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Cytology of Peritoneal Lavage Performed During Staging Laparoscopy for Gastrointestinal Malignancies: Is It Useful?

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Objective

To evaluate the potential benefit of cytology of the peritoneal lavage obtained during diagnostic laparoscopy for staging gastrointestinal (GI) malignancies.

Summary Background Data

Peritoneal lavage is a simple procedure that can be performed during laparotomy for GI tumors. Tumor cells in the lavage fluid are thought to indicate intraperitoneal tumor seeding and to have a negative effect on survival. For this reason, peritoneal lavage is frequently added to diagnostic laparoscopy for staging GI malignancies.

Methods

Patients who underwent peritoneal lavage during laparoscopic staging for GI malignancies between June 1992 and September 1997 were included. Lavage fluids were stained using Giemsa and Papanicolaou methods. Cytology results were correlated with the presence of metastases and tumor ingrowth found during laparoscopy and with survival.

Results

Cytology of peritoneal lavage was performed in 449 patients. Tumor cells were found in 28 patients (6%): 8/87 with an esophageal tumor, 2/32 with liver metastases, 11/72 with a proximal bile duct tumor, 7/236 with a periampullary tumor, and none in 7 and 15 patients with a primary liver tumor or pancreatic body or tail tumor, respectively. In 19 of the 28 patients (68%) in whom tumor cells were found, metastatic disease was detected during laparoscopy, and 3 of the 28 patients had a false-positive (n = 1) or a misleading positive (n = 2) lavage result. Therefore, lavage was beneficial in only 6/449 patients (1.3%); in these patients, the lavage result changed the assessment of tumor stage and adequately predicted irresectable disease. Univariate analysis showed a significant survival difference between patients in whom lavage detected tumor cells and those in whom it did not, but multivariate analysis revealed that these survival differences were caused by metastatic or ingrowing disease.

Conclusion

Cytology of peritoneal lavage with conventional staining should no longer be performed during laparoscopic staging of GI malignancies because it provides an additional benefit in only 1.3% of patients and has limited prognostic value for survival in this group of patients.

Diagnostic laparoscopy is frequently used for staging gastrointestinal (GI) malignancies. The most important advantages of laparoscopic staging are detection of peritoneal and superficial liver metastases, malignant lymph nodes, and tumor ingrowth.[1–5] An invasive staging method such as laparoscopy is warranted because patients with proven metastatic or ingrowing tumors can subsequently be excluded from laparotomy. Resection with curative intent is not indicated in these patients, and palliation can be performed by nonsurgical means. The development of small ultrasound probes enabled the use of laparoscopic ultrasonography, which can detect small intrahepatic metastases and vascular involvement by the tumor.[6–8] The combined method of laparoscopy and laparoscopic ultrasonography can change the assessment of tumor stage in 10% to 60% of patients and can prevent unnecessary laparotomies in 10% to 40% of patients with GI malignancies.[3,4,7–10]

Since the introduction of laparoscopic staging, lavage of the peritoneal cavity has been added to the procedure.[11]

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Although peritoneal lavage is easily performed during laparoscopy, little is known about the value of lavage for staging GI malignancies in addition to laparoscopy. Free cancer cells found in the peritoneal lavage fluid are thought to induce or indicate early peritoneal seeding with subsequent peritoneal metastases.[12–14] In studies describing a positive result of the lavage obtained during laparoscopic staging, it is often associated with metastatic disease.[11,15,16] In patients with gastric cancer, the presence of tumor cells in the peritoneal lavage performed during laparotomy was associated with a worse prognosis in one study.[17] It has been suggested that lavage during laparoscopy would be helpful because it is a simple procedure and can change the assessment of tumor stage, with consequences for further treatment.

In this study, we assessed the potential benefit of performing peritoneal lavage during laparoscopic staging of GI malignancies. This benefit was defined as the number of patients in whom the lavage result adequately changed the assessment of tumor stage and predicted irresectable disease, in addition to the laparoscopy results. Lavage fluids obtained during laparoscopy for staging GI malignancies underwent conventional cytologic examination, without immunocytology. We correlated the results with the presence of metastases or tumor ingrowth found during laparoscopy and with survival.

