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D2 lymphadenectomy can disseminate tumor cells into peritoneal cavity in patients with advanced gastric cancer

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We sought to determine the dissemination of gastric cancer cells before and after radical D2 surgery and to determine the effectiveness of EIPL in preventing post-operative peritoneal metastasis. 64 patients were recruited with advanced gastric cancer for our final analysis. Complete curative gastrectomy with D2 lymphadenectomy was performed on the 64 patients. Before surgery, peritoneal lavage fluid was collected for cytological analysis by cell smearing and immunohistochemistry to detect disseminated cancer cells (S1). Following tumor and lymph node resection, peritoneal lavage fluid was collected for cytological examination (S2). The patients were treated by extensive intra-operative peritoneal lavage (EIPL) with normal saline (n = 31) or distilled water (n = 33). The peritoneal lavage fluid was collected for cytological examination (S3). At S1 stage, 18 patients (28.1%) were positive for disseminated cancer cells in their abdominal fluid. After D2 lymphadenectomy, 34 patients (53.1%) had disseminated cancer cells in their abdominal fluid at stage S2, which indicated that the D2 lymphadenectomy caused in an additional 16 (16/46, 34.8%) patients positive for disseminated cancer cells. After EIPL with either normal saline or distilled water at the S3 stage), all the patients were negative for disseminated cancer cells in their abdominal fluid. A total of six patients died, and four patients had recurrencent cancer. These findings indicate that D2 lymphadenectomy can disseminate gastric cancer cells, and post-operative lavage of the abdominal cavity can eliminate cancer cell dissemination and decrease the risk of peritoneal metastasis.

Key words: Extensive intra-operative peritoneal lavage; cell shedding; peritoneal metastasis.

The staging and treatment of gastric carcinoma is becoming increasingly standardized based on the seventh edition of the American Joint Committee on Cancer Staging manual [1] and the Japanese Gastric Cancer Association [2]. In Asia, advanced gastric carcinoma is most commonly treated by curative gastrectomy with D2 lymphadenectomy. This procedure is associated with increased peritoneal metastasis occurring within a short time period following surgery [3, 4]. Stage IV peritoneal metastasis is the most common progression of advanced gastric carcinoma and is associated with poor prognosis [5, 6]. Approximately 50% of gastric carcinoma patients with serosa involvement will develop peritoneal metastasis and die within 2 years [6, 7]. Patients that are positive for peritoneal metastasis have a 5-year survival rate of less than 2% [6, 7]. Early gastric carcinoma patients without serosa involvement that undergo radical surgery may also develop peritoneal metastasis. However, the detection of surgical-induced peritoneal metastasis is largely overlooked during disease staging in the clinic. This omission can cause a wide gap between anticipated prognosis and actual therapeutic effectiveness [8].

Current research indicates that opening the lymphatic vessels after lymph node dissection is a major cause of cancer cell dissemination into the peritoneal cavity. Additionally, cancer cells can be released directly from the gastric lumen, which suggests that other contributing factors may also play a role both in iatrogenic tumor diffusion induced by surgery and in metastasis in the peritoneal cavity [9].

Since surgery can increase the risk of gastric cancer metastasis, safe and effective adjunct procedures must be implemented to reduce the risk of disseminating gastric cancer cells through surgery. Extensive intraoperative peritoneal lavage (EIPL) is a simple adjunct surgical technique that is thought may reduce the risk of peritoneal metastasis and increasing overall patient survival [5, 6, 10, 11].

EIPL uses the limiting dilution theory to reduce the risk of gastric cancer cells disseminated by surgery from becoming

metastatic. The limiting dilution theory assumes that soon after surgery gastric cancer cells disseminated by surgery have not yet implanted into the peritoneal cavity. The EIPL method aspirates the peritoneal cavity several times with physiological saline to effectively dilute and kill any disseminated cancer cells before they can become metastatic [5, 6].

Our present study confirms that D2 lymphadenectomy surgery greatly increases the level of disseminated gastric cancer cells in the peritoneal cavity. We also present evidence that prophylactic EIPL reduces the levels of cell dissemination after D2 lymphadenectomy surgery. These findings indicate an important adjunct surgical use of EIPL to prevent peritoneal metastasis and disease recurrence.

Material and methods

Patients and criteria for inclusion and exclusion. Gastric cancer patients who were scheduled for surgery were recruited from December 2009 to February 2010 in the Department of Gastrointestinal Surgery at the Third Affiliated Hospital of Harbin Medical University. All experimental protocols were reviewed and approved by the institutional review board of the hospital. All experiments were conducted in accordance with the Declaration of Helsinki. All patients understood and signed an informed consent statement.

