

DETECTION OF TUMOR DEPOSITS IN THE MESOGASTRIUM IN RESECTED GASTRIC CANCER PATIENTS

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Abstract

Background: This study aims to determine the presence of tumor deposits in the mesogastrium of patients who underwent radical D2 gastrectomy with en bloc CME.

Methods: Thirteen consecutive gastric cancer patients who underwent radical gastrectomy with D2 dissection and CME at the Abdominal Surgical Department of the National Cancer Institute INEN (Lima, Peru) between March and April 2019 were prospectively incorporated. The presence of TDs was investigated and clinicopathological data were compared between positive TDs patients and negative TDs patients.

Results: Thirteen patients entered the study, 10 of these patients were women, and 3 were male. The mean age of 56.3 years. Tumors were located at the middle third in 7 patients, at the distal third in 6 patients. Seven patients were diagnosed with diffuse-type and 6 patients with intestinal-type according to Lauren's Classification. The mean tumor size was 4.51cm (range :1.9cm-8cm). Patients were staged by the AJCC TNM 8th Edition staging system, T4a (5 patients), T3 (5 patients), T1a (2 patients), and T1b (1 patient). Tumor deposits were found in 4 of 13 patients (30.7%). TDs were evidenced in locally advanced patients (pT3a and pT4a), 3 patients with lymphatic metastasis (pN1 and pN2), and in 1 patient without lymphatic metastasis (pN0).

Conclusions: In the present study is demonstrated that tumor deposits are present in surgical specimens of gastric cancer patients who underwent D2 Radical Gastrectomy associated with CME, the presence of tumor deposits is not exclusive of patients with nodal metastasis. Further studies are necessary to evaluate the importance of the presence of TDs in long-term survival.

Keywords: Complete mesogastrium excision (CME); Gastric Cancer; Tumor Deposit (TD).

Introduction

Gastric cancer is the second cause of death among cancer patients representing 723, 000 deaths worldwide (1). Gastric cancer is the first gastrointestinal cancer in Perú most patients present with advanced gastric tumors(2). The milestone of the treatment is surgical resection is based on radical gastrectomy with D2 lymphadenectomy as proposed by Japanese Gastric Cancer guidelines (3). Despite the advances in the perioperative management of this disease, including chemotherapy and radiation therapy, the recurrence rate may reach 60% of surgical cases (4).

The recurrence is commonly explained by the dissemination of cancer cells through the four known pathways: direct invasion, hematogenous metastasis, lymphatic metastasis, and peritoneal seeding(5)(6). Although a radical D2 gastrectomy was performed, locoregional recurrence is still being a problem (concern) maybe because of cancer cell dissemination during resection or remaining tissue in the mesogastrium that may contain tumor deposits. Several authors have proposed the complete mesogastrium excision to perform en bloc D2

lymphadenectomy to improve survival rates and reduce relapse as observed in the surgical treatment of colon and rectal cancer(7). Nagatomo and Nakamura have reported the presence of microscopic cancer cells and tumor deposits in the tissue surrounding the lymph nodes (8)(9). The CME as proposed by Xie and Gong could bring a survival benefit because this surgical technique removes all the tissue of the nodal region, it means the resection of not only the lymph nodes but also the whole continent that includes vascular and lymphatic vessels, adipose tissue and nerves (10). The complement of this technique implies a comprehensive pathology study of the mesogastrium (11)(12). The current pathology report only includes the resected lymph nodes which represent the N category in AJCC staging classification and tumor deposits are not considered for the TNM stage as in colorectal cancer where is nominated as N1c (13).

In the National Cancer Center in Lima Peru, the standard surgical treatment for gastric cancer is radical gastrectomy with D2 lymphadenectomy following the Japanese guidelines, and the pathology study is restricted to the number of lymph nodes resected (3). The main purpose of this study is to determine the presence the tumor deposits in

the mesogastrum in patients who underwent radical D2 gastrectomy with en bloc CME.

Materials and Methods

Study Design:

This is a prospective series of cases, a non - randomized single-center study designed to evaluate the incidence of tumor deposits in the mesogastrum in patients who underwent radical D2 gastrectomy with en bloc CME. The patients included full file two conditions: 1. - Complete en bloc resection of the CME and 2. - The study of mesogastrum that includes lymphatic nodes and extranodal tissue in the pathology specimens.

Setting:

Gastric cancer patients were evaluated and operated at the Department of Abdominal Surgery at National Cancer Center INEN, Lima, Peru. In our institution 170 cases of gastric cancer are operated per year.

