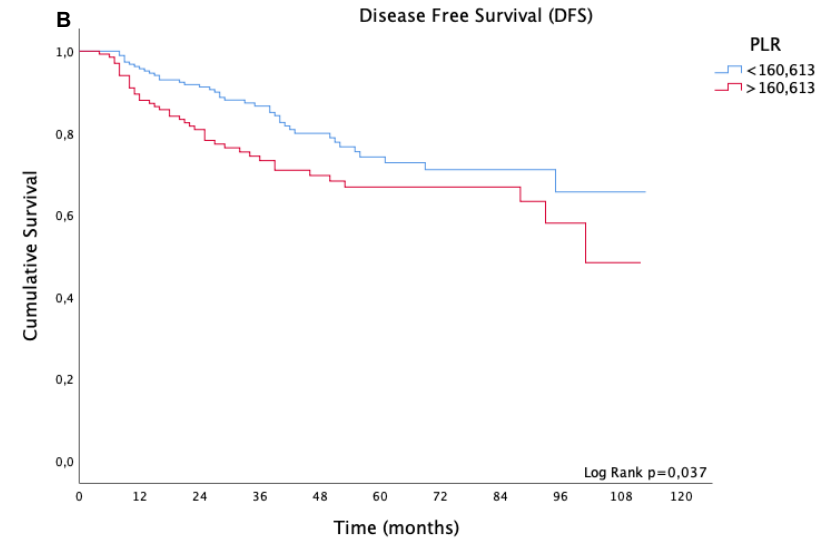


Figure 4: Comparative analysis HPLR versus LPLR - Survival analysis: Kaplan-Meier

A – KM curves for OS; **B** – KM curves for DFS

KM, Kaplan-Meier; OS, overall survival; DFS, disease free survival; LPLR, low platelet-lymphocyte ratio; HPLR, high platelet-lymphocyte ratio

Agradecimentos

Agradeço, primeiramente, ao Dr. Hugo Sousa e ao Dr. Jorge Nogueiro pela orientação, pelo empenho e pelos ensinamentos que levo para a vida futura. Um grande obrigado à Teresa e ao Daniel pela companhia e entreajuda ao longo desta jornada.

Um obrigado infinito aos meus pais, ao meu irmão e aos meus avós, sem os quais este percurso não teria feito sentido. Obrigado por me mostrarem a luz ao fundo do túnel e me darem alento para levar tudo isto a bom porto.

Um obrigado sem fim à Inês, pelo apoio de todas as horas, um obrigado por tudo.

Por fim, mas com igual importância, um obrigado a todos os meus amigos, pelos momentos de lazer, trabalho, aprendizagem, por todos os projetos, por todas as noites mal dormidas, por todos os dias bem passados. Obrigado por estes, sem dúvida memoráveis, 6 grandes anos.

Anexos

1 – Parecer da Comissão de Ética

2 – Normas da Revista

248-12 À Direcção Clínica
2012/13

↳ CA c/ proc
Prom DC
7.12.2013

AUTORIZADO
CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 28 FEV 2013
Presidente do Conselho de Administração
(Prof. Doutor António Ferreira)
Directora Clínica | Enfermeira Directora | Vogal Executiva | Vogal Executivo
(Dra Margarida Tavares) | (Enfermeira Eurídice Portela) | (Dra. Maria Ramos) | (Dr. João Oliveira)

Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Hugo Miguel Teixeira Ferraz dos Santos Sousa

Título do projecto de investigação: Surgical treatment for Gastric and GEJ cancer - A prospective study

Pretendendo realizar no(s) Serviço(s) de Cirurgia Geral do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 20 / Novembro / 2012

O INVESTIGADOR/PROMOTOR

SÃO JOÃO

Comissão de Ética para a Saúde – Centro Hospitalar São João

Parecer

Título do Projecto: Surgical Treatment for Gastric and GEJ câncer – A prospective study.

Nome do Investigador Principal: Dr. Hugo Miguel Teixeira Ferraz dos Santos Sousa.

Local onde sera realizado o estudo: Serviço de Cirurgia Geral – CHSJ, havendo autorização do respectivo Diretor de Serviço para a realização do mesmo.

Objectivo do estudo: Avaliação do perfil clínico-patológico dos doentes com cancro gástrico e da junção esófago-gástrica tratados na instituição.
Avaliação da sobrevida e dos padrões de recivida dos referidos doentes.

Período previsto de conclusão: 2014

Benefício / Risco: Não existem benefícios imediatos, nem riscos para os doentes.

Respeito pela liberdade e autonomia do sujeito do ensaio: *Não está previsto a obtenção de consentimento informado. No entanto, e uma vez que se trata de um estudo prospetivo, o protocolo deverá incluir o consentimento informado escrito, complementado por um suporte de informação escrita para os participantes, explicando os objetivos, e a liberdade em participar.*

Confidencialidade dos dados: está garantida a confidencialidade dos dados e esta informação será restrita ao investigador principal.

SÃO JOÃO

O Investigador Principal dispõe de competência técnica e científica para a realização do estudo.

Não prevê a realização de questionário.

Custos: O estudo não prevê custos acrescidos para os participantes nem para a instituição.

Parecer: Em face da análise do protocolo de estudo, proponho a sua aprovação pela CES do CHSJ.

Porto, CHSJ, 19 de dezembro de 2012

O Relator

John Rodrigues Preto CIRURGIA GERAL 35684

Dr. John Preto

03-01-2013

Foi entregue um exemplar do consentimento informado, junto com a informação escrita para o participante no estudo, pelo que proponho a sua aprovação pela CES.

John Rodrigues Preto CIRURGIA GERAL 35684

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☑
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Hugo Miguel Teixeira Ferraz dos Santos Sousa,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 20 / Novembro / 2012

21/12/12

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de ___/___/___

Considerados os esclarecimentos prestados pelo investigador

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

2013.01.03

EUROPEAN JOURNAL OF SURGICAL ONCOLOGY

AUTHOR INFORMATION PACK

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ISSN: 0748-7983

DESCRIPTION

The *EJSO* aims to advance surgical oncology research and practice through the publication of original research articles, review articles, editorials, debates and correspondence.

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INTRODUCTION

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Editorials. These may be proffered on any subject of relevance to surgical oncology. Editorials should offer informed comment on an issue of topical interest and should generally be less than 1500 words and contain no more than 10 references. Editorials do not require an abstract. Authors interested in preparing an Editorial should contact the Editorial Office prior to the preparation of their manuscript (ejso@elsevier.com).

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