Eligible patients had (1) pathologically proven gastric cancer; (2) no evidence of severe lung and/or heart disease; (3) no other apparent contraindications for surgery; (4) an Eastern Cooperative Oncology Group (ECOG) score of ≤ 2; (5) a Karnofsky score ≥ 60; (6) not received radiotherapy and/or chemotherapy before surgery; (7) no distant metastasis revealed by pre-operative three-dimension CT, ultrasonography, or X-ray; and (8) imaging examinations demonstrated that the patient was suitable for radical surgery. Patients were excluded from this study if they (1) had unresectable gastric cancer, (2) had shortcut surgery, (3) were not candidates for D2 surgery, (4) had residual cancer or lymph nodes, or (5) had unresectabel distant metastatic lesions as determined by exploratory laparotomy.

Surgical procedures. For this study, three specific stages were considered stages: S1, abdominal opening; S2, total removal of tumor and invaded lymphonodi; and S3, extensive intraoperative peritoneal lavage. Surgical procedures and abdominal lavage were performed by the same surgeon. Following the laparotomy and before surgery, 200 ml of normal saline (S1) was injected into abdominal cavity. The solution was allowed to flow through subphrenic, subhepatic, pelvic, and paracolic sulci spaces. Then, one mL heparin was added to the collected abdominal fluid, and the mixture was centrifuged. The cells were collected for later cytological analysis [5].

Next the radical D2 lymphadenectomy was performed (Figure 1A), making sure to avoid any possible contamination of the abdominal cavity with digestive juices. After the cancer was removed and the lymph nodes were dissected, the surgeon removed residual blood and exudates with sterilized gauze. Subsequently, 200 ml of normal saline (S2) was applied

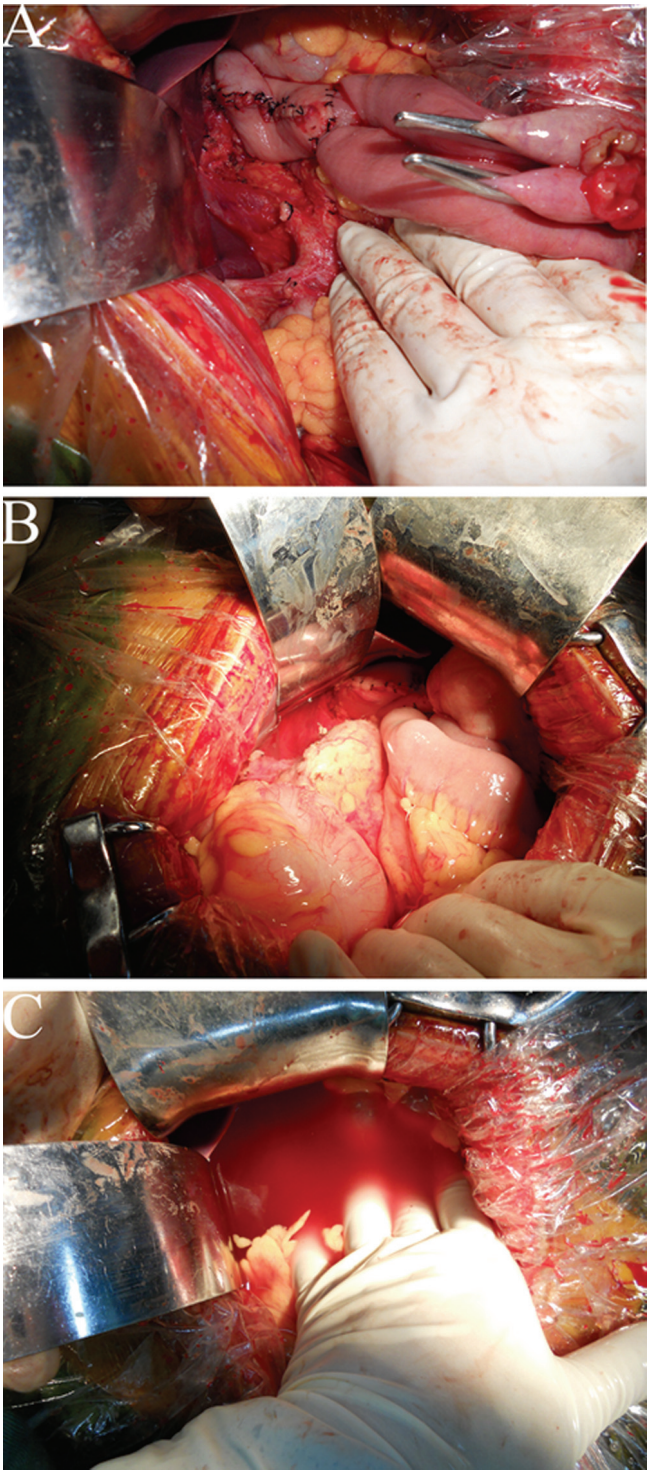

Figure 1. The representative procedure of the radical D2 lymphadenectomy surgery (A) and extensive intraoperative peritoneal lavage after the surgery (B and C).

