

CA72-4 ANTIGEN LEVELS IN SERUM AND PERITONEAL WASHING IN GASTRIC CANCER. Correlation with morphological aspects of neoplasia

Leonardo Landim **FERNANDES**¹, Lourdes Conceição **MARTINS**¹, Carlos Alberto **NAGASHIMA**², Ana Cibele **NAGAE**¹, Daniel Reis **WAISBERG**¹ and Jaques **WAISBERG**¹

ABSTRACT – *Background* - Determining levels of tumor markers in peritoneal washing enables likelihood of peritoneal recurrence to be ascertained in patients with high marker levels, thereby allowing provision of more accurate adjuvant treatment and postoperative follow up. *Aim* – To analyze the relationship between levels of tumor marker CA72-4 in serum and peritoneal washing, and morphological aspects of gastric carcinoma. *Method* - This study analyzed 32 consecutively-operated patients with gastric carcinoma, who underwent subtotal, total or palliative gastrectomy. The variables studied were CA72-4 levels in serum and peritoneal washing, lesion site, stage, degree of cell differentiation, operation performed, and number of extirpated and involvement lymph nodes. Of the 32 patient sample, 21 (65.6%) were male and 11 (34.4%) female. Mean age was 62.6 ± 14.2 years (29 to 91 years). Following anesthetic induction, peripheral venous blood was collected through percutaneous puncture of an upper limb vein. After the procedure, 50 mL of physiologic solution at 37°C was introduced into the cul-de-sac. A 10 mL volume of this liquid was aspirated from the cavity and the peritoneal washing tested for CA72-4 levels. Normal values for CA72-4 levels in serum were considered ≤ 7 U/mL and high levels as >7 U/mL, whilst for the peritoneal washing normal levels were ≤ 0.61 U/mL, and abnormal >0.61 U/mL. *Results* - Mean pre-operative serum levels for CA72-4 were 6.55 U/mL ± 15.30 (0.3 to 75.30 U/mL) whilst the mean level of CA72-4 in peritoneal washing was 8.50 U/mL ± 26.72 (0.3 to 142.00 U/mL); correlation between these levels was significant. Lymph nodes involvement by the gastric carcinoma correlated significantly with higher CA72-4 levels in both serum and peritoneal wash. There was no statistically significant correlation between serum level of CA72-4 and invasion into serosa by the gastric carcinoma. There was however, significant correlation between peritoneal washing levels of CA72-4 and involvement of serosa by gastric carcinoma. There was also a significant correlation between more advanced stages of gastric carcinoma and higher levels of CA72-4 in the peritoneal washing, although serum levels of CA72-4 and more advanced stage of gastric neoplasia showed no significant correlation. Degrees of cellular differentiation in the gastric carcinoma did not differ significantly with CA72-4 levels in serum or peritoneal washing. *Conclusions* - High levels of CA72-4 in peritoneal washing correlated significantly with lymph node metastasis and serosa involvement by the neoplasia, and also with more advanced stage of gastric carcinoma. The levels of CA72-4 in the blood correlated significantly with lymph node involvement by the gastric carcinoma, but not with serosa invasion or more advanced stage of neoplasia.

HEADINGS – Tumor markers, biological. Gastric neoplasms. Adenocarcinoma. Peritoneal lavage.

INTRODUCTION

Gastric carcinoma present high rates of recurrence particularly after potentially curative surgery for locally advanced disease, where peritoneal metastases remain the most common site of this recurrence^(12, 28, 37).

Recurrence is most often at an advanced stage of the neoplastic disease, generally precluding any curative treatment. Therefore perhaps preventing or reducing of recurrence should take precedent over early detection^(2, 22, 31).

The search for a more sensitive and specific tumor marker for gastric carcinoma has led to the discovery of monoclonal antibodies against tumor tissues and epithelial tumor cell lines. One such marker includes

the antigen against the 72-4 carbohydrate epitope (CA72-4) defined by the monoclonal antibodies CC49 and B72-3. These antibodies detect the presence of the respective epitopes in high molecular weight mucin-type glycoprotein, called TAG-72 found in plasma of patients with malignant gastrointestinal neoplasia^(4, 7, 9, 13, 30). The CA72-4 antigen is a glycoprotein weighing between 200,000 and 400,000 Daltons^(18, 25, 32, 33). No positive reaction has been detected in normal adult tissue⁽⁶⁾.