PATIENTS AND METHODS

All patients who underwent diagnostic laparoscopy for staging GI malignancies between June 1992 and September 1997 were included. Patients with gastric and small or large bowel tumors were not staged laparoscopically in our hospital because surgical resection is generally accepted even as palliative treatment. Laparoscopic staging was routinely performed in patients with distal esophageal or gastroesophageal junction tumors and hepatopancreatobiliary tumors, after conventional staging had shown no contraindications for a curative resection and patients were fit for major surgery. Patients with esophageal or gastroesophageal junction tumors were staged before laparoscopy with ultrasonography of the neck region, transabdominal ultrasonography combined with Doppler of the abdomen, endoscopy and endoscopic ultrasonography, laryngoscopy, and if indicated bronchoscopy. Patients with hepatopancreatobiliary malignancies were staged with computed tomography scans, ultrasonography combined with Doppler, and endoscopic retrograde cholangiopancreatography. Biopsy samples were taken from lesions suspected for distant metastases, and patients with histologically proven metastatic disease were excluded from laparoscopic staging.

Laparoscopy

The laparoscopic procedure has been described previously.[3,4,6,9,10] Peritoneal lavage was performed after the laparoscopic inspection. Between 0.5 and 1.5 l 0.9% sodium chloride was instilled through the right subcostal trocar and drained through the left subcostal trocar. The lavage fluid was drained into a sterile container without heparin. For lesions suspected for metastases outside the area of the potential field of resection, biopsy samples were taken after the lavage with a biopsy forceps, True-cut (Travenol, Baxter Healthcare Corp., Deerfield, IL), or Rotex (Ursus Konsult AB, Stockholm, Sweden) biopsy needles. No biopsy samples of the primary tumor were taken. Patients were excluded from exploratory laparotomy if they had laparoscopically detected and histologically proven metastases or ingrowing disease. Biopsy-proven tumor ingrowth comprised local tumor ingrowth at the Treitz ligament and mesocolon, which could be evaluated by lifting the mesocolon. Vascular involvement of a tumor could not be proven with biopsies; these patients underwent an exploratory laparotomy to prove irresectable disease.

Cytology

The samples were examined by an experienced pathologist. Four to eight cytospins were made from a representative sample of the peritoneal lavage fluid. The cytospins were stained using the Giemsa and Papanicolaou methods for cytologic evaluation. Cytospins were classified as either positive (cytology positive for malignant cells) or negative (cytology negative for malignant cells, suspect for malignant cells, or material insufficient for diagnosis) (Fig. 1). The lavage results were not used to plan further treatment.

Statistical Analysis

Results of the lavage were related to the patient's follow-up and compared with laparoscopic findings (i.e., the presence of metastases and/or tumor ingrowth). Differences between groups with a positive and negative lavage result were calculated with the chi square test. $P < 0.05$ was considered statistically significant. The survival time was calculated from the day of laparoscopy until death or censored at January 1, 1998. Survival was calculated using the Kaplan–Meier method and survival curves were compared with the log-rank test. Cox regression analysis was used to evaluate the influence of lavage on survival, adjusted for important covariates. All data were analyzed with SPSS version 7.5 for Windows.

RESULTS

Laparoscopic staging was performed in 502 patients. In 53 patients, a peritoneal lavage was not performed or could not be evaluated because of the presence of adhesions (7 patients) or a biloma (1 patient). Thirteen patients had overt metastatic disease, proven with frozen sections during laparoscopy, and a peritoneal lavage was therefore not performed. In 32 patients, no lavage was performed, without a

