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Original Article

# *Outcome of Peritoneal Washing Cytology Results and the Appropriate Management in Thai Patients with Gastric Adenocarcinoma*

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***Abstract***

***Objective:*** **To present an estimate of the prevalance of positive peritoneal washing cytology (+PWC) in gastric cancer and to identify risk facctors for +PWC.**

***Method:*** **Medical charts of 54 patients with gastric cancer who underwent D2 gastrectomy between January 2006 and December 2013 were reviewed.**

***Results:*** **A total of 12 patients (22%) had +PWC. Factor significantly associated with +PWC include serosal invasion, nodal metastasis and poorly differentiated histology. All patients with +PWC developed peritoneal recurrence. The 5-year overall survival rate for patients with +PWC and -PWC were 0% and 83%, respectively.**

***Conclusion:*** **Gastric cancer with +PWC should be considered as stage IV diseases. PWC should be included in the staging of gastric cancer.**

***Keywords:*** **Gastric cancer, peritoneal washing cytology, staging, prognosis**

## Introduction

About 50% of gastric cancer patients develop recurrent disease even after curative resection in the first two years of follow-up[1-4]. Peritoneal recurrence represents one of the most frequent patterns of recurrence in advanced gastric cancer[2,5-9]. Peritoneal dissemination is the most frequent cause of death, with a median survival time of only 3 to 6 months following peritoneal recurrence[9-12] and 5-year survival rate is almost nil[13-14].

The method of peritoneal lavage cytology was first described in 1961[15]. Intraperitoneal free cancer cell (IFCC) detection by conventional cytology is still the current gold standard[16]. The assessment of peritoneal lavage or ascitic fluid in gastric cancer patients serves to identify patients who, despite no evidence of gross peritoneal dissemination, have intraperitoneal free cancer cells (IFCC). Identification of IFCC in gastric cancer patients have been used to predict the risk of peritoneal recurrence and predict overall survival[17-18].

Diagnostic laparoscopy has been recommended for suspected advanced disease (serosal invasion or

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nodal metastasis on preoperative imaging) without evidence of distant metastasis[19]. However, its use remains uncommon. A study from Ontario in 2010 showed that only 5.1% of patients undergoing curative resection had diagnostic laparoscopy[20]. In the US, based on data from SEER-Medicare, 8.3% of patients with gastric cancer undergoing surgery had diagnostic laparoscopy[21]. Thus the use of diagnostic laparoscopy as an essential investigation in gastric cancer is not universally established[16].

Several studies supported the belief that IFCC detection is a potential useful tool for clinical decision-making, although this belief remains debatable. The purpose of the present study was to describe the detection rate of IFCC and to suggest an approach to the appropriate management of positive peritoneal washing cytology in Thai patients with gastric cancer.

## Patients and Methods

Between January 2006 and December 2013 (8 years) a series of 54 patients with gastric carcinoma underwent curative D2 gastrectomy with intraoperative peritoneal washing cytology (PWC) by one surgeon (CE) were reviewed.

Patients were included if there was no macroscopic evidence of peritoneal dissemination or distant metastasis, and if intraoperative peritoneal washing cytology was performed, as described elsewhere[22-23]. Briefly, after the surgeon had evaluated the possibility of performing a curative resection, 100 mL of normal saline solution (NSS) was instilled into the upper abdomen and manually dispersed. A sample of about 50 ml of the fluid was subsequently aspirated from the left subphrenic space and cul de sac (Pounch of Douglas). Cytological examination of this fluid was used for assessing the presence of intraperitoneal free cancer cell (IFCC). The result of cytological examination was reported one week after surgery, such that the D2 gastrectomy was carried out without the knowledge of the PWC status.

Disease recurrence was categorized as peritoneal, lecoregional or distant recurrence. The diagnosis of disease recurrence was made on the basis of radiological or endoscopic findings. Peritoneal recurrence was determined clinically, based on clinical symptoms or physical signs of bowel obstruction, ascites, and signs of peritoneal disease on digital rectal examination, and usually confirmed by barium study and CT scan. Cytological confirmation was obtained only for patients who underwent paracentesis or re-laparotomy.

The Chi-square test was used to test for differences in categorical variables between groups. The *t*-test or rank test was used for quantitative variables, as appropriate. The Kaplan-Meier method was used for constructing survival curves, and the log-rank test was used to test for significant differences in the survival curves between groups. Statistical significance was defined as a two-sided $p$-value $< 0.05$. Statistical analyses were performed using Stata version 12 (Stata Corp, College Station, TX, USA).