Study Duration:

This study is an initial report that 13 patients were recruited in March and April 2019, the final report of this study will be complete at 100 patients.

Patients:

A total of thirteen consecutive gastric cancer patients who underwent radical gastrectomy with D2 dissection and CME at the Gastrointestinal Surgical Department of the National Cancer Institute INEN (Lima, Peru) between March 2019 to April 2019 were enrolled in the study.

Inclusion criteria:

- 1.- Primary gastric cancer confirmed pathologically.
- 2.- Aged older than 18 years and younger than 80 years.
- 3.- Body mass index less than 30 kg/m².
- 4.- cT1 to cT4a according to the AJCC Cancer Staging Manual, Eighth Edition.
5. - cN0 to cN3 according to the AJCC Cancer Staging Manual, Eighth Edition.
6. - cMo according to the AJCC Cancer Staging Manual, Eighth Edition.
- 7.- Patients undergo D2 subtotal distal gastrectomy or total gastrectomy with CME.
- 8.- Expected curative resection via laparotomy or laparoscopic radical gastrectomy.
- 9.- Eastern Cooperative Oncology Group Performance Status (ECOG) 0 or 1.
- 10.- American Society of Anesthesiologists (ASA) class I, II, or III.

Exclusion criteria:

- 1.- Patients with Bormann IV tumors at preoperative evaluation.
- 2.-Patients undergo proximal gastrectomy or gastrectomy less than D2 lymphadenectomy.

3.-cT4b according to the AJCC Cancer Staging Manual, Eighth Edition.

4.-cM1 according to the AJCC Cancer Staging Manual, Eighth Edition.

5.- Presence of residual disease R1 or R2 after surgery.

6.- Previous neoadjuvant chemotherapy or radiotherapy treatment.

7.- Other malignant diseases or another gastric malignant tumor.

Gastrectomy Selection:

The selection of gastrectomy was based on Japanese Gastric Cancer Guidelines Version 4 (3). Subtotal radical gastrectomy was performed based on tumor localization and when a sufficient resection margin could be achieved, at least 3cm of proximal margin in T2 tumors with expansive growth pattern (type 1 and 2) and at least 5cm of proximal margin in T3 or T4 tumors. If this margin cannot be ensured with a subtotal radical gastrectomy, we performed a total radical gastrectomy with an R0 resection margin at the esophagus.

Surgical Team:

The gastrectomies were performed by four experienced gastrointestinal oncology surgeons.

Surgical Procedure:

Patients underwent radical gastrectomy with D2 lymphadenectomy according to Japanese Gastric Cancer treatment guidelines English version 4. The extended lymphadenectomy in subtotal radical gastrectomy included Nos. 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a. For total radical gastrectomy, the extended lymphadenectomy included Nos. 1, 2, 3,4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 10 (only in cases necessitating splenectomy, 11p, 11d, and 12a. Complete mesogastrum excision (CME) was performed according to the procedure proposed by the Tongji Hospital surgical team and should meet the following criteria (7):

1. Exposing five mesogastrum (left gastroepiploic mesentery, right gastroepiploic mesentery, left gastric mesentery, right gastric mesentery, and post gastric mesentery)
2. En bloc separation of the mesentery from the mesenteric bed.
3. Dissecting along the root of the mesentery.
4. Ligation should reach the root of the blood vessels.
5. After the mesentery is dissected, the lower side of the mesogastrum should be flat and smooth.

Management of the specimen:

The regular management of the lymph nodes in our Pathology Department consisted of the digital identification of lymph nodes in the fresh specimen to separate them from the surrounding tissue for microscopical study, only lymph nodes were examined and reported. In the present study, pathologists were asked to modify the regular management

by including the extranodal tissue for microscopically analysis to search for extranodal disease. The lymph nodes of the surgical specimen were labeled for identification and each nodal region was mounted in a cassette and study separately. The lymph nodes deemed normal at the macroscopic observation were studied with slices each 2 mm. For the suspected metastatic nodes only one representative slice was included. The selected tissue was processed by the standard method and stained with Hematoxylin and Eosin. The technique for the study of the stomach remains unchanged.

Definition of Tumor Deposit:

Tumor deposits are defined as a group of cancer cells that are discontinuous from the primary tumor and the lymph nodes. These tumor deposits should not contain residual lymphatic tissue, vascular or perineural structures. It must be reminded that this concept is not included in the 8th AJCC TNM staging system.

