Clinical Significance of CA125 Level with Clinicopathological Variables and Peritoneal Dissemination in Patients with Gastric Carcinoma

Abstract

Background: Serum tumor markers have been shown to correlate with the clinical status of patients with advanced gastric cancer. However, the clinical significance of tumor marker in patients with peritoneal dissemination has not been fully verified. Peritoneal metastasis is a crucial factor for the prognosis in gastric cancer, but its diagnosis is difficult before laparotomy. This study analyzed the usefulness of tumor marker CA125 level in gastric cancer & diagnosis of peritoneal metastasis in gastric cancer.

Objective: This study is an evaluation of serum levels in the tumor markers CA125 in gastric cancer patients in preoperative periods to determine the Relationship of preoperative CA125 level with clinicopathological variables & to predict association of CA125 level with peritoneal dissemination in gastric carcinoma.

Methods: A prospective cross sectional study was done of 61 patients diagnosed with gastric cancer treated at a single institution in Bangladesh National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, Bangladesh from July 2010 - December 2011. Analyses were performed to identify patient and tumor-related characteristics and to identify peritoneal metastasis. The sera from 61 patients with gastric cancer were measured for CA125 levels using a commercial immunoradiometric assay. All the patients underwent diagnostic imaging with computed tomography (CT) or ultrasound (US) before laparotomy. Peritoneal involvement was confirmed by either ascites diagnosed by USG or CT, direct visualization of metastatic deposits during surgery and detection of cancer cell by peritoneal wash fluid taken after laparotomy.

Results: The serum levels of CA125 the cutoff value of 35 U/ml was regarded as positive. Preoperative levels of CA125 were above the cut-off levels in 23% of all cases. A total of 30 (49.2%) patients were showed peritoneal involvement. The CA125 level was significantly correlated with the degree of peritoneal dissemination and the existence of malignant ascites. In particular, the serum CA125 levels showed sensitivity 73%, specificity 86%, and the highest odd ratio (18.33 95% CI) for predicting peritoneal metastasis. The positive and negative predictive values of CA125 were 65% and 91%, respectively. So in this study preoperative serum CA125 levels may provide a value in determining depth of invasion, lymph node involvement & metastasis in patients with gastric cancer. CA125 was very sensitive in detecting peritoneal dissemination in gastric carcinoma patients.

Conclusion: In this study Preoperative serum Measurement of the serum CA125 titer may be a powerful predictor of peritoneal metastases in patients with gastric carcinoma & may provide a value in determining depth of invasion, lymph node involvement & metastasis in patients with gastric cancer.

Keywords: CA125 level; Peritoneal metastasis; Gastric carcinoma

Introduction

Serum CA125 levels are known to be elevated in peritoneal inflammation and in carcinomatosis, and are widely used in the diagnosis of ovarian cancer [1]. A significant relationship between CA125 and gastric cancer with peritoneal dissemination has also been reported [2].

Recently, various tumors markers have been developed and it is known that the serum levels of markers such as carcino-embryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and carbohydrate antigen 125 (CA125) are elevated in patients with advanced gastric cancer [3]. However, the clinical usefulness of tumor markers has not been well defined from a diagnostic and therapeutic point of view. Tumor markers are not useful in diagnosis or screening disease because of low sensitivity and specificity. Reports have shown the value of tumor markers as a prognostic factor for patients with advanced gastric cancer [4].
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To determine the Relationship of preoperative CA125 level with clinicopathological variables & to predict association of CA125 level with peritoneal dissemination in gastric carcinoma. Inclusion criteria for the study was histologically diagnosed cases of gastric adenocarcinoma and exclusion criteria were patients already received operative treatment, chemotherapy and radiotherapy, patients who have no CA125 level and who do not want to include in the study.

Results

From July 2010-December 2011, sixty one patients diagnosed as adenocarcinoma of stomach was undertaken for study from National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, Bangladesh. The patients’ clinicopathological factors are shown in Table 1. In the study 37 patients’ age was <55 years (60.7%) and 24 patients’ age was >55 years (37.3%). The mean age of the patients was 52.99 years (±SD, 12.11 years; range, 20-80 years). Table 2 showed that the majority of patients were male (46, 75.4%) with a male female ratio of 3:1. A total of 17 (27.9%) patients were positive for serum 125 (range = 0.80 -1747.80 ng/mL).