## Results

Of the 54 patients in the study, 12 (22%) had a positive peritoneal washing cytology (+PWC). Clinicopathological characteristics of all patients are presented in Table 1. In patients with positive peritoneal washing cytology, serosal invasion was more likely to be present (100% vs. 33%; $p = < 0.001$), as was nodal metastasis (100% vs. 91%; $p = 0.267$), and poorly differentiated tumors (83% vs. 67%; $p = 0.265$), although the latter two observations were not statistically significant. In our series, cytological positivity did not occur in any patient without serosa invasion or without nodal metastases.

**Table 1** Differences in the clinical and pathological characteristics and peritoneal recurrence between positive and negative cytology groups in the current series of gastric cancer patients

| Characteristic | Positive cytology N = 12 | Negative cytology N = 42 | *p*-value |
|---|---|---|---|
| Serosal invasion | 12 (100%) | 14 (33%) | < 0.001 |
| Lymph node metastasis | 12 (100%) | 38 (91%) | 0.267 |
| Poorly differentiated/signet ring cell | 10 (83%) | 28 (67%) | 0.265 |
| Peritoneal recurrence | 12 (100%) | 4 (10%) | < 0.001 |

**Table 2** Comparing follow-up time, deaths, and 5-year survival between positive and negative cytology groups in the current series of gastric cancer patients

| Outcome | Positive cytology N = 12 | Negative cytology N = 42 | *p*-value |
|---|---|---|---|
| Follow-up time (months) | | | |
| Median (range) | 13.5 (7 to 42) | 25.5 (5 to 84) | 0.005 |
| Mean (SD) | 18 (10.5) | 31 (18.1) | 0.022 |
| Death | 12 (100%) | 6 (14%) | < 0.001 |
| 5-year survival (95% Confidence Interval) | 0 | 83% (65.2% to 92.2%) | < 0.001* |

*p-value by log-rank test

**Table 3** Differences in the clinical and pathological characteristics and peritoneal recurrence between positive and negative cytology groups in the previous series of gastric cancer patients (2007)42

| Characteristic | Positive cytology N = 22 | Negative cytology N = 75 | *p*-value |
|---|---|---|---|
| Serosal invasion | 22 (100%) | 61 (81%) | 0.028 |
| Lymph node metastasis | 22 (100%) | 61 (81%) | 0.028 |
| Poorly differentiated/signet ring cell | 20 (91%) | 50 (67%) | 0.026 |
| Peritoneal recurrence | 22 (100%) | 14 (19%) | < 0.001 |

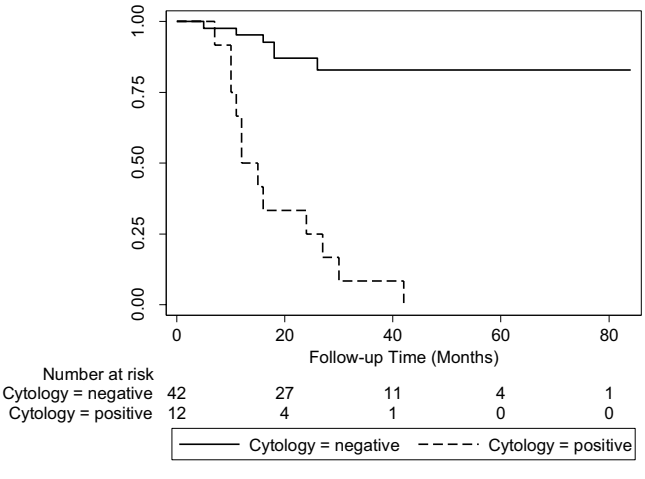


**Figure 1** Comparing survival curves between peritoneal washing cytology positive and cytology negative groups (log-rank test p-value < 0.001) in the current series of gastric cancer patients

All 12 patients with +PWC developed peritoneal recurrence. Patients with negative PWC, however, developed peritoneal recurrence in only 10%. Also, all 12 patients with +PWC died from peritoneal recurrence. Most of the deaths occurred within two years after surgery (Table 2). The median survival time for +PWC patients was 13.5 months (range 7 to 42 months) and for patients with negative PWC, the median survival time was 25.5 months (range 5 to 84 months).

There was no 5-year survival for patients with +PWC. Patients with negative PWC had a 5-year survival rate of 83%. The Kaplan-Meier estimates of the survival curves for patients with positive or negative PWC are presented in Figure 1.