to lavage the surgical sites and the peritoneal fluid was then collected for cytological examination. Gastrointestinal reconstruction was performed. Before the wound was closed, the

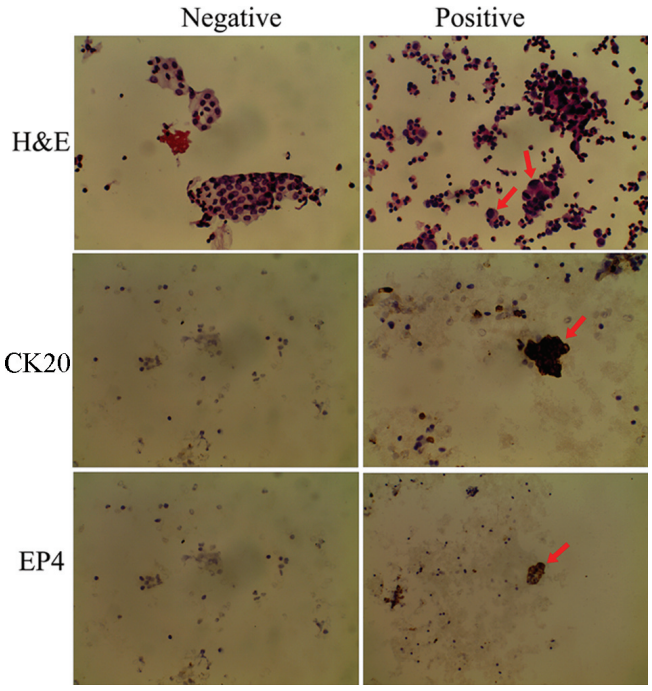

Figure 2. Cytological analysis of the collected abdominal fluid for positive disseminated tumor cells, where red arrows indicate the positive staining of tumor cells.

abdominal cavity was lavaged again and EIPL was performed (Figure 1B & C).

Extensive intraoperative peritoneal lavage. With a few modifications, EIPL was performed as described previously [5, 6]. Briefly, patients were divided into two groups, with one group receiving lavage with 1 L normal saline (patients with odd numbered medical records) and the other receiving 1 L distilled water (patients with even numbered medical records). The lavage stayed in the abdominal cavity for three to five minutes. Lavage was repeated 10 times until 10 L of normal saline or distilled water were applied. Finally, 200 ml of normal saline (S3) was used to lavage the abdominal cavity, and subsequently the peritoneal fluid was collected.

Cytological analysis. Cells were smeared onto slides and stained with Papanicolaou staining as previously described [5, 9]. When the Papanicolaou staining was negative (Figure 2), we performed immunohistochemistry (IHC) as previously described [9] to confirm the absence of cancer cells in the collected abdominal fluid. Briefly, slides were incubated with antibodies against the known tumor markers CK20 and EP4 (Figure 2). Two experienced pathologists, who were blinded to the data, evaluated the IHC slides. Patients were regarded as positive for disseminated and/or metastatic cancer cells if their collected abdominal fluid was positive by Papanicolaou staining and IHC examination.

Statistics analysis. Demographics and patient characteristics are summarized as n (%). The follow-up status, including positive rate of disseminated cells, survival status, and recurrence are presented as n (%) and were compared with Pearson Chi-square test, Fishers' exact test for cell numbers less than five, or the Mann-Whitney U test for ordinal data. All statistical assessments were two-tailed, and considered significant when $P < 0.05$. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA).

Results

A total of 75 patients were recruited prior to surgery. During the surgery, peritoneal metastasis was noted in 4 patients and micronodules were found in 2 patients in which subsequent pathological examination prooved metastatic adenocarcinoma. Palliative surgery was performed on two patients due to unresectable cancer that in one patient was gastrojejunostomy and in the other gastrostomosis. Three patients had residual cancer and lymph node after non-radical surgery, and one patient did not receive radical surgery.

Sixty-four patients (45 males and 19 females) with a mean age of 59.2 years (range: 26 to 83 years) met all included criteria and were enrolled in the study. The median time to last follow-up was 19 months, with 90% of patients surviving during the follow-up period (only 6 patients died). The range of survival time was 8 to 19 months.

Patient demographics and disease characteristics are presented on Table 1. The locations of the tumors were the gastric antrum in 35 patients (54.7%), the gastric body in 17 (26.6%), and the gastric cardia in 12 (18.7%). A total of 29 patients (45.3%) were at TNM stage III, 18 (28.1%) at stage II, and 17 (26.6%) at stage I. The abnormality rate was 17.2% for CEA, 17.2% for CA199, and 15.6% for fibrogen. After surgery, 12 patients (18.8%) received oral chemotherapy, 41 (64%) received chemotherapy via injection, 10 (15.6%) did not receive any therapy, and one (1.6%) was lost to follow-up.