The patients’ sex distribution were shown in Figure 1. In the study 46 patients was male (75%) and 15 patients was female (25%) with a male female ratio of 3:1. Among the patients histogram (Figure 2) showed that most of the patients age was more than 45 years (19 patients’ age was 45-54 years, 17 patients was 55-64 years and 12 patients was >65 years) at the time of presentation.

Table 2 showed Demography of the patients with gastric cancer in 61 cases. Symptoms at presentation, were weight loss in 41.0%, vomiting in 67.2%. Pain on epigastrium was presented by 63.9%, anorexia by 55.7%, of patients. Malena was presented in 36.1 % patients. Gastroenterostomy was presented by 61.9%, vomiting in 67.2%. Pain on epigastrium was presented by 63.9%, anorexia by 55.7%, of patients. Malena was presented in 36.1 % patients.

Table 3 showed that most of the patients were at stage III (29.5%) and at stage IV (50.8%). Among differentiation moderately differentiated 45.9% & poorly differentiated was 39.3%. Distal gastrectomy was performed in 45.9% and gastric bypass surgery in 14.8% patients.

Collection of blood sample

Peripheral blood samples for CA125 were obtained from each patient before surgery. Their data were used for comparison with the patients clinicopathological parameters & with the patients in whom peritoneal carcinomatosis was present in carcinoma stomach.

Specimen collection

The presence of peritoneal metastasis was diagnosed though one of the following means USG/computed tomography, a positive cytology after peritoneal aspiration or lavage, or direct visualization through open surgery. Peritoneal washing for cytologic examination was performed immediately after the laparotomy or ascitic fluid before and in some cases after laparotomy.

Methodology

Aims and objective

To determine the Relationship of preoperative CA125 level with clinicopathological variables & to predict association of CA125 level with peritoneal dissemination in gastric carcinoma. Peritoneal cytology was the gold standard for determining peritoneal spread of gastric carcinoma, yet its sensitivity is relatively low, lying in the 14% to 21% range for peritoneal metastasis in gastric cancer. Therefore this study analyzed the usefulness of tumor marker with clinicopathological parameters and peritoneal metastasis in gastric cancer.

Assay:
The sera were assayed for CA125 with an immunoradiometric assay using a Pathozyme ovarian cancer antigen (OD287), Omega Diagnostics Ltd. UK.

Intraoperative staging:
At operation, gastric cancers were staged for local, nodal and metastatic spread.

Results

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The sensitivity and specificity of CA125 were found to be 73% and 86% and the positive and negative predictive values of CA125 were 65% and 91%, respectively Table 7.

Table 1: Patient Characteristics (n=61).

| Variable   | Number | %   |
|------------|--------|-----|
| Age        |        |     |
| <55        | 37     | 60.7|
| >55        | 24     | 39.3|
| Sex        |        |     |
| Male       | 46     | 75.4|
| Female     | 15     | 24.6|
| CA125 level|        |     |
| 35IU/L     | 44     | 72.1|
| >35IU/L    | 17     | 27.9|

CA 125 (Cancer antigen! 25)

Table 2: Demography of the patients with gastric cancer (n=61).

| Variable                        | Value | %   |
|---------------------------------|-------|-----|
| Symptoms at Presentation        |       |     |
| Weight loss                     | 25    | 41  |
| Vomiting                        | 41    | 67.2|
| Pain on epigastrium             | 39    | 63.9|
| Anorexia                        | 34    | 55.7|
| Dysphagia                       | 4     | 6.8 |
| Malena                          | 8     | 13.1|
| Lump on abdomen                 | 18    | 21.3|
| Haemoglobin Level               |       |     |
| 5-7 gm/dl                       | 4     | 6.6 |
| 7-10 gm/dl                      | 30    | 55.7|
| > 10 gm/dl                      | 23    | 37.7|
| Nutritional Status              |       |     |
| Poor                            | 23    | 37.7|
| Average                         | 29    | 47.5|
| Good                            | 9     | 14.8|
| Anemia requiring Transfusion    | 24    | 39.3|
| History of Smoking              | 37    | 60.7|
| History of Alcohol use          | 2     | 3.3 |
| Primary Tumor Site              |       |     |
| Pyloric part                    | 26    | 42.6|
| Body and antrum                 | 12    | 19.7|
| Fundus & GO junction            | 1     | 1.6 |
| Diffuse involvement             | 22    | 36.1|