Results

Between March 2019 and April 2019, 13 patients entered the study, 10 of these patients were women, and 3 patients were male with a mean age of 56.3 years. The mean tumor size was 4.51cm (range :1.9cm-8cm). Tumors were located at middle third in 7 patients, at distal third 6 patients. Seven patients were diagnosed with diffuse-type and 6 patients with intestinal-type according to Lauren's Classification. Histology grade was also reported, 9 patients had poor differentiation grade, 3 patients had moderate

differentiation grade and only 1 patient had well differentiation grade. Patients were staged by the AJCC TNM 8th Edition staging system, T4a (5 patients), T3 (5 patients), T1a (2 patients), and T1b (1 patient).

In 4 (30.7%) out of 13 patients, tumor deposits in the surrounding tissue were found. According to TNM classification depth tumor invasion, two patients were T4a and two patients were T3. Although three patients with tumor deposits were N (+) and one patient was N0 (T4a). The relation between positive tumor deposits at mesogastrium and clinicopathological data are shown in Table 1. Of these patients, two had poorly differentiated histology grade and two patients had moderately differentiated histology grade, patients without lymph nodes metastasis were poorly differentiated.

The localization of tumor deposits concerning the primary tumor was also studied. In three out of four patients with TDs, the localization of the primary tumor was in the middle third (body) and one patient in the distal third(antrum). Tumor deposits were found in the surrounding mesogastrium of lymph nodes stations 3, 4, and 5 in patients with primary tumor at the middle third (body), one patient with primary tumor localized at distal third (antrum) the TDs were found at surrounding mesogastrium of lymph node station 6. The clinicopathological data of patients with positive tumor deposits at the mesogastrium are described in Table 2.

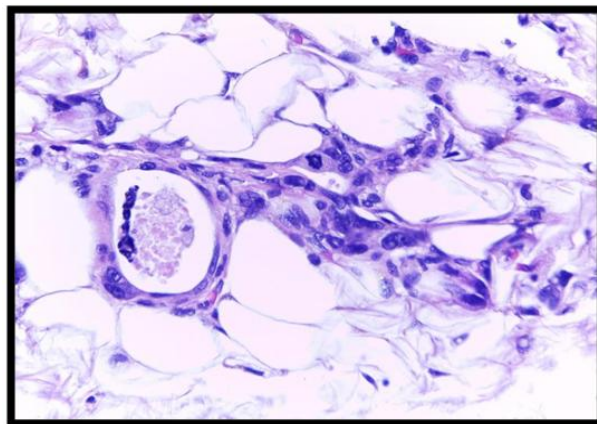
Table 1: Clinicopathological characteristics of patients who underwent Distal and Total D2 gastrectomy.

	All Gastrectomies	Tumor Deposits (+)	Tumor Deposits (-)
	N= 13 (100%)	N=4 (30.8%)	N=9 (69.2%)
Age mean (range) a	56.3 (25-74)	65.25 (57-74)	52.3 (25-67)
Gender			
Male n (%)	3 (23.1%)	1 (25%)	2 (22.3%)
Female n (%)	10 (76.9%)	3 (75%)	7 (77.7%)
Tumor Location n (%)			
Upper	0	0	0
Middle	7 (53.8%)	3 (75%)	4 (45.5%)
Distal	6 (46.2%)	1 (25%)	5 (55.5%)
Histology (Lauren Classification)			
Intestinal Type	6 (46.2%)	3 (75%)	3 (33.4%)
Diffuse Type	7 (53.8%)	1 (25%)	6 (66.6%)
Tumor Grade n (%)			
Good	1 (7.7%)	0	1 (11.15%)
Moderate	3 (23.1%)	2 (50%)	1 (11.15%)
Poor	9 (69.2%)	2 (50%)	7 (77.7%)
Depth of Invasion (pT) n (%)			
T1a	2 (15.4%)	0	2 (22.2%)
T1b	1 (7.7%)	0	1
T2	0	0	0
T3	5 (38.45%)	2 (50%)	3 (33.4%)
T4a	5 (38.45%)	2 (50%)	3 (33.4%)
T4b	0	0	0
Lymph Nodes Resected (median, range)	60.61(32-139)	56.75 (37-73)	62.3(32-139)
Lymph Nodes Metastasis (pN) n (%)			
N0	3 (23.1%)	1 (25%)	2 (22.2%)