Studies have shown CA72-4 assay sensitivity to be lower than or equal to CEA in colorectal carcinoma, but greater than or equal to CEA in gastric carcinoma^(5, 8, 10, 13, 15, 36).

¹Surgical Gastroenterology and ²Clinical Laboratory Departments, "Hospital do Servidor Público Estadual", São Paulo, SP, Brazil.

Correspondence: Dr. Jaques Waisberg – Rua das Figueiras, 550 – apt. 134 – Bairro Jardim – 09080-300 – Santo André, SP. Email: jaqueswaisberg@uol.com.br

Determining levels of tumor markers in peritoneal washing enables likelihood of peritoneal recurrence to be ascertained in patients with high levels. This event may allow provision of more accurate adjunct treatment and post-operative follow up. To date however, few studies have addressed this issue^(3, 17, 23, 29).

The objective of this study was to analyze the relationship between levels of tumor marker CA72-4 in the serum and peritoneal washing of patients operated on gastric carcinoma, along with morphological aspects of the neoplasia.

METHOD

This study analyzed 32 gastric carcinoma patients who underwent curative or palliative surgical treatment between July 2004 and June 2005. The study was approved by the Ethics Committee of the hospital and all patients signed an informed consent.

The term curative denoted absence of macroscopic neoplastic residual disease following the operation, according to pre-operative stage and intra-operative assessment by the surgeon, and the presence of free surgical margins in of the resection specimen. The term palliation was used to designate operations in which all neoplastic macroscopic removal was not achieved, and where procedures to improve patient's quality of life were performed.

Of the 32 patient sample, 21 (65.6%) were male and 11 (34.4%) female. Twenty five (78.1%) were white and seven (21.9%) were black. Mean age was 62.6 ±14.2 years (29 to 91 years).

The control group, formed to establish the normal level of CA72-4 in peritoneal washing, comprised patients with uncomplicated calculous disease of the gallbladder submitted to laparoscopic cholecystectomy. The control group consisted of 18 patients, 4 (22.2%) men and 14 (77.8%) women, all white and with a mean age of 46.2 ± 8.2 years. All subjects had undergone gastroscopy revealing no gastric neoplasia.

Peripheral venous blood samples were collected from the upper member vein from both patient groups immediately after anesthetic induction, in order to determine serum levels of CA72-4. Following the operative procedure, 50 mL of physiologic solution at 37°C was introduced into the Douglas sack and 10 mL aspirated to determine CA72-4 levels in peritoneal washing.

The CA72-4 assay was used to determine glycoprotein associated to the TAG72 tumor antigen. This test uses two monoclonal antibodies: B72.3, a monoclonal antibody developed against breast cancer metastasis extract, and CC49, a monoclonal antibody which purifies TAG 72⁽⁶⁾. The level of CA72-4 was determined using electrochemoluminescence immunoassay (Elecsys 2010, Roche, Basel, Switzerland) where results were expressed in U/mL.

Normal pre-operative levels for CA72-4 in serum of patients with gastric carcinoma were considered less than or equal to 7 U/mL, whilst high levels as greater than 7 U/mL.

Levels of CA72-4 in peripheral blood and peritoneal wash were compared against the site of the gastric lesion, operation type performed, number of lymph nodes involved by the neoplasia, initial stage (stages I or II on TNM classification) or advanced

stage (stages III or IV on TNM classification), invasion of serosa by the gastric carcinoma and degree of cellular differentiation.

The following statistical models were employed: arithmetic mean and standard deviation, Pearson's correlation test, Fisher's exact test, the Mann-Whitney test, Wilcoxon's test and the Kruskal-Wallis test. For all tests, a level of 0.05 was set for rejection of the null hypothesis (95% confidence interval) in line with current biological study standards.

RESULTS

The gastric carcinoma was located at the antral region in 20 of our patients (62.5%) and in the gastric body or cardia in the remaining 12 (37.6%) subjects. In the present study, a total of 20 patients (62.5%) underwent subtotal gastrectomy, 10 patients (31.2%) had total gastrectomy and 2 palliative gastrectomies (6.25%). The mean number of lymph nodes extirpated from the 30 individuals who underwent curative operations (subtotal or total gastrectomy) was 17.2 lymph nodes.

The mean pre-operative serum level of CA72-4 was 6.5 U/mL ± 15.3 (0.3 to 75.3 U/mL). Five (15.6%) patients presented CA72-4 serum levels of over 7.0 U/mL, whilst the remaining 27 patients (84.4%) had levels less than or equal to 7.0 U/mL.