Table 4 a total of 49.2% patients were showed peritoneal involvement. Peritoneal involvement was confirmed by either ascites diagnosed by USG or CT, direct visualization of metastatic deposits during surgery and detection of cancer cell by peritoneal wash fluid taken after laparotomy. Ascites was present in 24.6% patients. Ascites was diagnosed by USG or CT in 16.4% and after laparotomy 8.2% cases. Ten patients (16.4%) were diagnosed with peritoneal disseminations metastatic deposits during surgery. Free cancer cells were detected in 5 patients (8.2%).

In Table 5 clinico-pathological factors was compared with patients positive and negative for Serum CA 125. There was no correlation with CA125 and age (P .32), sex (P .09) & with depth of invasion (P .25). There was significant correlation with the histologic type and CA125 positivity (P .01), Lymph node metastasis (P .03). The CA125 level was significantly associated with the peritoneal involvement (P<.001). Significant difference was not observed for CA125 (P .2) with early and advanced stages of gastric carcinoma confirmed after surgery.

Table 6 shows a comparison of tumor marker for peritoneal dissemination. For CA125 cutoff value ≥35 U/ml was used as a reference value for peritoneal dissemination. However, CA125 had a very high odds ratio of 18.33 for predicting peritoneal dissemination among the markers tested. CA 125 level was more significantly associated with the peritoneal involvement (P<.001).
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Table 3: Pathological characteristics and operability of the patients in gastric cancer (n=61).

| Variable                  | Number | % |
|---------------------------|--------|---|
| Stage                     |        |   |
| I                         | 4      | 6.6 |
| II                        | 8      | 13.1|
| III                       | 18     | 29.5|
| IV                        | 31     | 50.8|
| Resectability             |        |   |
| Resectable                | 33     | 54.1|
| Non resectable            | 18     | 29.5|
| Not operated              | 10     | 16.4|
| Grading                   |        |   |
| Well differentiated       | 9      | 14.8|
| Moderately differentiated | 28     | 45.9|
| Poorly differentiated     | 24     | 39.3|
| Type of Operation         |        |   |
| Distal radical gastrectomy (D1) | 24 | 39.3|
| Palliative distal radical gastrectomy | 4 | 6.6|
| Total radical gastrectomy | 5      | 8.2 |
| Palliative gastrojejunostomy | 9   | 14.8|
| Feeding jejunostomy       | 8      | 13.1|
| No operation              | 11     | 18  |

Table 4: Characteristics of peritoneal dissemination.

| Peritoneal Dissemination | Number | % |
|--------------------------|--------|---|
| Peritoneal cytology +ve  | 5      | 8.2 |
| Visible seedling on OT   | 10     | 16.4|
| Ascites on USG or CT     | 10     | 16.4|
| Ascites on OT            | 5      | 8.2 |
| Peritoneal cytology -ve  | 31     | 50.8|

Table 5: Comparison of Clinico-pathological Factors in Patients.

| Factor                      | CA 125 + ve | CA 125 - ve | p value |
|-----------------------------|-------------|-------------|---------|
| Sex                         |             |             |         |
| Male                        | 10          | 36          | 0.09    |
| Female                      | 7           | 8           |         |
| Age                         |             |             |         |
| ≤ 55                        | 12          | 5           | 0.32    |
| > 55                        | 25          | 19          |         |
| Histological Type           |             |             |         |
| Differentiated              | 6           | 31          | 0.013   |
| Undifferentiated            | 11          | 13          |         |
| Depth of Invasion           |             |             |         |
| Upto Serosa (T1+T2+T3)     | 4           | 27          | 0.078   |
| Beyond Serosa(T4)           | 7           | 14          |         |
| Lymph Node Metastasis       |             |             |         |
| Perigastric (N0+N1)         | 3           | 29          | 0.012   |
| Beyond (N2+N3)              | 8           | 12          |         |
| Peritoneal Involvement      |             |             |         |
| Negative                    | 3           | 28          | <.001   |
| Positive                    | 14          | 16          | 36.4    |
| Stage                       |             |             |         |
| Early stage                 | 1           | 11          | 0.2*    |
| Advanced stage              | 16          | 11          | 50      |