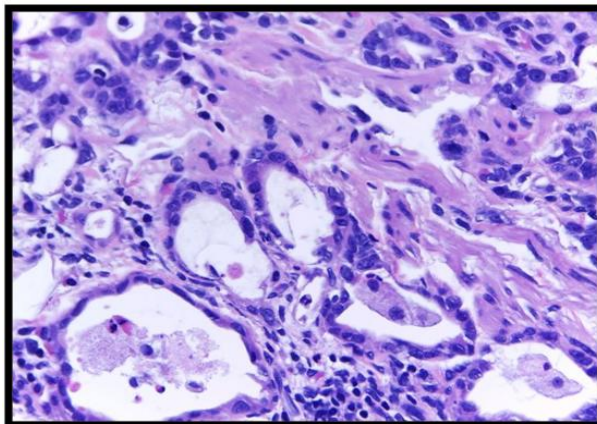
N1	4 (30.7%)	2 (50%)	2 (22.2%)
N2	1 (7.7%)	1 (25%)	0
N3a	3 (23.1%)	0	3 (33.4%)
N3b	2 (15.4%)	0	2 (22.2%)
Lymphovascular Invasion <i>n</i> (%)			
Absent	2 (15.4%)	0	2 (22.3%)
Present	11 (84.6%)	4 (100%)	7 (77.7%)
Perineural Invasion <i>n</i> (%)			
Absent	7 (53.8%)	3 (75%)	4 (45.5%)
Present	6 (46.2%)	1 (25%)	5 (55.5%)
Tumor Size (median) b	4.51	6.12	4.07
<i>n</i> : Number of patients			
a : median and range in years			
b: median in centimeters			

Table 2: Clinicopathological data of patients with positive tumor deposits at mesogastrium

Case	Age	Sex	Type of gastrectomy	Size (cm)	Tumor location	Location of TDs	Histology	Grade	(pT)	(pN)
1	57	M	Total	5	Middle	Group 5	Intestinal	Poor	t4a	N0 0/37
2	58	F	Total	5	Middle	Group 3	Intestinal	Moderate	t3	N1 2/69
3	72	F	Subtotal	6.5	Distal	Group 6	Intestinal	Moderate	t3	N1 2/48
4	74	F	Total	8	Middle	Group 4	Diffuse	Poor	t4a	N1 3/73



Picture 1: Low power field with hematoxylin-eosin (HE) staining is observed in the region of the mesogastrium, observing the presence of a tumor deposit that infiltrates the fatty tissue, conditioning desmoplastic reaction and inflammatory response.



Picture 2: High power image is observed with HE staining, with atypical glands surrounded by desmoplastic tissue and mononuclear inflammatory cells.

Discussion

Mesogastrium is a remnant of embryologic mesentery that is covered by a layer of deep fascia (bare area) (5), it is located at the edge of the stomach and involving main blood vessels, neural structures, and regional lymph nodes. The mesogastrium is divided into dorsal and ventral mesogastrium. Dorsal mesogastrium is divided into root, intermediate, and perigastric sectors. Root sector included stations 9, intermediate sector included stations 7, 8, 10 and 11 and perigastric sector included stations 1, 2, 3a, and 4. The rest of the stations: 3b, 5, and 12 are included in the ventral mesogastrium (14). The main vascular vessels are almost included in the mesogastrium, the principal vessels that are study are left gastroepiploic vessels (mLGEV), right gastroepiploic vessels (mRGEV), right gastric vessels (mRGV), and left gastric vessels (mLGV)(5).

It is accepted worldwide that gastric cancer cells dissemination may occur by four pathways mentioned above, Xie (5) proposed the Metastasis V hypothesis defined as the fifth pathway of metastasis in gastric cancer, in this hypothesis cancer cells migrate from the primary tumor and pass through the bare area and then infiltrate adipose mesenteric tissue by the attraction of cytokines. This concept in addition to the several studies that describe tumor deposits at mesogastrium (8,9), asseverated the importance of the complete mesogastrium excision in gastric cancer surgery and the relationship with an increase of overall survival rate. Shinohara (14,15) described the surgical technique of complete mesogastrium excision, to perform this surgery, dissection layers must be identified and separated from surrounding mesentery, this concept is similar to the holy plane in complete mesorectal excision (16). The importance of maintaining the integrity of the mesorectal tissue is a mainstay in rectal cancer surgical treatment because it is an important prognostic and local recurrence factor. At the time the hole mesogastrium is dissected, lymphatic nodes, vascular and neural vessels with the surrounding connective tissue must be resected complete and en bloc with the stomach, with this approach cancer cell dissemination, may be avoided and all the neoplastic disease is extracted.