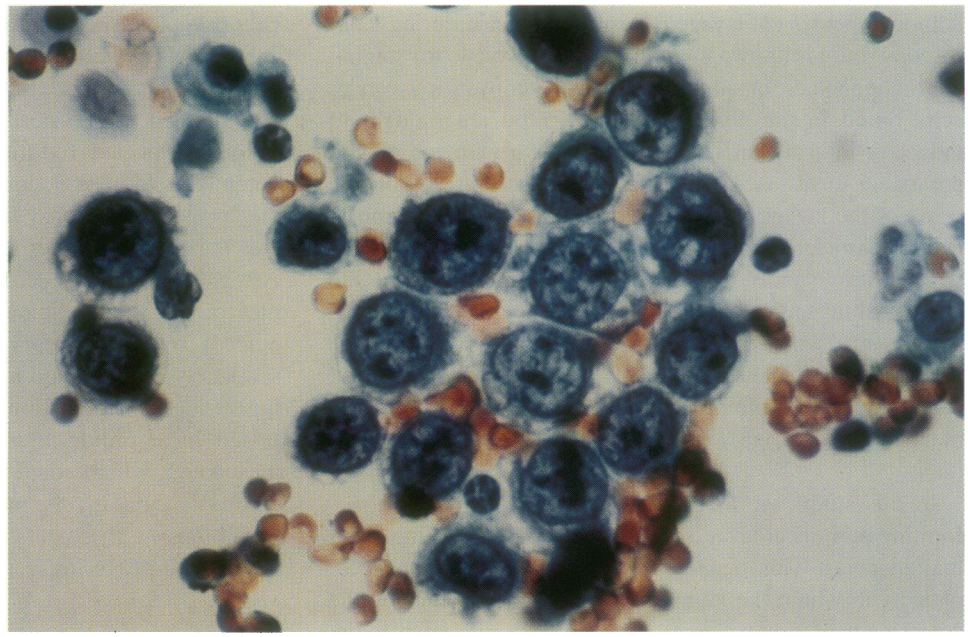

Figure 1. Cytospin of a positive sample of the peritoneal lavage fluid from a patient with periampullary cancer.

reason being given; none of these 32 patients had metastases proven with laparoscopy.

Characteristics of the 449 patients included in this study are summarized in Table 1. No complications that could be ascribed to the peritoneal lavage occurred in these patients.

Lavage fluids were found to contain tumor cells in 28 of the 449 patients (6%); no tumor cells were found in the lavage fluids in the other 421 patients (Table 2). Nineteen of the 28 patients (68%) with a positive lavage result had metastases proven during laparoscopy. Nine patients had a positive lavage result without metastatic disease found during laparoscopy. Of these nine patients, four underwent exploratory laparotomy without resection as a result of tumor ingrowth (one proximal bile duct tumor, one esophageal tumor, and two periampullary tumors). One patient with an esophageal tumor refused exploration, although no contraindications for resection were found at laparoscopy; he died within 2 months after laparoscopy. One patient with liver metastasis underwent a nonradical resection in another hospital. Therefore, in six of these nine patients, the positive lavage result correlated with irresectable disease and a poor prognosis. In one patient with a proximal bile duct tumor, the positive result was considered a false-positive result because the patient's primary lesion was eventually diagnosed as primary sclerosing cholangitis; she is still alive and well more than 5 years after laparoscopy. Two other patients with gastroesophageal tumors underwent radical resection; one patient survived 20 months, and the other is still alive after 13 months. The positive lavage results in these two patients were considered not helpful to predict irresectable disease.

Overall, there was potential benefit of the peritoneal lavage in addition to the laparoscopy results in only 1.3% of the patients; in other words, in only 6 of the 449 patients did the lavage adequately predict irresectable disease.

The peritoneal lavage results were related to the laparoscopy results in terms of metastases and tumor ingrowth (Table 3). Diagnostic laparoscopy detected metastatic disease in $^{73}/_{449}$ patients (16%). Patients with a positive lavage result had metastases significantly more frequently than did patients with a negative lavage ($p < 0.001$). In the 19 patients with a positive lavage result, metastases were located in the liver in 6 patients, at the peritoneum in 7 patients, both in the liver and peritoneum in 3 patients, or at other sites in 3 patients. Of the 421 patients with a negative lavage, 54 patients (13%) had metastatic disease. These metastases were located in the liver in 24 patients, at the peritoneum in 4 patients, and at other sites in 26 patients. The sensitivity and specificity of the lavage for metastatic disease was 26% and 98%, respectively.

Tumor ingrowth was suspected during laparoscopy in 77 of the 449 patients (19%). Because tumor ingrowth was not pathologically proven, it was not an exclusion criterion for exploratory laparotomy. Thirteen of the 28 patients (46%) with suspected tumor ingrowth had a positive lavage result

Table 1. PATIENT CHARACTERISTICS

	Laparoscopy and Lavage		Mean Age
Tumor Location	n	M:F	Yrs (range)
Esophagus/cardia	87	66:21	61 (39–83)
Primary liver	7	5:2	49 (15–73)
Liver metastases	32	16:16	59 (20–78)
Proximal bile duct	72	38:34	58 (24–76)
Periampullary	236	144:92	63 (30–83)
Pancreatic body/tail	15	7:8	57 (36–78)
Total	449	276:173	58 (15–83)

Table 2. RESULTS OF THE PERITONEAL LAVAGE AND CONCOMITANT DETECTION OF HISTOLOGICALLY PROVEN METASTASES DURING LAPAROSCOPIC STAGING

	Laparoscopy and Positive Lavage	Positive Lavage With Metastases	Positive Lavage Without Metastases
Tumor Location	**n (%)**	**n (%)**	**n (%)**
Esophagus/cardia	8/87 (9)	4	4*
Primary liver	0/7	0	0
Liver metastases	2/32 (6)	1	1
Proximal bile duct	11/72 (15)	9	2†
Periampullary	7/236 (3)	5	2
Pancreatic body/tail	0/15	0	0
Total	28/449 (6)	19/449 (6)	9/449 (2)