Chi- square test is done to detect significance
*Fisuric Exact test was done to detect significance
Positive and Negative for Serum CA 125.
Table 6: Comparison of the Diagnostic Ability of Serum Tumour Marker.

| Tumour Marker | Peritoneal Dissemination | Odds ratio | 95% CI | χ² test | P value |
|---------------|--------------------------|------------|--------|---------|---------|
|               | Positive (no. of patients) | Negative (no. of patients) |
| CA 125 Positive | 11 | 6 | 18.33 | 4.39-76.64 | 20.45 | <.001 |
| CA 125 Negative | 4 | 40 | |

Level for Peritoneal Dissemination
95% CI: 95% confidence interval.

Table 7: Sensitivity, Specificity positive and negative predictive value of the Tumour markers. 95% CI: 95% confidence interval.

| Tumor Marker | Sensitivity (95% CI) | Specificity (95% CI) | Predictive Value Positive (95% CI) | Predictive Value Negative (95% CI) |
|--------------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| CA 125       | 73% (44-91)          | 86% (73-94)          | 65% (39-85)                       | 91% (77-97)                      |

Discussion

Despite progress in recent years towards the early detection of gastric cancer in the western country and Japan, most patients will already have advanced disease at diagnosis in our country. The majority of patients will die of recurrent disease, even if surgery is thought to be curative at the time.

Recent advances in preoperative diagnosis using ultrasonography or computed tomography provide much more information on peritoneal metastasis before operation. However, it is impossible to obtain information about small peritoneal metastasis preoperatively. Therefore, PWC must be performed in addition to macroscopic observation and palpation in patients with advanced gastric cancer. Therefore, cases positive for PWC are considered as peritoneal metastasis, according to the JCGC [10,11].

The prognostic value of positive cytology findings was recently confirmed also in the West, and a new stage classification for gastric carcinoma, recently published by Japanese Gastric Cancer Association, employs the result of cytologic examination (Cy categories) as one of the key prognostic factors [12].

Gastric cancer-specific tumor markers have not yet been identified, and the tumor markers currently in use have very little benefit as screening tests due to their low sensitivity in early gastric cancer. Although CEA and CA 19-9 are not applied to TNM staging according to the American Joint Committee on Cancer (AJCC) 7th edition [13], they have been recognized as prognostic factors [14].

Although not produced by gastric Cancer cells and with no relation to the histological Subtypes, CA125 is usually elevated in serum when the disease has invaded the serous membrane and...
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In the study mean age of the patients was 52.89 years (SD, 12.11 years; range, 20-80 years). Male & female ratio was 3:1. The mean age of the patients was 52.89 years (SD, 12.11 years; range, 20-80 years). Similar to our study the mean age of the patients with gastric carcinoma were 59 years & 58 years [15,16]. But in other studies mean age was 63.6 ± 11.7 years [9], the mean age of the patient was 61.4 years [12].

Serum CA125 level was measured preoperatively in patients with gastric cancer. A total of 17 (27.9%) patients were positive for serum 125. Nakata B [2] found that in the patients with gastric carcinoma, serum CA125 values had values above the cutoff value in 7.3 cases. According to Hwang GI [8], tumor markers, CA125 showed detection rates of peritoneal metastasis 38.6% cases. As the degree of peritoneal dissemination increased positive rate of CA125 increased. Preoperative serum CA125 level were elevated in 28(52.8%) cases in the study conducted by Bold RJ et al. [19].