In the present study in 4 of 13 patients (30.7%) tumor deposits were found at the mesogastrium, Nagatomo (8) described 3 of 37 patients (8%) with similar findings and Nakamura (9) also describe 39 of 134 patients (29%) with the extracapsular spread. These tumor deposits were more frequent in patients with subserosal infiltration T3 (2/4 patients) and serosa infiltration T4a (2/4 patients), similar findings were published by Xie (11) with 8 of 9 patients with T3 and T4a tumors and one patient with T1. Zhe Sun (17) also reported 21 of 491 (4.3%) patients with T1 tumors had tumor deposits and the survival rate of these patients was worse. Even these findings are less frequent in early gastric cancer this data corroborates that TDs can be found

not only in locally advanced and advanced patients but also in T1a and T1b tumors.

Several studies also reported that TDs are related to nodal compromise, but they can be found even in patients without lymphatic metastasis. Xie (11) reported tumor deposits in one of nine patients without lymphatic metastasis, this patient had a T3 tumor with moderated histological grade. Zhe Sun (17) also described 90 of 1044 patients (7.9%) with tumor deposits with no nodal involvement, Chen (18) detected TDs in 16 of 562 N0 patients (3%), these N0 patients with tumor deposits despite the depth of invasion, nodal status, and tumor differentiation had a worse survival rate compared with patients without tumor deposits (21.2% vs 59.8% respectively). In our patients with tumor deposits, 3 out of 4 had nodal metastasis (N+), the remaining patient was N0 with tumor localization at the middle third of the stomach and poorly differentiated tumor with diffuse-type histology [Picture 1-2]. The finding of tumor deposits in patients without lymphatic metastasis avouch the metastasis V concept because cancer cells can be disseminated not only by regional lymph nodes but also infiltrating the mesogastrium, by these premise complete mesogastrium excision is an important part of the surgical management of gastric cancer or also defined as the third principal of radical gastrectomy (5).

The presence of tumor deposits in the mesogastrium is related to poor survival rates compared to patients without tumor deposits. Nakamura (9) calculated 5 years survival rate for patients without lymph node metastasis (Group A), patients with intranodal metastasis (Group B), and patients with extranodal metastasis (Group C), results were 91%, 61%, and 23% respectively, these results corroborated that the presence of TDs in mesogastrium is a negative prognostic factor. Also, Xie (11) evidenced that Metastasis V positive patients had a worse prognosis compared with Metastasis V negative patients especially in patients with T3 tumors. Sun (17) compared the 5 years survival rate of patients without TDs versus patients with TD (58.7% vs 27.4% respectively), but patients with peritoneal metastasis had worse outcome compare with TDs positive patients (27.4% vs 6.7% respectively), this finding asseverated that the presence of TDs in mesogastrium is a different pathway of metastasis and it is not a precursor of peritoneal metastasis. This study also analyzed the 5 years survival rate of patients with TD and the number of TDs founded: 34.3% for those without TD, 27% for 2-3 TDs, and 11.3% for > 3 TDs. Chen (18) had similar results with a significant difference in 5 years survival rate between patients with TD vs patients without TD (21.2% vs 59.8% respectively) and in multivariate analysis, the presence of TD was an independent prognostic factor ($p < 0.001$).

Based on these results several investigators had proposed the incorporation of TD in the AJCC Staging System, Sun (17) found that the prognosis for patients with TDs in the pT1-4a category was similar to those without TDs in the

pT4a category but significantly better than patients with or without TDs in pT4b category, with these results they proposed that the presence of TDs should be treated and classify as T4a. Conversely, Lee (19) proposed that TDs must be counted as another lymph node metastasis in N Stage.

Several studies had corroborated that the presence of TDs independently of the depth of tumor invasion, lymph node metastasis, histology, differentiation grade, and lymphovascular or neural invasion is an important prognostic factor in the outcome of gastric cancer patients and could be soon incorporate as a part of AJCC Staging System like N1c in colorectal cancer(20).

In conclusion, tumor deposits are present in the mesogastrium of surgical specimens of gastric cancer patients who underwent D2 Radical Gastrectomy associated with CME. The finding of TDs is not exclusive of patients with nodal metastasis. Further studies are necessary to incorporate the presence of TDs in the AJCC Staging System.

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