## Discussion

PWC for detecting IFCC was first established by Moore et al. in 1961[15]. Previous studies reported that PWC was a good prognostic factor[3,8,17,24-29]. In the present study the prevalence of +PWC was 22%. The prevalence of +PWC in the literature ranged from 4.4 to 55%[6,17,22-23,29-31]. This wide variation reflects differences in case selection, as some studies considered only patients undergoing curative gastrectomy, while others focused on patients with serosal invasion, or patients with macroscopic peritoneal dissemination or malignant ascites.

The first step in peritoneal dissemination is considered to be the detachment of cancer cells from the serosal surface of the primary tumor, followed by their dissemination within the peritoneal cavity. These floating cancer cells reach the peritoneal surface,

invade the subperitoneal connective tissue and proliferate to form peritoneal nodules[27].

In the present study, serosal invasion, nodal metastases and poorly differentiated histology were associated with +PWC. When tumor invasion was limited to the gastric wall, PWC was usually negative. Previous studies also reported that serosal invasion was associated with a higher cytological positivity[3,6]. All +PWC patients had nodal metastases in the present series. Similarly, other reports found nodal metastases to be associated with a high prevalence of +PWC[6,18]. These results suggested that the rate of +PWC could increase proportionately when the tumor invades the serosal wall or regional nodes, and when the tumor has lost differentiation[32-36].

Despite variability in the prevalence of +PWC, all studies uniformly showed that patients with IFCC (+PWC) had a significantly higher risk of peritoneal recurrence and lower survival rate compared to patients with negative IFCC (negative PWC)[29,34,37-41]. From our previous report[42] (Table 3), 23% had +PWC. Positive washing cytology was often found in tumors invading the serosa or with LN metastases. All patients with+PWC developed peritoneal recurrence. The peritoneal recurrence rate in curative gastric cancer patients with +PWC ranged from 51 to 100%[24,42-46], while the peritoneal recurrence rate in curative gastric cancer patients with negative PWC ranged from 2.5 to 51%[24,42-48].

The treatment strategy for patients with gastric cancer depends on the stage of their disease at the time of diagnosis and treatment[44-50]. Although peritoneal dissemination commonly occurs in advanced gastric cancer, neither ultrasonography nor CT scan is sufficiently accurate for staging gastric cancers, especially for patients in whom the peritoneal or omental deposits are small and ascites is not yet present[51-55].

Hence, the idea behind staging laparoscopy for gastric cancer is that accurate preoperative staging can avoid unnecessary laparotomy. Staging laparoscopy (SL) is usually performed in the operating room under general anesthesia, and is thus invasive and expensive. It is difficult to justify SL as a routine preoperative examination. Because of its invasiveness, risk of complications and relatively high cost, studies of preoperative SL have been limited to relatively small cohorts[55-58]. Some investigators have suggested that SL should be limited to patients who have radiologic suspicion of peritoneal metastases on CT scans[59].

Although the prognostic significance of IFCC in gastric cancer is widely accepted, clinical applications remain unclear. There is no consensus regarding the incorporation of peritoneal washing cytology into the algorithm of gastric cancer treatment.

Obtaining PWC at the time of diagnostic laparoscopy was recommended by the Society of American Gastroenterologists and Endoscopic Surgeons (SAGEST) in 2008[19], but they failed to indicate how the results of PWC should impact management decisions. The European Society for Medical Oncology (ESMO) in 2010[61] considered obtaining PWC to be optional and not routine. The NCCN guidelines of 2010[60] did not incorporate PWC into the gastric cancer treatment algorithm, despite later considering +PWC a criterion of unresectability and an indication for palliative therapy[61]. The most recent TNM classification (7th edition 2010) included IFCC detection as part of the staging process, denoting M1 disease[62]. In the 2nd English edition 1998 of the Japanese Gastric Cancer Association (JGCA) guidelines, the presence of IFCC was considered an independent prognostic marker in gastric cancer[63].

All patients with +PWC in the present study developed peritoneal recurrence and was associated with poor prognosis, even following curative resection, with no 5-year survival. Positive PWC as an independent predictor of survival has been previously reported by many investigators[6,17,26,33,41]. Patients with +PWC are considered to have stage IV disease even in the absence of macroscopic peritoneal dissemination.

From our previous study of 97 patients (1995-2005), 22 patients (23%) had +PWC. Positive peritoneal washing cytology was also found only in tumors involving the serosa and all patients with +PWC developed peritoneal recurrence[42].

Through the designation as stage IV disease[42] and the well-established associated poor prognosis, patients with +PWC have traditionally been offered palliative treatment[64-65]. There is, however, controversy regarding whether the initial palliative treatment should be a gastrectomy or systemic chemotherapy[66-70]. Although the optimal management for patients with +PWC is unknown, some investigators suggest that the prognosis of patients with +PWC can be improved.