Demography of the patients with gastric cancer in 61 cases showed on Table 2. Symptoms at presentation were weight loss in 25 (41.0%) Wt loss by Sougioultzis [20] was 28.9% & similar to our study. Vomiting was presented in 41(67.2%) but it was 75% of cases in study by SA Chowdhury [21]. Pain on epigastrum was presented by 39 (63.9%) but in Sougioultzis [20] Malena was presented in 8 (13.1%) in our study but by SA Chowdhury [21]. Hemetemesis and Melena presented by 6.94% cases Anemia requiring transfusion was in 24 (39.3%) in this study which was similar to Sougioultzis [20] where blood transfusion needed in 41.2% cases. History of smoking in this group was 37 (60.7%) Smoking was 57% cases by SA Chowdhury [21]. Primary tumor site was the pyloric part 26 (42.6%) body and antrum in 12 (19.7%) diffuse involvement of stomach in 22(36.1%) patients. Similar involvement of antrum recorded by Sougioultzis [20] (42.4%).

Those finding demarcate that most of our patients had tumors on pyloric part, most of them suffer from anaemia requiring blood transfusion. They had tendency of smoking but less alcohol intake. Most of the patients had tumors on pyloric part so vomiting was more presented by our patients than dysphagia.

The tumor staging was completed according to AJCC classification of gastric carcinoma. Most patients were at tumor at stage III (29.5%) and 31 at stage IV (50.8%). Most of the patients were also in stage IV in many other studies also [16,22,23]. Among differentiation moderately differentiated 45.9% & poorly differentiated was 39.3%. In a study of our country. Most 57.12% of the gastric adenocarcinomas were poorly differentiated, 13.44% were moderately differentiated [18].

Distal radical gastrectomy was performed in 39.3% patients, palliative distal gastrectomy in 6.6%, similar result was found in other studies of our country. The maximum palliative surgery was distal partial gastrectomy [15]. But in our series gastric bypass surgery in 14.8% patients. In other series Gastrojejunostomy done in older group was 42% cases [21]. In other series by pass operation was done in 7.23% and 5% cases [18]. Among the resectable cases, distal gastrectomy in 45.9%, total gastrectomy 8.2% cases. Among the non resectable cases gastric bypass surgery in 14.8% patients. Fanelli F et al. [23] Forty percent of the patients underwent gastrectomy. Ucar E et al. [16], Total gastrectomy was performed in 58 patients, subtotal gastrectomy in 25, and gastric bypass surgery in 12. Study by Hayes N et al. [22] out of 85 patients thirteen cases were unsuitable for resection and simple bypass was performed in five of these, 11 cases with advanced disease had palliative resections. The tumor staging was completed according to AJCC classification of gastric carcinoma. Most patients were at tumor at stage III (29.5%) and 31 at stage IV (50.8%). Strikingly most of the patients in the study group was in advanced stage and a significant proportion was not suitable for operation. Most of the patients were also in stage IV in many other studies also [16,22,23].

The incidence of peritoneal cytology-positive cases seems to vary considerably among institutions. Total of 49.2% patients were showed peritoneal involvement in our study. It seems to be higher as we included curatively resected and also nonresectable cases in our study. The presence of peritoneal involvement was diagnosed though one of the following means: ultrasonography or computed tomography, a positive cytology after peritoneal aspiration or lavage, ascetic fluid aspiration or direct visualization through open surgery. Fanelli F et al. [23] also include same criteria for peritoneal metastasis.

Kodera Y et al. [12] in their study, cytology was positive in 21% patients. Hwang GI et al. [8] in his study revealed peritoneal dissemination in 15 of 88 patients. Study by Rosenberg R et al. [24] 21.4% per cent had detected free peritoneal cytology-positive in the peritoneal lavage. The cytological study of peritoneal washing conducted by Filho RC et al. [9] was positive in 15.2% patients.

In Table 5 clinico-pathological factors was compared with patients positive and negative for Serum CA 125. There was no correlation with CA125 and age (P.032) and sex (.09). There was significant correlation with the histologic type and CA125 positivity (P.01). But Emoto S [25] in their series, positive expression of CA125 did not correlate with the histological type of gastric cancer (p = 0.73).