At S1 stage, 18 patients (28.1%) were positive for disseminated cancer cells in their abdominal fluid (Table 2). After D2 lymphadenectomy, 34 patients (53.1%) had disseminated cancer cells in their abdominal fluid at S2 stage. This was an increase of 16 additional patients (34.8%, excluding the 18 positive patients in S1 stage who were still positive at S2 stage) with tumor cells in their peritoneal cavity resulting from D2 lymphadenectomy only. Notably, not all patients at T3 or T4 stage had positive disseminated cells in S1 stage. Additionally, tumor dissemination was even observed in patients with T1 and N0 tumors. All patients positive of disseminated cells in S1 stage were excluded from the analysis of patients whose cells were disseminated at the S2 stage. Folloing EIPL treatment with either normal saline or distilled water at S3 stage, all of the patients were negative for disseminated cancer cells in their abdominal fluid.

Six patients died (4 in the normal saline group and 2 in the distilled water group) and 4 patients (2 in each group) had cancer recurrence (Table 2). Peritoneal recurrences were diagnosed if patients during follow-up had disseminated tumor cells in the ascites, or if patients had refractory ileus combined with marasmus and abnormal increases in CEA

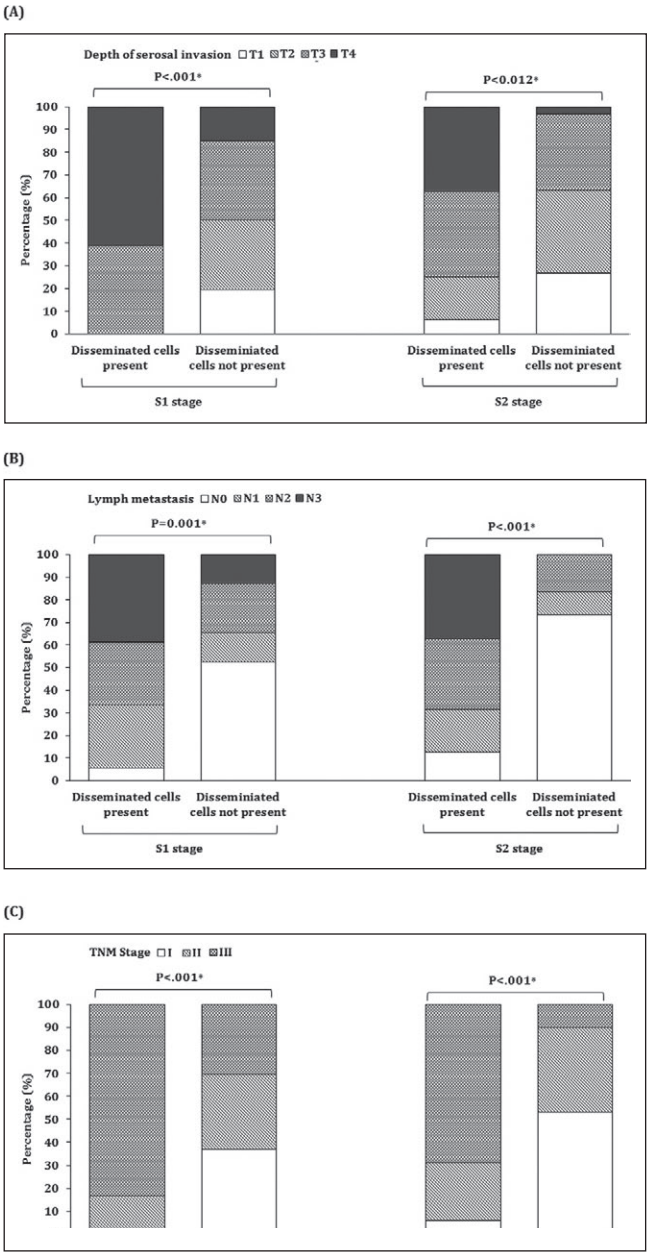

Figure 3. Frequency of the presence or absence of disseminated cells at S1 and S2 stages according to the (A) depth of serosal invasion, (B) lymph metastasis, and (C) TNM stages. *P*-values were derived by Mann-Whitney U test. * < 0.05, indicates significantly different between disseminated cells present or not.

or CA1999. Both the mortality rates and recurrent rates were similar between the normal saline and distilled water.