ROC curves (Receiver Operating Characteristics)⁽⁸⁾ revealed sensitivity and specificity values defined for CA72-4 levels in peritoneal washing for the cut-off points, in comparison of values obtained in the control group and patient group with gastric carcinoma. This result showed low sensitivity and high specificity of CA72-4 in peritoneal washing. Concerning this result, normal levels for CA72-4 in peritoneal washing of patients with gastric carcinoma extirpation were considered less than or equal to 0.61 U/mL, and abnormal levels as greater than 0.61 U/mL (specificity of 100% and sensitivity of 40.6%). There was significant correlation ($P=0.006$) between serum and peritoneal washing levels of CA72-4.

Mean CA72-4 levels in peritoneal washing were 8.60 U/mL ± 26.72 (0.3 to 142.0 U/mL). Three patients (40.6%) presented CA72-4 peritoneal washing levels of over 0.61 U/mL, whilst 19 patients (59.4%) had values less than or equal to 0.61 U/mL. There was significant correlation ($P=0.006$) between CA72-4 levels in the serum and peritoneal washing (Table 1).

Extirpated lymph nodes revealed metastases in 19 patients (59.4%), whereas a further 11 (34.4%) patients exhibited lymph nodes free. Two (6.25%) patients underwent palliative operations. Significant difference was observed between CA72-4 levels in serum ($P=0.05$) and peritoneal washing ($P=0.03$), and lymph node infiltration by the gastric carcinoma (Table 1).

TABLE 1. Correlation of serum and peritoneal wash levels of CA72-4 marker with lymph nodes involvement in gastric carcinoma

Lymph nodes involvement	Levels			
	Serum		Peritoneal wash	
	Negative	Positive	Negative	Positive
Absent	11 (34.3%)	--	20 (31.25%)	1 (3.12%)*
Present	16 (50%)	5 (15.65%)	9 (28.12%)	12 (37.5%)

* $P=0.03$

The lesion did not compromise the serosa in 6 (18.8%) patients but invaded the layer in 26 (81.2%) subjects. There was no significant correlation ($P = 0.55$) between serum CA72-4 levels and invasion of gastric serosa by the carcinoma. There was however, significant correlation ($P = 0.02$) between CA72-4 levels in peritoneal washing and compromise of serosa by the gastric carcinoma (Table 2).

TABLE 2. Correlation of serum and peritoneal wash levels of CA72-4 with serosa compromise by the gastric carcinoma

Serosa involvement	Levels			
	Serum		Peritoneal wash	
	Negative	Positive	Negative	Positive
Absent	6 (18.75%)	--	6 (18.75%)	--
Present	21 (65.62%)	5 (15.62%)	13 (40.62%)	13 (40.62%)*

* $P = 0.02$

With regard to TNM stage classification, 9 (28.1%) patients were at initial stages (stages I and II), 23 (71.9%) were at advanced stages (stages III and IV). No significant correlation ($P = 0.13$) was found between the CA72-4 serum levels and more advanced stages of gastric neoplasia (Table 3), but significant correlation (0.03) was observed between CA72-4 levels in peritoneal washing and advanced stages of gastric carcinoma.

Concerning degree of cellular differentiation, 7 (21.9%) patients showed non-differentiated gastric neoplasia, 14 (43.8%) poor differentiated, 9 (28.1%) moderately differentiated and 1 (6.3%) well differentiated. No significant correlation was seen between CA72-4 levels in serum ($P = 0.24$) or peritoneal washing ($P = 0.81$), and different degrees of cellular differentiation.

TABLE 3. Correlation of serum and peritoneal wash levels of CA72-4 marker with initial (I/II) and advanced (III/IV) stages of the gastric carcinoma

Stage	Levels			
	Serum		Peritoneal wash	
	Negative	Positive	Negative	Positive
Stage I/II	9 (28.12%)	--	8 (25%)	1 (3.12%)*
Stage III/IV	18 (56.25%)	5 (15.62%)	11 (34.38%)	12 (37.5%)

* $P = 0.03$

DISCUSSION

Different lesion stages may determine varying degrees of CA72-4 marker access to systemic circulation and consequently return different values^(16,20,24,26). Studies correlating levels of CA72-4 with findings of pathologic exams in gastric carcinoma have shown significantly higher marker levels associated with gastric serosa invasion by the neoplasia, lymphonodal metastases and invasion of veins or lymphatic vessels into the gastric wall^(11, 14, 19, 21, 27, 34). MATTAR et al.⁽²⁷⁾, on comparing serum CA72-4 levels in 44 patients with gastric carcinoma, and correlating with neoplasia stage, histology type and presence of lymphonodal metastases, found

9% positivity in patients at stages I and II, and 60.6% at stages III and IV, concluding that pre-operative levels of CA72-4 in serum are predictive for advanced stages of gastric carcinoma.