We accept that curative gastrectomy alone does

not provide a survival benefit for these patients. The problem is that the results of intraoperative PWC require a one week waiting period. Thus, if intraoperative PWC is positive, a more aggressive and multimodal approach would be necessary to prevent peritoneal recurrence. Even when curative gastrectomy is performed on patients with positive intraoperative PWC, some adjuvant therapy specifically focused on peritoneal recurrence is needed.

There is no universally accepted regimen for gastric cancer with peritoneal dissemination. ECF (epirubicin + cisplatin + 5FU) and DCF (docetaxel+ cisplatin + 5FU) regimen are often used in Western countries[70-74]. In Japan, the S-1 plus cisplatin regimen is the standard for metastatic gastric cancer[75].

The administration of most chemotherapeutic agents cannot hope to achieve therapeutic doses in the peritoneum because of the blood-peritoneum barrier[76]. S-1 has been reported to pass through the blood-peritoneum barrier and enter the ascetic fluid decreasing peritoneal recurrence[77], and to prolong the survival of gastric cancer patients with peritoneal dissemination[12,78-81]. S-1 for gastric cancer patients seemed to be more effective than conventional chemotherapy against peritoneal dissemination[77,82-84].

Kodera et al in 2007 reported a phase III study of radical surgery followed by postoperative S-1 for gastric cancer with IFCC[85]. The median survival time was 23.5 months and the 2-year survival rate was 47%. Because a higher response rate has been reported with S-1 plus cisplatin compared with S-1 alone in a phase III study of metastatic gastric cancers[75], we expect S-1 plus cisplatin to be more effective against peritoneal recurrence than S-1 alone. Some investigators reported the complete disappearance of peritoneal metastases in gastric cancer patients with S-1 plus cisplatin[86-87]. At present, S-1 plus cisplatin is recognized as the standard chemotherapy for patients with +PWC in Japan[88].

Kobayashi et al. in 2006 demonstrated paclitaxel to be a promising drug for the treatment of malignant ascites in gastric cancer patients[89]. The concentration of paclitaxel in the ascetic fluid was maintained within the optimal level for the killing of cancer cells for up to 72 hours after IV administration.

In patients with +PWC obtained during staging laparoscopy, eradication of IFCC may improve outcomes in medically fit patients. These patients should receive induction chemotherapy[37,76]. If subsequent restaging reveals response to induction chemotherapy (negative PWC without macroscopic evidence of peritoneal dissemination), the patient may be offered curative gastrectomy with postoperative systemic chemotherapy and/or intraperitoneal chemotherapy[90]. Induction chemotherapy can lead to IFCC negativity in a subset of patients and improves their survival[90].

Mezhir et al. in 2010 proposed that patients with positive IFCC alone should undergo chemotherapy for 6 to 12 months. If there is no clinical progression, repeat PWC is performed. Patients who remain positive for IFCC are treated palliatively[90]. Patients who become IFCC-negative ("converted") and have good performance status are considered for curative gastrectomy. They stressed the importance of both patient status and re-evaluation in determining the aggressiveness of subsequent treatment. They reported a resection rate of 74% for IFCC-positive patients who become converted.

Lorenzen et al. in 2010 demonstrated that gastric cancer patients whose IFCC status converted from positive to negative following induction chemotherapy had an improved median survival time (36.1 months vs. 9.2 months) and longer 2-year survival (71% vs 25%) compared with persistently IFCC-positive patients[91]. This allows the surgeon to selectively offer aggressive resection to patients in whom there is a response to induction chemotherapy.

Some investigators reported good outcomes with intraperitoneal chemotherapy for peritoneal dissemination[92]. There is also a strong rationale for using intraperitoneal chemotherapy to prevent peritoneal recurrence. Drug concentration within the peritoneal cavity is higher than what can be achieved after IV administration[85]. Intraperitoneal chemotherapy was demonstrated to be prophylactic against peritoneal recurrence and to result in improved survival[19,93]. The use of extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy has also been demonstrated in a phase III study to improve the survival of advanced gastric cancer with +PWC[94].

## Conclusion

Approximately 22% of patients undergoing curative D2 gastrectomy for gastric cancer had +PWC.

There were significant associations between +PWC and serosal invasion, nodal metastasis and poorly differentiated histology. Positive PWC was a significant predictor of peritoneal recurrence, indicating poor prognosis and no 5-year survival. These patients should be considered to have stage IV disease and may benefit from additional chemotherapy rather than surgery alone.

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