Next, we sought to determine the disease or patient characteristics that were associated with cancer cells dissemination, both spontaneously at the S1 stage and with D2 lymphadenectomy at S2 stage (Table 3). We assessed the associations of the positive rate of disseminated tumor cells in the abdominal cavity with the depth of serosal invasion at T4, lymph metastasis at N3, TNM stage at III (Figure 3), and fibrogen abnormality

Table 1. Subject demographics and characteristics. (N = 64)

Variables*	(N = 64)
Sex	
Males	45 (70.7%)
Females	19 (29.3%)
Age	
< 60 years	29 (45.3%)
≧60 years	35 (54.7%)
Location	
Gastric antrum	35 (54.7%)
Gastric body	17 (26.6%)
Gastric cardia	12 (18.7%)
Differentiation	
Poorly differentiated	30 (46.9%)
Moderate or poorly differentiated	17 (26.5%)
Moderately differentiated	12 (18.8%)
Well- differentiated	5 (7.8%)
Surface Morphology	
1	13 (20.3%)
2	10 (15.6%)
3	34 (53.2%)
4	7 (10.9%)
Depth of serosal invasion	
T1	9 (14.1%)
T2	14 (21.8%)
T3	23 (36.0%)
T4	18 (28.1%)
Lymph metastasis	
N0	25 (39.1%)
N1	11 (17.2%)
N2	15 (23.4%)
N3	13 (20.3%)
TNM stage	
I	17 (26.6%)
II	18 (28.1%)
III	29 (45.3%)
CEA examination	
Normal	53 (82.8%)
Abnormal	11 (17.2%)
CA199 examination	
Normal	53 (82.8%)
Abnormal	11 (17.2%)
Fibrogen	
Normal	54 (84.4%)
Abnormal	10 (15.6%)
Type of Fluid	
Normal saline	31 (48.4%)
Distilled water	33 (51.6%)
Totally intraoperative washing	64 (100%)
Post-operative treatment	
No	10 (15.6%)
Oral chemotherapy	12 (18.8%)
Chemotherapy via injection	41 (64.0%)
Lost to follow-up	1 (1.6%)

*Data are summarized as n (%).

Table 2. Effects of rinse solution on follow-up status (N = 64)

Variables*	Total (n = 64)	Normal saline (n = 31)	Distilled water (n = 33)	*P*-value
Positive rate of disseminated cells				
S1 stage	18 (28.1%)	8 (25.8%)	10 (30.3%)	0.689
S2 stage	34 (53.1%)	16 (51.6%)	18 (54.5%)	0.814
S3 stage	0 (0%)	0 (0%)	0 (0%)	NA
Survival status				0.419
Survived	58 (90.6%)	27 (87.1%)	31 (93.9%)	
Deceased	6 (9.4%)	4 (12.9%)	2 (6.1%)	
Recurrence				1.000
Recurrent	4 (6.2%)	2 (6.5%)	2 (6.1%)	
Non-recurrent	60 (93.8%)	29 (93.5%)	31 (93.9%)	

Abbreviation: NA, not assessed.
*Data were summarized as n (%) for a given type of rinse solution, and compared using Chi-square or Fisher's exact test.

in S1 stage (all $P < 0.05$). A total of 12 of 34 patients who had a Borrmann classification 3 had cancer cells spontaneously disseminate at S1 stage. Among the 16 patients positive of disseminated tumor cells at S2 stage (excluding the 18 patients who were positive for disseminated cells at S1 stage), their characteristics were similar at S1 stage. Among the 22 patients with Borrmann classification 3, 10 patients (45.2%) had cancer cells disseminated into the abdominal cavity following surgery at the S2 stage while only 12 out of 34 patients (35.3%) with Borrmann classification 3 had cancer cells dissemeinated into abdominal cavity before surgery at S1 stage. At the S2 stage, those patients with abnormal CA199 were more likely to have already of disseminated cancer cells. Patients with high level of disseminated cells at S1 and S2 stages received postoperative chemotherapy via injection.

Discussion

In this study of patients with advanced gastric cancer, tumor cells were disseminated in the peritoneal cavity before surgery in 28% of patients (18 out of 64) and by D2 lymphadenectomy in 34% of patients (16 out of 46). Patients with advanced gastric cancer (Borrmann classification 3) were more likely to have alreadytumor cells disseminated into the peritoneal cavity both spontaneously and following surgery. The risk factors for disseminating tumor cells in the peritoneal cavity at S1 and S2 stage were depth of serosal invasion at T4, lymph metastasis at N3, TNM stage at III, and fibrogen abnormality. Postoperative EIPL rinsing with either normal saline or distilled water completely eliminated disseminated tumor cells from abdominal cavity.

Radical gastrectomy with D2 lymphadenectomy is one of the most commonly used surgical treatment options for advanced gastric cancer in Asia. Unfortunately, this surgical treatment is associated with a high incidence of peritoneal metastasis and decreased patient prognosis when cancer invaded serosa and or of the lymph nodes [5, 12]. Our cytological analysis of peritoneal lavage found that disseminated volume of gastric tumor cells into the peritoneal cavity increased following radical D2 surgery than after the initial surgical opening of the abdomen. Increased levels of disseminated gastric cancer cells in the peritoneal cavity are often associated with poorer patient prognosis and disease recurrence [8, 9].