Data from the present series has shown that patients at a more advanced stage of disease (stages III and IV) have higher levels of CA72-4 in serum, resembling results observed by TOMASICH et al.⁽³⁴⁾. The relationship between increased serum CA72-4 levels and serosa invasion by the gastric carcinoma did not prove significant, but higher levels did reach significance for lymphonodal compromise. It is possible the CA72-4 antigen of neoplastic cells is not released into the blood stream at early stages of carcinoma, but may enter circulation if lymphatic vessels or veins have been invaded by neoplasia spread. This may partly explain the finding of higher serum CA72-4 levels in gastric carcinoma which are locally more advanced.

We observed no significant correlation between degree of cellular differentiation of gastric carcinoma and high levels of CA72-4, as also related by other authors^(14, 16, 34).

In the context of the peritoneal metastases formation mechanism, free neoplastic cells, released when the carcinoma invades the serosa, are considered factors in its development⁽²⁹⁾. Production of tumor markers by neoplastic cells present in the peritoneal cavity is considered the determining factor for levels in the peritoneal washing. Such levels depend on the number of cells present in the peritoneal cavity as well as their capacity to produce the marker^(1, 3, 17, 23, 29, 35). Thus, raised serum levels of the tumor marker may be the result of increased production within the peritoneal cavity which, in turn, results in higher peritoneal and serum levels. However, tumor marker produced by the primary neoplasia or its metastases can be captured by the systemic circulation, and discharged in the peritoneal cavity thereby increasing local levels of CA72-4^(1, 3, 17, 29, 35).

Therefore, the level of CA72-4 in the peritoneal washing may essentially reflect the presence of malignant cells within the peritoneal cavity. If these cells maintain their ability to produce tumor markers then determining levels of these substances may be able to indicate the presence of such cells in the peritoneum and consequently suggest adoption of adjunct therapy to treat the microscopic disease^(1, 17, 35). Less raised levels of CA72-4 in a patient may indicate the presence of few cells in the peritoneal cavity, resulting in the possibility of longer survival times than in patients with higher peritoneal levels of CA72-4. On the other hand, less raised levels of CA72-4 could reflect differences in CA72-4 marker producing capacity of neoplastic cells in the peritoneal cavity^(3, 23, 29).

This raises the question as to whether findings of high peritoneal levels of CA72-4 necessarily imply the presence of neoplastic cells in the cavity. Given that neoplastic cells can normally only be exfoliated from lesions which have invaded the serosa organ, discharge mechanisms may exist that release tumor markers from gastric mucous to the serosa and on to the peritoneal cavity. Early gastric carcinoma can be associated to raise tumor marker in the peritoneal washing, suggesting the presence of paths of tumor cell penetration through the stomach wall without there being organ serosa invasion. The existence of lymphatic channels throughout the whole gastric wall, or

lymphonodal micrometastases, number some of these possible routes. This possibility is partially supported by the fact that peritoneal recurrence takes place in around 1% of patients with early gastric carcinoma^(1, 17, 23, 29, 35).

Although CA72-4 marker secretion by the gastric neoplasia depends, among other factors, on lesion volume and vascularity as well as patient immunity, levels of CA72-4 in the peritoneum and serum are considered closely related^(17, 29, 35). The present study demonstrated significant correlation between serum and peritoneal levels of CA72-4. This close relationship revealed that the sensitivity of histological prediction of serosa invasion according to the level of CA72-4 in peritoneal washing was higher than for levels found in serum.

MANDORWSKI et al.⁽²³⁾ studied levels of CA72-4 in the serum and peritoneal washing of 40 patients with gastric carcinoma. Eleven of these patients were classified as stage I or II, and 29 at stage III or IV. These authors observed that serum and peritoneal washing values of CA72-4 marker was raised in 47.5% of stage I/II patients and 57.5% of those at stage II/IV, respectively. These authors observed no difference in values between patients with stage I/II gastric carcinoma versus the control group. This contrasts the present series which found peritoneal levels of CA72-4 to be significantly higher in patients with more advanced stage gastric carcinoma.