* Two patients with a positive lavage underwent a radical esophagectomy and are considered misleading results of the peritoneal lavage.
† One patient with a primary sclerosing cholangitis (PSC) and a survival of more then 5 years without signs of malignant disease is considered false positive result of the peritoneal lavage.

compared with 64/421 patients (15%) with tumor ingrowth and a negative lavage result ($p < 0.001$). The sensitivity and specificity of the lavage for detection of tumor ingrowth was 17% and 96%, respectively.

Survival Analysis

Survival analysis was performed in 339 patients with sufficient follow-up—76 of the 87 patients (87%) with esophageal tumors, 62 of the 72 patients (86%) with proximal bile duct tumors, and 201 of the 236 patients (85%) with periampullary tumors. Patients with liver tumors or pancreatic body or tail tumors were not included in the survival analysis because too few patients had a positive lavage result. The patient with primary sclerosing cholangitis and a false-positive lavage result was excluded from this survival analysis. The two patients with a positive lavage result who underwent radical esophagectomy were analyzed as having a positive lavage result. Patients with insufficient follow-up all had a negative lavage. A total of 21 patients with esophageal tumors, 31 patients with proximal bile duct tumors, and 80 patients with periampullary tumors were still alive as of January 1998 and were therefore censored.

Median survival times were significantly decreased in patients with a positive lavage result in all three patient groups (Table 4). Survival time was further analyzed with Cox regression analysis for the results of lavage as well as metastases, tumor ingrowth, patient age, and treatment (radical or nonradical resection or palliative treatment). Because metastases and tumor ingrowth detected at laparoscopy underestimate the total number of metastases and tumor ingrowth, analysis was performed using the overall number of metastases and ingrowing tumors found at laparoscopy as well as laparotomy. The relative risk for metastatic disease and tumor ingrowth was greater than one in the three tumor groups, in contrast with the relative risk for a positive lavage result. The difference in survival for patients with a positive lavage result, as shown with univariate analysis, therefore

Table 3. LAVAGE RESULTS COMPARED TO LAPAROSCOPY RESULTS

	Metastases Proven During Laparoscopy		Ingrowth Seen During Laparoscopy	
Tumor Location	**Positive Lavage (%)**	**Negative Lavage (%)**	**Positive Lavage (%)**	**Negative Lavage (%)**
Esophagus/cardia	4/8 (50)	8/79 (10)	2/8 (25)	4/79 (5)
Primary liver	0	1/7 (14)	0	4/7 (57)
Liver metastases	1/2 (50)	2/30 (7)	0	1/30 (3)
Proximal bile duct	9/11 (82)	16/61 (26)	7/11 (64)	16/61 (26)
Periampullary	5/7 (71)	23/229 (10)	4/7 (57)	49/229 (21)
Pancreatic body/tail	0	4/15 (27)	0	0
Total	19/28 (68)*	54/421 (13)*	13/28 (46)†	64/421 (15)†

* $p < 0.001$ (chi-square).
† $p < 0.001$ (chi-square).

Table 4. SURVIVAL ANALYSIS

Tumor Location	Median Survival Time (Months) (95% CI) Positive lavage	Negative lavage	Log Rank Test
Esophagus/cardia	5 (3–7)	12 (9–15)	p <0.001
Proximal bile duct	8 (7–9)	19 (8–30)	p =0.044
Periampullary	3 (0–6)	13 (11–15)	p <0.001

results from the association of a positive lavage result with metastatic and ingrowing disease (Table 5).

DISCUSSION

The value of cytology of peritoneal lavage performed during laparoscopic staging of GI malignancies was evaluated in a large series of patients. The additional value of the lavage was defined as the number of patients in whom a positive lavage result adequately predicted irresectable disease in addition to the laparoscopy results. Conventional cytology, without immunocytology, of peritoneal lavage performed during laparoscopic staging was in this series not useful as an additional staging method for patients with upper GI malignancies. Peritoneal lavage contained tumor cells in 6% of the 449 patients. Only 3% of patients with periampullary tumors had a positive lavage result, lower than the 29% and 17% reported in patients with pancreatic head malignancies.[11,16] Also in these studies, the incidence of metastases was greater, which indicates a different patient selection. In one series, a 7% positive lavage rate was reported in patients with resectable pancreatic head tumors after radiologic work-up.[18] In our study, 9% of patients with esophageal tumors had a positive lavage result; this percentage is similar to the results of others.[15] The patients with primary liver tumors and pancreatic body or tail tumors had negative lavage results. Warshaw reported 40% positive lavage results in patients with pancreatic body or tail tumors. Our results may be influenced by our patient selection.[11] It is noteworthy that all patients selected for diagnostic laparoscopy in our institution had resectable tumors according to presurgical staging. Biopsy samples were taken before laparoscopy only to prove metastatic disease, and patients with positive biopsy results did not undergo further laparoscopic staging. Patients with proximal bile duct tumors and secondary liver tumors had a positive lavage result in 15% and 6%, respectively, in our study; comparative results from other studies are lacking.