Our study shows that D2 lymphadenectomy, a standard treatment option for advanced gastric cancer, can directly contribute to iatrogenic tumor diffusion, increase the likelihood of peritoneal metastasis, and potentially reduce patient survival. Our data is supported by *ex vivo* experimental data demonstrating that D2 lymphadenectomy could induce the release of cancer cells during gastric cancer surgery [9]. Additionally, previous research has found that EIPL significantly improved the 5-year survival rate of advanced gastric cancer patients with cancer cells disseminated in the intraperitoneal space [6].

The popularity of EIPL is increasing, since it is a cheap, effective, and simple prophylactic strategy to prevent and reduce the rate of post-surgical peritoneal metastasis and cancer recurrence. Based on the limiting dilution theory, EIPL washes the peritoneal cavity with 10 separate, 1L serial saline washes. On a logarithmic scale, these washes can reduce disseminated cancer cell levels to zero and prevent post-surgical peritoneal metastasis [5, 6]. The use of EIPL as a prophylactic strategy successfully prevents surgery-induced peritoneal metastasis and ultimately increases overall survival of patients with both gastric and pancreatic cancer [5, 6, 11].

These findings are also supported by our study, which indicates that EIPL effectively decreased the level of cancer cells disseminated in the peritoneal cavity by D2 lymphadenectomy. We also found that using distilled water in the EIPL procedure had similar effectiveness as normal saline. Hypotonic solutions can be cytotoxic against cancer cells [13] and administering a chemotherapy agent dissolved in distilled water is well-tolerated in advanced gastric cancer patients [14]. We found that EIPL with either normal saline or distilled water could

Table 3. Associations between characteristics of stage 1 and 2 subjects and positive rate of disseminated cells

	S1 stage (n = 64)			S2 stage(n=46)[a]		
Variables[b]	Disseminated cells present (n = 18)	Disseminated cells not present (n = 46)	*P*-value	Disseminated cells present (n = 16)	Disseminiated cells not present (n = 30)	*P*-value
Sex			0.154			0.777
Male	3 (16.7%)	16 (34.8%)		6 (37.5%)	10 (33.3%)	
Female	15 (83.3%)	30 (65.2%)		10 (62.5%)	20 (66.7%)	
Age			0.637			0.550
< 60 years	9 (50%)	20 (43.5%)		6 (37.5%)	14 (46.7%)	
≧ 60 years	9 (50%)	26 (56.5%)		10 (62.5%)	16 (53.3%)	
Location			1.000			0.915
Gastric antrum	10 (55.6%)	25 (54.3%)		8 (50%)	17 (56.7%)	
Gastric body	5 (27.8%)	12 (26.1%)		5 (31.2%)	7 (23.3%)	
Gastric pylorus	3 (16.6%)	9 (19.6%)		3 (18.8%)	6 (20.0%)	
Differentiation			0.423			0.547
Poorly differentiated	9 (50%)	21 (45.7%)		9 (56.2%)	12 (40%)	
Moderate or poorly differentiated	4 (22.2%)	13 (28.3%)		5 (31.2%)	8 (26.7%)	
Moderately differentiated	5 (27.8%)	7 (15.2%)		1 (6.3%)	6 (20%)	
Well- differentiated	0 (0%)	5 (10.8%)		1 (6.3%)	4 (13.3%)	
Borrmann classification			0.576			0.097
1	2 (11.1%)	11 (23.9%)		1 (6.3%)	10 (33.3%)	
2	2 (11.1%)	8 (17.4%)		2 (12.5%)	6 (20%)	
3	12 (66.7%)	22 (47.8%)		10 (62.5%)	12 (40%)	
4	2 (11.1%)	5 (10.9%)		3 (18.7%)	2 (6.7%)	
CEA			1.000			0.105
Normal	15 (83.3%)	38 (82.6%)		11 (68.7%)	27 (90%)	
Abnormal	3 (16.7%)	8 (17.4%)		5 (31.3%)	3 (10%)	
CA199			0.487			0.005 *
Normal	14 (77.8%)	39 (84.8%)		10 (62.5%)	29 (96.7%)	
Abnormal	4 (22.2%)	7 (15.2%)		6 (37.5%)	1 (3.3%)	
Fibrinogen			0.024 *			0.011*
Normal	12 (66.7%)	42 (91.3%)		12 (75%)	30 (100%)	
Abnormal	6 (33.3%)	4 (8.7%)		4 (25%)	0 (0%)	
post-operative treatment			0.005*			0.003*
No	0 (0%)	10 (21.7%)		0 (0%)	10 (33.3%)	
Oral chemotherapy	1 (5.6%)	11 (23.9%)		2 (12.5%)	9 (30%)	
Chemotherapy via injection	16 (88.8%)	25 (54.4%)		14 (87.5%)	11 (36.7%)	
Lost to follow-up	1 (5.6%)	0 (0%)		0 (0%)	0 (0%)	
Survival status			0.338			0.274
Survived	15 (83.3%)	43 (93.5%)		2 (12.5%)	1 (3.3%)	
Deceased	3 (16.7%)	3 (6.5%)		14 (87.5%)	29 (96.7%)	
Recurrence			0.313			1.000
Recurrent	2 (11.1%)	2 (4.3%)		1 (6.3%)	1 (3.3%)	
Non-recurrent	16 (88.9%)	44 (95.7%)		15 (93.8%)	29 (96.7%)	