As the prognostic of patients with recurrent previously operated gastric carcinoma is poor, selection for adjunct postoperative systemic and/or regional therapy based on risk of recurrence may represent an acceptable approach to improve the prognostic^(22, 28, 37). In patients with raised preoperative serum and/or peritoneal washing levels of CA72-4, peritoneal recurrence of gastric carcinoma may occur soon after surgery^(3, 17, 29, 35). The level of CA72-4 in the peritoneal washing can prove useful as an indicator for detecting occult peritoneal spread in patients with curatively operated gastric carcinomas.

CONCLUSIONS

Raised levels of CA72-4 in the peritoneal washing correlated significantly with involvement of lymph nodes and gastric serosa by the neoplasia, as well as with more advanced stage of gastric carcinoma. Serum levels of CA72-4 correlated significantly with lymph nodes involvement by the gastric carcinoma, but not with serosa organ invasion or more advanced stage of neoplasia.

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RESUMO – Racional - A determinação dos níveis de marcadores tumorais no lavado peritoneal apresenta a possibilidade de indicar tendência à recidiva peritoneal nos doentes com níveis elevados, o que pode indicar tratamento adjuvante e seguimento pós-operatório mais acurado. **Objetivo** - Analisar a relação entre os níveis do marcador tumoral CA72-4 no sangue e no lavado peritoneal e os aspectos morfológicos do carcinoma gástrico. **Método** - Foram analisados 32 doentes operados consecutivamente, com carcinoma gástrico e submetidos a gastrectomia subtotal, total ou paliativa. Foram estudadas as seguintes variáveis: nível sérico e no lavado peritoneal do CA72-4, localização da lesão, estágio, grau de diferenciação celular, operação realizada, e número de linfonodos extirpados e acometidos. Dos 32 doentes do estudo, 21 (65,6%) eram homens e 11 (34,4%) mulheres. A média de idade foi de 62,6 ± 14,2 anos (29 a 91 anos). Logo após a indução anestésica, o sangue venoso periférico foi coletado por punção percutânea de veia do membro superior. Após o término da operação, 50 mL de solução fisiológica aquecida a 37°C foi derramado no fundo de saco. Desse líquido, foi aspirado o volume de 10 mL e encaminhado para a determinação do nível do CA72-4 no lavado peritoneal. Para o nível sérico do CA72-4 foram considerados normais os valores ≤ a 7 U/mL e elevados os valores > que 7 U/mL. Para o nível no lavado peritoneal do CA72-4 foram considerados normais os valores ≤ 0,61 U/mL, e alterados os valores > que 0,61 U/mL. **Resultados** - A média do nível sérico do CA72-4 no pré-operatório foi de 6,55 U/mL ± 15,30 (0,3 a 75,30 U/mL) e a média do nível do CA72-4 no lavado peritoneal foi de 8,60 U/mL ± 26,72 (0,3 a 142,00 U/mL); a correlação entre esses níveis foi significativa. O acometimento linfonodal pelo carcinoma gástrico correlacionou-se significativamente com os níveis mais elevados do CA72-4 sérico e peritoneal. Não houve diferença significativa entre o nível sérico do CA72-4 e a invasão da serosa do estômago pelo carcinoma gástrico. Houve correlação significativa entre os níveis do CA72-4 no lavado peritoneal e o acometimento da serosa do estômago pelo carcinoma gástrico. Houve diferença significativa entre o estágio mais avançado do carcinoma gástrico e o nível mais elevado do CA72-4 no lavado peritoneal, porém o nível sérico do CA72-4 e o estágio mais avançado da neoplasia gástrica não mostraram correlação significativa. Os diferentes graus de diferenciação celular do carcinoma gástrico não mostraram diferenças significativas com os níveis do CA72-4 no sangue e no lavado peritoneal. **Conclusões** - O nível aumentado do CA72-4 no lavado peritoneal correlacionou-se significativamente com o acometimento linfonodal e da serosa gástrica pela neoplasia e com estágio mais avançado do carcinoma gástrico. O nível sérico do CA72-4 correlacionou-se significativamente com o acometimento linfonodal pelo carcinoma gástrico, porém não mostrou correlação com a invasão da serosa do órgão e com o estágio mais avançado da neoplasia.

DESCRITORES – Marcadores biológicos de tumor. Neoplasias gástricas. Adenocarcinoma. Lavagem peritoneal.

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