There was correlation with Lymph node metastasis (P<0.03) and Stage (P<0.02). The CA125 level had no correlation with depth of invasion (P.25) in this study. Bold RJ [19] correlated both serum and peritoneal tumor markers where they found no association of the marker (CEA &CA125) and T & N stage except T4 lesions. But they determined marker level from peritoneal fluid only.
Study showed that although not produced by gastric cancer cells and with no relation to the histological subtypes, CA125 is usually elevated in serum when the disease has invaded the serous membrane and the peritoneal cavity [5]. CA125 level was significantly associated with the peritoneal involvement (P<.001). The degree of peritoneal metastasis was also correlated with CA125 in study by [2,8,25].

The CA125 antigen has been observed in the peritoneum, particularly in areas of inflammation and adhesion. Peritoneal dissemination may cause inflammation of the peritoneum; therefore, one would expect that an elevation of serum CA125 would be observed in patients with peritoneal dissemination [2]. Emoto S [25] stated that the positivity of serum CA125 was significantly correlated with the presence of ascites. Their results also suggest that serum CA125 reflects the status of peritoneal lesions of gastric as well as ovarian cancer.

CA125 had the highest odds ratio 18.33(4.39-76.64) for predicting peritoneal dissemination among the markers tested (chi-square test). Similar to Hwang GI [8], where CA125 had also the highest odds ratio (24.46, 95% CI: 11.17-53.37). Nakata B [2] also proved that CA125 had the highest odds ratio for predicting peritoneal dissemination among the markers tested by chi-square test.

The sensitivity of CA125 was 73% (44%-91%), specificity 86% (73%-94%). So in this study CA125 was more sensitive in detecting peritoneal dissemination in gastric carcinoma patients. Similar result stated by Emoto S [25]. The sensitivities of CA125 were 46.1 Hwang GI[8], CA125 had the best sensitivity 38.6% and best specificity 98.4%, diagnostic accuracy (91.5%) and Nakata B [2] the sensitivity of CA125 was 39.4% (13 of 33 patients) CA125 had the best specificity (95.7%).

Finding suggests that CA125 may have biological relevance in the progression or reduction of the peritoneal lesions of gastric cancer. Elevated CA125 may not simply be a result of disease progression, but may in fact have a causal relationship with the progression of peritoneal metastasis [25]. Emoto S [25] stated that serum CA125 and CA72-4 can now be considered valuable markers that reflect the quantitative volume of peritoneal dissemination in gastric cancer.

Finally extreme elevation of tumor marker in the setting of resectable gastric cancer should alert the oncologist of the high potential for recurrence & may warrant aggressive adjuvant therapy following curative gastrectomy [19].

Previous study showed that Adachi and colleagues [26] reported that in ovarian cancer, the serum CA125 level could be influenced not only by CA125 production by the primary tumor but also by CA125 production in the mesothelium. They suggested that an increase in serum CA125 level in the CA125-positive tumor group might reflect tumor progression; in the CA125-negative tumor group, this might reflect the development of ascites or peritonitis carcinomatosa. In fact, a previous study has shown that the production of CA125 by gastrointestinal tract cancer cells is infrequent [27]. Therefore, it may be more reasonable that an elevated level of CA125 is not derived from increased cancer cell volume but mainly reflects the severity of peritonitis caused by carcinomatosis.

Sensitivity of CA125 was 73% which was more than any other study. This might be due to the fact that advanced cases with ascites were also included in this study. This significance of increased sensitivity suggests that the serum levels of serum CA125 is a clinically useful markers in diagnosis & would be highly suitable for monitoring peritoneal metastasis.

**Conclusion**

In this study Preoperative serum Measurement of the serum CA125 titer may be a powerful predictor of peritoneal metastases in patients with gastric carcinoma & may provide a value in determining depth of invasion, lymph node involvement & metastasis in patients with gastric cancer. Like previous other studies we do not propose CA125 as a convenient marker for gastric cancer. But it may be useful in patients with high suspicious peritoneal metastasis prior to surgery. Therefore, surgeons can prevent unneessecery exploration and can be better prepared for available alternative therapy.

The limitations of this study include the relatively brief study period and the small sample size The use of diagnostic laparoscopy, which might allow more complete and reliable staging of recurrent abdominal disease, is rarely performed. Further research will be required to rectify these problems.

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