[a] Those 18 patients who were positive for disseminated cells at stage 1 were excluded at stage 2.

[b] Results are presented as n (%). The results were compared by Pearson Chi-square test, Fishers' exact test, or Mann-Whitney U test.

* $P < 0.05$ indicates significantly different between disseminated cells present or not.

completely clean disseminated tumor cells from abdominal cavity.

Peritoneal metastases of gastric and pancreatic cancer are thought to be directly related to metastatic lymph node resection [5, 6, 11]. Higher levels of disseminated cancer cells in the peritoneal cavity are likely due to opening lymphatic vessels after lymph dissection [8]. Our findings support this hypothesis. However, other pathways of metastasis are also important, as *ex vivo* experiments have demonstrated that D2 lymphadenectomy can also induce the release of cancer cells

directly from the gastric lumen [8]. We also found high levels of disseminated cancer cells after surgery in patients who did not have lymph node metastasis. Further in basic research is necessary to fully elucidate the underlying mechanisms regulating metastasis induced by D2 lymphadenectomy.

Our study has several limitations. The use of cell smearing and IHC is one limitation [5]. Though these techniques are a well-accepted gold standard to measure disseminated cancer cell levels in peritoneal lavage fluid, several publications have questioned these techniques due to their low sensitivity and high rate of false negatives [7, 10]. Our data could be strengthened by using quantitative real-time PCR combined with other standard cytological methods to provide a faster and more sensitive approach to cytological analysis of the disseminated cancer cells [7, 10, 15, 16]. Real-time PCR could effectively and rapidly analyze both tumor markers (such as CK20 and EP4) and a larger panel of peritoneal metastasis biomarkers, such as regenerating islet-derived family member 4 (REGIV), matrix metalloproteinase 9 (mmp-9), vascular endothelial growth factor (VEGF), and CXC chemokine receptors. These analyses would provide greater insight into the mechanisms regulating the peritoneal metastasis of gastric cancer [17-19]. Another limitation is that any tumor cells in the lymphovascular pedicles, which are nearly invisible to the naked eye, may circulate into the blood system. We left the lymphovascular pedicles open and attempted to clean disseminated tumor cells through EIPL. An additional limitation is that this study did not compare gastric resection with and without D2 lymphadenectomy to determine if D2 lymphadenectomy is the cause of the presence of disseminating tumor cells. Radical resection of gastric cancer should obey the en block principle, and so neither ethical approval nor patient consent could be obtained to compare gastric resection without lymphadenectomy. This study is also limited by the differing chemotherapy regimens that the patients in this study received, due to the different disease stages and different postoperative physical conditions of the patients.

Conclusions

Our study demonstrated that D2 lymphadenectomy can directly increase the disseminated cancer cells within the peritoneal cavity which can increase the incidence of peritoneal metastasis and lower the prognosis of advanced gastric cancer patients. Furthermore, while our EIPL data has limitations and are largely supportive of previously published works, this report focuses on the necessity of prophylactic EIPL to prevent iatrogenic tumor diffusion induced by surgery. This study is strengthened by its relatively large size (N = 64) and by the analysis of factors associated with dissemination. Tumor dissemination was observed even in patients with T1 and N0 tumors, which further supports the use of routine EIPL. By adopting a standard clinical use of EIPL for advanced gastric cancer, which is a simple adjuvant surgical procedure, decreasing the incidence of disease recurrence will likely result in better clinical outcomes.

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References

[1] EDGE SB, BYRD DR, COMPTON CC, FRITZ AG (eds): AJCC Cancer Staging Manual 7th Edition. New York, NY: Springer; 2009.

[2] JAPANESE GASTRIC CANCER ASSOCIATION. (eds): Japanese Classification of Gastric Cancer. 14th edition ed. Tokyo, Japan: Kanehara & Co. Ltd.; 2010.

[3] SONGUN II, VAN DE VELDE CJ. Can Surgical Treatment Results in Gastric Cancer Be Improved? Oncologist. 1996; 1(1 & 2): 36–40.