False-positive results of the lavage are not mentioned in previous studies. In our study, one patient with primary sclerosing cholangitis had a false-positive result of the lavage. Even after revision of the cytology, the cytologic diagnosis remained positive for malignant cells. This false-positive result may be caused by mesothelial cells with reactive inflammatory changes that resemble malignant cells. Further, two patients had positive lavage results that were considered misleading for subsequent treatment because they could undergo radical tumor resections with considerable survival. Had the lavage result been an exclusion criterion for further surgery, these patients would have been considered to have irresectable disease.

A positive lavage result could have additional value for laparoscopic staging only if it were a unique finding, without the presence of metastases or ingrowing disease. When the lavage results were combined with the laparoscopy results, the additional value of the lavage decreased because 19/28 patients (68%) with a positive lavage result also had metastases proven with laparoscopic staging. Other authors have also shown a high number of patients with a positive lavage result and peritoneal or hepatic metastases.[15,16] In this study, hepatic as well as peritoneal metastases were present in the positive lavage group; therefore, we cannot conclude that the presence of tumor cells in the lavage fluid indicates peritoneal metastases. However, a clear differentiation between superficial hepatic metastases and peritoneal deposits at the liver surface could not be made. We also did not examine whether the tumor cells in the peritoneal cavity induce peritoneal deposits. Tumor ingrowth was also associated with a positive lavage result: significantly more patients with a positive lavage result had tumor ingrowth compared with patients with a negative lavage result.

As a result of the association between a positive lavage result and metastases as well as tumor ingrowth, a decreased survival in patients with a positive lavage result should be further analyzed, because metastases and tumor ingrowth are both known to decrease survival. The survival curves showed a clear survival benefit for patients with a negative

Table 5. RELATIVE RISKS (95% CONFIDENCE INTERVAL), ADJUSTED FOR AGE, SEX AND TREATMENT

Tumor Location	Positive Lavage	Metastases	Tumor Ingrowth
Esophagus/cardia	0.32 (0.13–0.83)	1.74 (0.94–3.22)	1.70 (0.87–3.33)
Proximal bile duct	0.93 (0.34–2.58)	3.88 (1.68–8.95)	1.47 (0.65–3.31)
Periampullary	0.99 (0.88–1.12)	3.40 (2.36–4.89)	1.77 (1.26–2.47)

lavage result, but after regression analysis metastases and tumor ingrowth had more influence on survival than the result of the lavage.

Considering the low rate of positive results, and taking into account the false-positive (1/28) and misleading (2/28) results and the lack of a clear prognostic factor for survival, conventional cytology of lavage should no longer be performed during diagnostic laparoscopy.

Diagnostic laparoscopy is always performed as a separate procedure, a few days before a planned resection, because cytology cannot be performed instantaneously. But if cytology of the lavage fluid has no additional value for laparoscopic tumor staging, laparoscopy no longer has to be performed as a separate procedure and can be performed at the same session as the planned laparotomy.[19]

New techniques such as polymerase chain reaction and immunocytochemistry, which may be more sensitive for the detection of tumor cells, are being investigated.[20,21] A recent paper in *Annals of Surgery* described a higher incidence of the detection of tumor cells in bone marrow and the peritoneal cavity with immunocytology.[22] Of the patients with gastric and colorectal cancer, 53% and 31%, respectively, had tumor cells in the lavage fluid, and positive lavage results correlated with decreased survival. However, these results cannot be extrapolated to all GI malignancies. It is doubtful if specific monoclonal antibodies are available for hepatopancreatobiliary tumors, and that study also showed that 2/7 patients with pancreatitis had positive results on immunocytology. But if these techniques are proven adequate for other GI malignancies and also have an additional value in the specific group of patients who are candidates for laparoscopic tumor staging, the role of peritoneal lavage during laparoscopy should be reconsidered.

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