[4] WANG CS, HSIEH CC, CHAO TC, JAN YY, JENG LB, et al. Resectable gastric cancer: operative mortality and survival analysis. Chang Gung Med J. 2002; 25: 216–227.

[5] SHIMADA S, TANAKA E, MARUTSUKA T, HONMYO U, TOKUNAGA H, et al. Extensive intraoperative peritoneal lavage and chemotherapy for gastric cancer patients with peritoneal free cancer cells. Gastric Cancer. 2002; 5: 168–172. http://dx.doi.org/10.1007/s101200200029

[6] KURAMOTO M, SHIMADA S, IKESHIMA S, MATSUO A, YAGI Y, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009; 250: 242–246. http://dx.doi.org/10.1097/SLA.0b013e3181b0c80e

[7] MARUTSUKA T, SHIMADA S, SHIOMORI K, HAYASHI N, YAGI Y, et al. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. Clin Cancer Res. 2003; 9: 678–685.

[8] ROSENBERG R, NEKARDA H, BAUER P, SCHENCK U, HOEFLER H, et al. Free peritoneal tumour cells are an independent prognostic factor in curatively resected stage IB gastric carcinoma. Br J Surg. 2006; 93: 325–331. http://dx.doi.org/10.1002/bjs.5196

[9] HAN TS, KONG SH, LEE HJ, AHN HS, HUR K, et al. Dissemination of free cancer cells from the gastric lumen and from perigastric lymphovascular pedicles during radical gastric cancer surgery. Ann Surg Oncol. 2011; 18: 2818–2825. http://dx.doi.org/10.1245/s10434-011-1620-8

[10] KODERA Y, NAKANISHI H, ITO S, YAMAMURA Y, FUJIWARA M, et al. Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: detection of cytokeratin 20 mRNA in peritoneal washes, in addition to detection of carcinoembryonic antigen. Gastric Cancer. 2005; 8: 142–148. http://dx.doi.org/10.1007/s10120-005-0318-7

[11] YAMAMOTO K, SHIMADA S, HIROTA M, YAGI Y, MATSUDA M, et al. EIPL (extensive intraoperative peritoneal lavage) therapy significantly reduces peritoneal recurrence after pancreatectomy in patients with pancreatic cancer. Int J Oncol. 2005; 27: 1321–1328.

[12] MEYER H-J, WILKE H. Treatment strategies in gastric cancer. Dtsch Arztebl Int. 2011; 108: 698–705.

[13] SELZNER N, SELZNER M, GRAF R, UNGETHUEM U, FITZ JG, et al. Water induces autocrine stimulation of tumor cell killing through ATP release and P2 receptor binding. Cell Death Differ. 2004; 11 Suppl 2: S172–180. http://dx.doi.org/10.1038/sj.cdd.4401505

[14] TSUJITANI S, FUKUDA K, SAITO H, KONDO A, IKEGUCHI M, et al. The administration of hypotonic intraperitoneal cisplatin during operation as a treatment for the peritoneal dissemination of gastric cancer. Surgery. 2002; 131(1 Suppl): S98–104. http://dx.doi.org/10.1067/msy.2002.119359

[15] KODERA Y, NAKANISHI H, ITO S, YAMAMURA Y, KANEMITSU Y, et al. Quantitative detection of disseminated cancer cells in the greater omentum of gastric carcinoma patients with real-time RT-PCR: a comparison with peritoneal lavage cytology. Gastric Cancer. 2002; 5: 69–76. http://dx.doi.org/10.1007/s101200200012

[16] FUJIWARA Y, DOKI Y, TANIGUCHI H, SOHMA I, TAKIGUCHI S, et al. Genetic detection of free cancer cells in the peritoneal cavity of the patient with gastric cancer: present status and future perspectives. Gastric Cancer. 2007; 10: 197–204. http://dx.doi.org/10.1007/s10120-007-0436-5

[17] MOON JH, FUJIWARA Y, NAKAMURA Y, OKADA K, HANADA H, et al. REGIV as a potential biomarker for peritoneal dissemination in gastric adenocarcinoma. J Surg Oncol. 2012; 105: 189–194. http://dx.doi.org/10.1002/jso.22021

[18] KOIZUMI K, HOJO S, AKASHI T, YASUMOTO K, SAIKI I. Chemokine receptors in cancer metastasis and cancer cell-derived chemokines in host immune response. Cancer Sci. 2007; 98: 1652–1658. http://dx.doi.org/10.1111/j.1349-7006.2007.00606.x

[19] YANG Q, YE ZY, ZHANG JX, TAO HQ, LI SG, et al. Expression of matrix metalloproteinase-9 mRNA and vascular endothelial growth factor protein in gastric carcinoma and its relationship to its pathological features and prognosis. Anat Rec (Hoboken). 2010; 293: 2012–2019. http://dx.doi.org/10.1002/ar.21071